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Structure and Total Synthesis of (−)-Myrionidine and (−)-Schoberine, Antimalarial Alkaloids from *Myrioneuron nutans*

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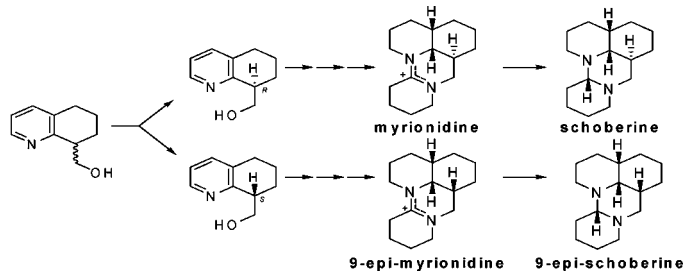

Two new alkaloids, (5*S*,9*S*,10*R*)-myrionidine (**1**) and (5*S*,9*S*,10*R*,13*S*)-myrionamide (**2**), along with the known schoberine (**3**), were isolated from the leaves of *Myrioneuron nutans* (Rubiaceae), and their structures were determined from spectral analysis, including mass spectrometry and 2D NMR. The total asymmetric syntheses of (−)-myrionidine (**1**), (−)-schoberine (**3**), their enantiomers as well as their 9-epimers derivatives were performed, allowing the determination of their absolute configuration together with that of myrionamide (**2**). (−)-Myrionidine (**1**) and its synthetic enantiomer (**18**) showed a significant antimalarial activity on *Plasmodium falciparum*.

Introduction

An ongoing research interest in our group is the identification of alkaloids from *Myrioneuron nutans*, a small shrub of North-Vietnam. We have previously isolated from this plant several novel alkaloid skeletons,[1a−d] containing the *cis*-decahydroquinoline (*cis*-DHQ) motif which is rare in plant source,[2] but characterized from some neotropical frogs[3a−d] and ants.[4] The plants known to produce DHQs derivatives are restricted to several *Lycopodium*[5a−e] and *Nitraria* species.[6a,b] Analysis of the alkaloidal fraction of *M. nutans* has led to the isolation of two new tetracyclic alkaloids, (−)-myrionidine (**1**) and (+)-myrionamide (**2**), along with the known (−)-schoberine (**3**).[7a−c]

Previous reported papers on schoberine isolated from several *Nitraria* species, described it as a mixture of enantiomers.[7a−c] In addition, the schoberine skeleton has not been synthesized yet. In this paper, we described the structure elucidation by spectral methods, and the total asymmetric syntheses of (−)-myrionidine (**1**) and (−)-schoberine (**3**), together with the syntheses of their enantiomers and their epimers at C-9. Furthermore, the absolute configuration of (+)-myrionamide (**2**) was determined by its transformation into (−)-schoberine (**3**), the absolute stereochemistry of which has been established by its total synthesis. The cytotoxic and antimalarial activities of all the natural and synthetic compounds were evaluated. (−)-Myrionidine (**1**) and its synthetic enantiomer (**18**) showed an important antimalarial activity on *Plasmodium falciparum* with IC_{50} of 0.3 and 0.5 μg/mL, respectively. Finally, a plausible

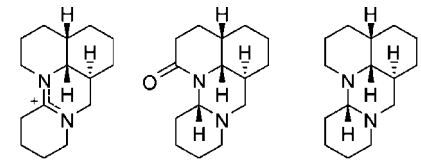

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TABLE 1. NMR Data for (−)-Myrionidine (1) and (+)-Myrionamide (2) (^{1}H: 400.13 MHz, ^{13}C: 75.47 MHz, $CDCl_3$, 298 K)

(−)-myrionidine (**1**)			(+)-myrionamide (**2**)		
Cn°	δ_C	δ_H m (*J*, Hz)	Cn°	δ_C	δ_H m (*J*, Hz)
2	40.3	3.62 ddd (14.2,7.1, 1.3)	2	168.1	−
	−	3.38 m			
3	21.2	1.83 m	3	32.7	2.44 ddd (17.5, 5.4, 1.7)
	−	1.68 m		−	2.29 ddd (17.5, 12.6, 6.5)
4	19.5	1.55 m	4	21.7	1.90 dddd (13.3, 13.3, 12.6, 5.4)
	−	1.38 m		−	1.41 m
5	29.0	2.33 m	5	32.5	2.03 ddddd (13.3, 5.2, 5.2,5.2, 2.6)
6	28.8	1.55 m	6	30.3	1.68 m
	−	1.55 m		−	1.65 m
7	19.1	1.43 m	7	20.3	1.48 m
	−	1.27 m		−	1.35 m
8	27.4	1.72 m		29.8	1.53 m
	−	0.88 dddd (13.0, 13.0, 13.0, 3.9)		−	1.04 m
9	29.5	1.97 ddddd (13.0, 12.5, 10.7, 5.4, 3.9)	9	34.7	1.75 m
10	58.6	3.50 dd (10.7, 6.1)	10	54.9	3.29 dd (11.0, 5.2)
11	54.6	3.25 dd (12.5, 5.4)	11	52.8	2.68 dd (11.3, 8.7)
	−	3.16 dd (12.5,12.5)		−	2.49 dd (11.3, 5.6)
13	160.1	−	13	68.2	5.07 dd (11.4, 2.9)
14	27.2	2.74 br. d (17.1)	14	23.1	1.78 m
	−	2.65 ddd (17.1, 8.1, 8.1)		−	1.43 m
15	18.7	1.88 m	15	24.1	1.79 m
	−	1.71 m		−	1.52 m
16	20.9	1.81 m	16	19.9	1.55 m
	−	1.70 m		−	1.22 m
17	51.3	3.42 m	17	53.6	2.81 ddd (13.3, 3.8, 1.8)
	−	3.33 m		−	2.75 ddd (13.3, 12.3, 3.0)

biosynthesis pathway was proposed for these alkaloids based on their structure.

Results and Discussion

1. Isolation and Structure Elucidation of (−)-Myrionidine (1), (+)-Myrionamide (2), and (−)-Schoberine (3). The crude alkaloid fraction (29.5 g) obtained from the dried leaves of *M. nutans* (5.5 kg) was purified by repeated open column chromatography over silica gel eluted with CH_2Cl_2/MeOH gradient to afford (−)-myrionidine (**1**, 3.7 g), (+)-myrionamide (**2**, 55 mg), and (−)-schoberine (**3**, 24 mg).

(−)-Myrionidine (**1**) was obtained as an optically active colorless crystalline solid, $[\alpha]_D^{20}$ −60 (*c* 1, MeOH). The ESI-MS showed the molecular ion at *m/z* 233.2003 (calcd. 233.2018 for $C_{15}H_{25}N_2$). The IR spectrum indicated the presence of an imine (1626 cm^{-1}) functionality. The 1D-NMR (^{1}H and ^{13}C) spectra indicated 11 methylenes, 3 methines, and 1 quaternary carbon at δ_C 160.1 (C-13). The five degrees of unsaturation were thus assigned to one double bond and four rings. In the ^{1}H−^{1}H COSY spectrum, connections were depicted from CH_2-2 (δ_H 3.38 and 3.62) to CH-10 (δ_H 3.50), which was then correlated to CH-5 (δ_H 2.33), and the correlations between CH-9 (δ_H 1.97) and CH_2-11 (δ_H 3.16 and 3.25) were also observed. The ^{1}H and ^{13}C chemical shifts of CH_2-2 and CH-10 (Table 1) suggested their direct linkage to a nitrogen atom. All of these data defined the substructure I, marked with bold bonds in Figure 1A. On the other hand, a set of connections from CH_2-17 (δ_H 3.33 and 3.42) to CH_2-14 (δ_H 2.65 and 2.74), via CH_2-16 (δ_H 1.70 and 1.81) and CH_2-15 (δ_H 1.71 and 1.88), formed a -$(CH_2)_4$- system (substructure II), in which CH_2-17 was linked to a nitrogen atom, in agreement with its ^{1}H and ^{13}C chemical shifts (δ_C 51.3). The planar structure of **1** was then established from HMBC data: cross peaks of sp^2 quaternary carbon C-13 (δ_C 160.1) with CH_2-2 (δ_H 3.38 and 3.62), CH-10 (δ_H 3.50), CH_2-11 (δ_H 3.16 and 3.25), CH_2-15 (δ_H 1.71 and 1.88), and CH_2-17 (δ_H 3.33 and 3.42) indicated that C-13 was linked to CH_2-14 and both N-1 and N-12 and methylene CH_2-11 was connected to CH_2-17 through N-12. Further HMBC correlations between H-10 (δ_H 3.50) and carbon C-2 (δ_C 40.3) established the presence of a DHQ motif. The structure of **1** was thus determined to be an iminium salt, in which the double bond could be delocalized on the N1−C13−N12 system (Figure 1A).

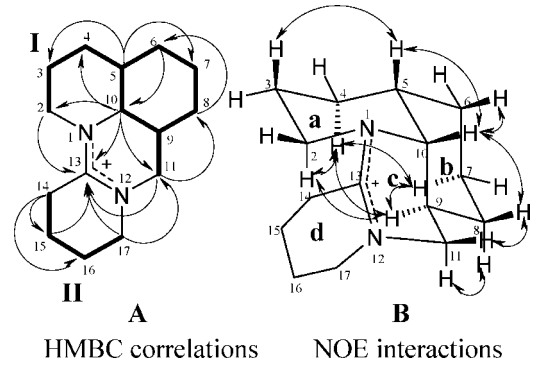

FIGURE 1. Selected HMBC and NOE correlations for (−)-myrionidine (**1**).

The relative stereochemistry of the ring junctions at C-5, C-9, and C-10 was determined from ^3J ^{1}H−^{1}H coupling constants and NOESY data. The three large coupling constants (10.7, 12.5, and 13.0 Hz), characteristic of *trans*-diaxial couplings and the two *gauche* interactions (3.9 and 5.4 Hz) observed for H-9, indicated its *trans*-diaxial relationship with H-10. In addition, the signal for H-10 was a doublet of doublet (J_{H10-H9} = 10.7 Hz and J_{H10-H5} = 6.1 Hz), corresponding to a *gauche* relationship between H-10 and H-5. This relative stereochemistry was confirmed from the NOESY experiment in which spatial interactions of H-10 with H-5, H-6_{ax}, and H-8_{ax}, together with those of H-9 with H-4_{ax} and H-7_{ax}, were observed (Figure 1B). These data indicated the *cis*-fused junction for the

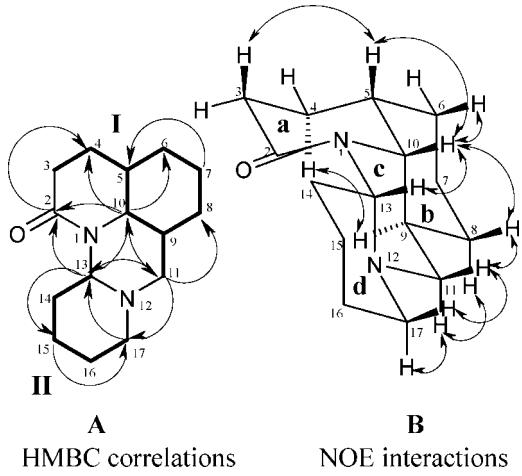

FIGURE 2. Key HMBC (A) and NOE (B) correlations for (+)-myrionamide (**2**).

a/b-rings and the *trans*-junction for the **b/c**-rings. The relative configuration of this new tetracyclic iminium alkaloid **1** which was named myrionidine, was thus 5*S**, 9*S**, 10*R**.

(+)-Myrionamide (**2**) was isolated as a colorless solid (mp. 154−155 °C, MeOH), optically active ($[\alpha]_D^{20}$ +17.0, *c* 1, MeOH). In its ESI mass spectrum, the protonated molecular ion $[M+H]^+$ at *m/z* 249.1965 (calcd. 249.1967 for $C_{15}H_{25}N_2O$) was in agreement with the molecular formula $C_{15}H_{24}N_2O$. The IR absorption band at 1637 cm^{-1} was characteristic of an amide carbonyl. The five degrees of unsaturation were distributed into one double bond and four rings. The 1D NMR (^1H and ^{13}C) spectra of **2** were nearly similar with those of **1**, except the presence of the methine CH-13 (δ_H 5.07 and δ_C 68.2) instead of a sp^2 quaternary carbon (C-13), and that of a carbonyl in place of a methylene. $^1H-^1H$ COSY and HSQC analyses determined the two fragments (**I** and **II**) shown in bold bonds in Figure 2A. The gross planar structure of **2** was established from HMBC cross-peaks of CH_2-4 (δ_H 1.41 and 1.90), H-10 (δ_H 3.29) and H-13 (δ_H 5.07) with C-2 (δ_C 168.1), and those of H-10, CH_2-11 (δ_H 2.49 and 2.68) and CH_2-17 (δ_H 2.75 and 2.81) with C-13 (δ_C 68.2) allowed linking the two fragments **I** and **II**.

The relative configuration of **2** was deduced from the observed NOE correlations and the values of the $^1H-^1H$ vicinal coupling constants. A *trans*-diaxial (J_{H10-H9} = 11.0 Hz) and a gauche (J_{H10-H5} = 5.2 Hz) couplings were depicted for H-10, suggesting the relative stereochemistry at C-5, C-9, and C-10 to be identical with that of (−)-myrionidine (**1**). Finally, the coupling constants of H-13 ($J_{H13-H14eq}$ = 2.9 Hz and $J_{H13-H14ax}$ = 11.4 Hz) pointed its axial disposition on the **d**-ring. This agreed with the observed NOE correlations of H-10 with H-6_{ax}, H-11_{ax}, H-8_{ax}, and H-13, which are all on the same side (Figure 2B), and furthermore of H-9 with both H-4_{ax} and H-7_{ax}, which are on the opposite side. The 1,3-diaxial relationship of H-13 with H-10 on the **c**-ring was depicted and the data indicated the relative configuration for **2** as 5*S**, 9*S**, 10*R**, 13*S**. This original tetracyclic alkaloid is named myrionamide.

The upfield chemical shifts of H-8_{ax} (Table 1) of both myrionidine (**1**) and myrionamide (**2**) were characteristic of N-outside conformation for the decahydroquinoline system (**a**- and **b**-ring). This N-outside conformation was constrained by the **c**-ring.

(−)-Schoberine (**3**) was obtained as microcrystals (mp. 62−63 °C, MeOH), optically active ($[\alpha]_D^{20}$ −12.2, *c* 1, MeOH). The

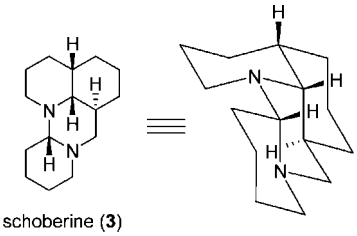

FIGURE 3. Structure of (−)-schoberine (**3**).

protonated molecular $[M+H]^+$ ion at *m/z* 235.2141 (calcd. 235.2174 for $C_{15}H_{27}N_2$) was observed in the ESI mass spectrum. The 1D NMR spectra (^1H and ^{13}C) were close to those of **2**, except for the presence of one additional methylene in the sp^3 region and the disappearance of the carbonyl group. The planar structure of **3** was determined from 2D NMR and its relative configuration was further established from $^1H-^1H$ vicinal coupling constants and NOESY experiment (Figure 3). All of these data indicated that **3** was identical to schoberine, which has been previously isolated from several *Nitraria* species.[7a−c] It is important to note that the schoberine previously isolated from *Nitraria* species was described as racemic form, and it was suggested to be biosynthesized by a nonenzymatic way.[7a−c] However, the sample of (−)-schoberine (**3**) that we isolated from *M. nutans* was optically active, as discussed above ($[\alpha]_D^{20}$ −12.2), suggesting it was a single enantiomer. This point was further confirmed by its total asymmetric synthesis yielding a unique compound having the same rotatory power ($[\alpha]_D^{20}$ −12.6) as described below.

2. Synthesis of (−)-Myrionidine (1), (−)-Schoberine (3), and their Enantiomers and 9-Epimers. Schoberine (**3**) was isolated for the first time in 1989[7a] and no synthesis has been reported yet. To confirm the structures of (−)-myrionidine (**1**), (+)-myrionamide (**2**), and (−)-schoberine (**3**) and also to determine their absolute configuration, we attempted their total synthesis, as well as those of their enantiomers and epimers at C-9. Retrosynthesis analysis of **1** and **3** suggested that they could be obtained from the tetrahydroquinoline (*R*)-**7** (Scheme 1).

The two enantiomers (*R*)-**7** and (*S*)-**7** were separated from the racemic mixture **4**[1,9] via the two diastereoisomers **5** and **6**, respectively. These diastereoisomers **5** and **6** were obtained by

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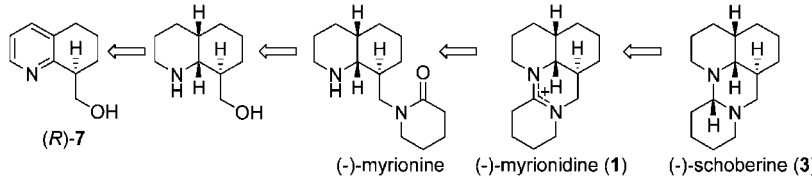
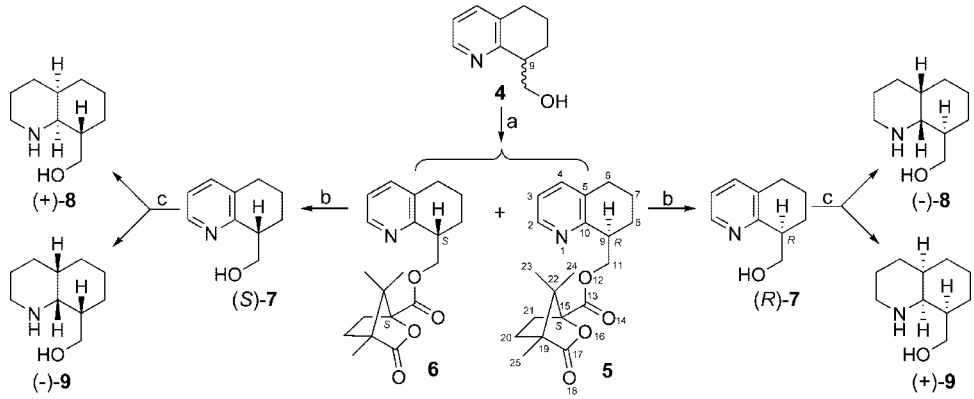
SCHEME 1. Retrosynthesis of (−)-Myrionidine (1) and (−)-Schoberine (2)

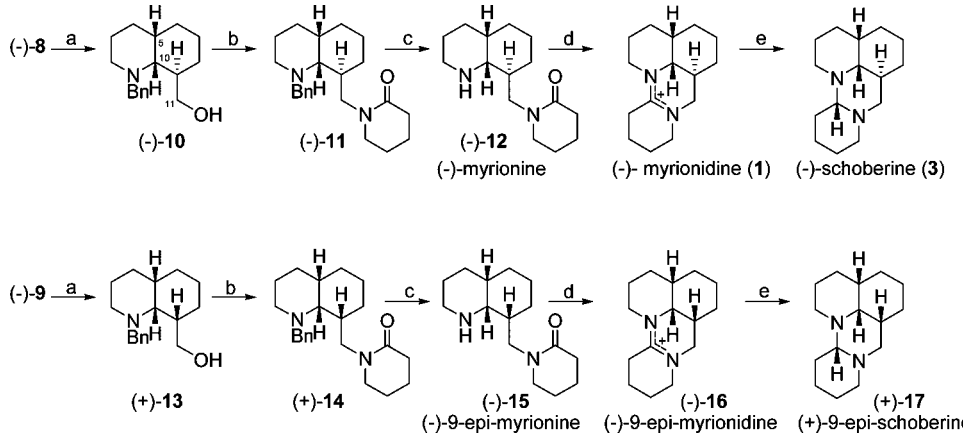


SCHEME 2. Synthesis of 9-Methanol-DHQs[a]



[a] Reagents and conditions: (a) (1*S*)-(−)-camphanoyl chloride, Et_3N, CH_2Cl_2, 25 °C, 12 h, 48% for **5** and 46% for **6**. (b) Aq. NaOH/MeOH, 50 °C, 3 h, 97% for (*R*)-**7** and 95% for (*S*)-**7**. (c) H_2/PtO_2, AcOH, 25 °C, 15 h, (−)-**8** (59%, $[\alpha]_D^{20}$ −2.1), (+)-**9** (18%, $[\alpha]_D^{20}$ +33.2), (+)-**8** (63%, $[\alpha]_D^{20}$ +1.8), and (−)-**9** (19%, $[\alpha]_D^{20}$ −33.8).

SCHEME 3. Synthesis of (−)-Schoberine and Its (+)-9-Epimer[a]



[a] Reagents and conditions: (a) BnBr, CH_2Cl_2/aq. $NaHCO_3$, 25 °C, 12h, (−)-**10** (93%) and (+)-**13** (82%). (b) i. MsCl, CH_2Cl_2, −5 °C, 1 h. ii. 2-piperidinone, KH, DMF, −5 to 25 °C, 12h, (−)-**11** (75%), and (+)-**14** (75%). (c) H_2/Pd−C, AcOH, 25 °C, 3 h, (−)-**12** (90%, $[\alpha]_D^{20}$ −16.8), and (−)-**15** (89%, $[\alpha]_D^{20}$ −21.8). (d) i. $POCl_3$, toluene, reflux, 12 h. ii. Aq. NaOH/MeOH, **1** (97%, $[\alpha]_D^{20}$ −60.1), and (−)-**16** (92%, $[\alpha]_D^{20}$ −53.2). (e) $LiAlH_4$, THF, 0 to 25 °C, 12 h, **3** (87%, $[\alpha]_D^{20}$ −12.6), and (+)-**17** (90%, $[\alpha]_D^{20}$ +32.4).

esterification of the racemic compound **4** with the chiral, (1*S*)-(−)-camphanoyl chloride, followed by basic hydrolysis. X-ray analysis of the ester **5** allowed determining of the absolute stereochemistry at C-9 chiral center as *R* and it was thus *S* in the ester **6**.[1] Catalytic hydrogenation of (*R*)-**7** and (*S*)-**7** gave the two pairs of diastereoisomers (−)-**8**/(+)-**9** and (+)-**8**/(−)-**9**, respectively (Scheme 2).[10a,b] The resulting diastereoisomers were successfully separated by column chromatography.

The relative configurations at C-10 and C-5 of (−)-**8** [or (+)-**8**] and for (+)-**9** [or (−)-**9**] were determined from ^3J $^1H-^1H$ coupling constants analysis of H-10 which in **8**, showed a strong (J_1 = 10.6 Hz) and a small (J_2 = 2.8 Hz) coupling constants with H-9 and H-5, respectively, while it had two small ones (J_1 = J_2 = 2.7 Hz) for **9**. This indicated that H-10 and H-9 were in a *trans*-diaxial relationship in (+)- and (−)-**8** and in a *cis*-disposition in (+)- and (−)-**9**, and that a *cis*-fused junction characterized the DHQ moiety. The absolute stereochemistry at C-5 and C-10 of (+)- and (−)-**8** and (+)- and (−)-**9** was then established on the basis of the known absolute configuration at C-9 of (*R*)-7 and (*S*)-7. The amino group of (−)-**8** was then protected with a benzyl group (Scheme 3).[11] The resulting benzyl protected (−)-**10** was first transformed into its mesyl derivative with MsCl and then coupled with 2-piperidinone in

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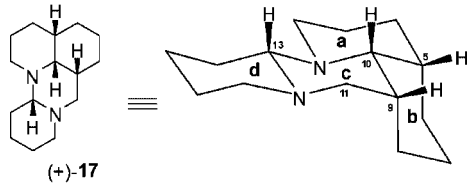


FIGURE 4. Stereochemistry of (+)-9-epi-schoberine [(+)-17].

the presence of KH to afford (−)-**11**. Benzyl deprotection of (−)-**11** by catalytic hydrogenation (H_2/Pd−C) in methanol,[12a,b] provided (−)-myrionine, (−)-**12**. Intramolecular cyclization of (−)-**12** carried out with $POCl_3$ in toluene at reflux, followed by treatment with NaOH in methanol gave the iminium **1** in good yield (97%).[13a,b] Reduction of **1** by $NaBH_4$ in methanol afforded **3** in poor yield (50%), however higher yield (87%) was obtained when using $LiAlH_4$ in THF for the reduction of **1**.[14a,b]

The following isomers, (−)-9-epi-myrionine [(−)-**15**], (−)-9-epi-myrionidine [(−)-**16**] and (+)-9-epi-schoberine [(+)-**17**], were subsequently synthesized from (−)-**9** by similar procedure as above. Interestingly, the reduction of the iminiums **1** and (−)-**16** by $LiAlH_4$ selectively afforded (−)-shoberine **3** and (+)-**17**, respectively. No formation of the 13-epimer of the two last compounds was observed.

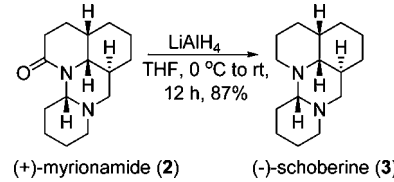
In the ^{1}H NMR spectrum of (+)-**17**, the signal for H-13 was a doublet of doublet (J_1 = 11.8; J_2 = 3.1 Hz), indicating its axial disposition on the **d**-ring and its 1,3-diaxial relationship with H-10 on the **c**-ring (Figure 4). This was confirmed by the strong NOE between H-10 with both H-13 and H-11_{ax}.

The enantiomers, (+)-myrionine [(+)-**12**], (+)-9-epi-myrionine [(+)-**15**], (+)-9-epi-myrionidine [(+)-**16**], (+)-myrionidine (**18**), (+)-9-epi-myrionidine [(−)-**17**], and (+)-schoberine (**19**) were also synthesized according to the above procedure: (+)-myrionidine (**18**) and (+)-schoberine (**19**) were prepared from (+)-**8**, and (+)-9-epi-myrionidine, (+)-**16** and (−)-9-epi-schoberine (−)-**17** from (+)-**9** (Figure 5). Comparison of the NMR data and the optical rotations of the natural compounds with those of synthetic ones, revealed that the absolute configuration of (−)-myrionidine (**1**) was *5S*, *9S*, *10R*, and that of (−)-schoberine (**3**) was *5S*, *9S*, *10R*, *13S*.

3. Absolute Configuration of (+)-Myrionamide (2). As discussed above, the relative configuration of (+)-myrionamide (**2**) was identical to that of (−)-schoberine (**3**). With the absolute stereochemistry of (−)-schoberine (**3**) in hand, the absolute configuration of (+)-myrionamide (**2**) could be deduced from its transformation into (−)-schoberine (**3**) as shown in Scheme 4. Exposure of **2** to $LiAlH_4$[15] in THF afforded (−)-schoberine (**3**) which was determined by comparison of their NMR data and optical activity of the natural (−)-schoberine and the synthetic one under the same condition ($[\alpha]_D^{20}$ −12.9 for the synthetic (−)-schoberine and $[\alpha]_D^{20}$ −12.2 for the natural (−)-schoberine). Thus, (+)-myrionamide (**2**) and (−)-schoberine (**3**) have the same absolute configuration *5S*, *9S*, *10R*, *13S* at the asymmetric centers.

4. Plausible Biosynthesis Pathway of Myrioneuron Alkaloids. Analysis of the structures of the alkaloids isolated from

SCHEME 4. Reduction of (+)-Myrionamide (2) into (−)-Shoberine (3)



M. nutans suggested that they are oligomeric (dimeric and trimeric) Δ^2-piperideines. They could thus arise from lysine *via* piperideine as previously proposed for alkaloids of *Nicotiana*[16] and *Nitraria*[17] as well as for *Lupin* alkaloids such as matrine (**23**).[18] The intermediate **20**, a precursor for many alkaloid types,[19] could be on one hand hydrolyzed, affording the quinolizidine derivative **21** which is then condensed with a third Δ^2-piperideine unit to provide **22**. Cyclization of **22** yields matrine **23** (route A).[18] On the other hand, the intermediate **20** could be hydrolyzed to form the aldehyde **24** (route B) which, as demonstrated by Wanner and Koomen, affords **25** by addition of a third Δ^2-piperideine unit. Then, an intramolecular 1,4-addition cyclization of **25** provides the DHQ system **26**. Selective reduction of **26** results in the formation of **27** which can be cyclized into (−)-schoberine (**3**)[17c] or oxidized to form the (−)-myrionine [(−)-**12**]. Intramolecular cyclization of myrionine provides (−)-myrionidine (**1**). In fact, (−)-myrionidine (**1**) was the main alkaloid of *M. nutans* (0.07% from dry leaves), suggesting that (−)-schoberine (**3**) could be also obtained from hydrogenation of (−)-myrionidine (**1**). Finally, oxidation of **1** can yield (+)-myrionamide (**2**) (Scheme 5). On the other hand, compound **26** could be hydrolyzed to yield the amino aldehyde **28**, the reduction of which, followed by condensation with formaldehyde and cyclization, could afford myrioxazine A (**30**).

It is important to note that the 9-epimers of (−)-myrionine, (−)-myrionidine, and (−)-schoberine were not found in the extracts of *M. nutans*. The presence of myrioxazine B, **33** (9-epimer of myrioxazine A) in the plant should be thus explained by tautomerisation of the aldehyde function of **28**, and the resulting enol **31** is reduced, condensed with formaldehyde and then cyclized affording myrioxazine B (Scheme 5). Hence, the difference of the biosynthesis pathways of myrionidine and matrine concerns the intermediate **20**, which can evolve according to two possible routes: either the formation of quinolizidine **21** (route A) to yield matrine or the formation of the *cis*-decahydroquinoline derivative **26** (route B) to afford (−)-myrionidine.

5. Cytotoxic and Antimalarial Activities. All of the synthetic and natural compounds were tested for their cytotoxic

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(13) (a) Fordor, G.; Nagubandi, S. *Tetrahedron* **1980**, *36*, 1279. (b) Whaley, W. M.; Govindachari, T. R. *Org. Reactions* **1951**, *VI*, 74.

(14) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 918. (b) Finholt, A. E.; Bond, A. C.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, *69*, 1199.

(15) Micovic, V.; Mihailovic, M. *J. Org. Chem.* **1953**, *18*, 1190.

(16) Leete, E. *J. Am. Chem. Soc.* **1969**, *91*, 1697.

(17) (a) Gravel, E.; Poupon, E.; Hocquemiller, R. *Tetrahedron* **2006**, *62*, 5248. (b) Wanner, M. J.; Koomen, G. J. *J. Org. Chem.* **1995**, *60*, 5634. (c) Wanner, M. J.; Koomen, G. J. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1994; Vol. 14, p 731. (d) Wanner, M. J.; Koomen, G. J. *Tetrahedron* **1992**, *48*, 3935.

(18) (a) Golebiewski, W. M.; Spenser, I. D. *J. Am. Chem. Soc.* **1976**, *98*, 6726. (b) Leeper, F. J.; Grue-Sorensen, G.; Spenser, I. D. *Can. J. Chem.* **1981**, *59*, 106.

(19) (a) Golebiewski, W. M.; Spenser, I. D. *J. Am. Chem. Soc.* **1984**, *106*, 7925. (b) Fraser, A. M.; Robins, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 1477.

(20) Frappier, F.; Jossang, A.; Soudon, J.; Calvo, F.; Rasoanaivo, P.; Rastimamanga-Urveg, S.; Saez, J.; Schrevel, J.; Grellier, P. *Antimicrob. Agents Chemother.* **1996**, *6*, 1476.

(21) Desjardins, R. E.; Candfield, C. J.; Haynes, J. D.; Chulay, J. D. *Antimicrob. Agents Chemother.* **1979**, *16*, 710.

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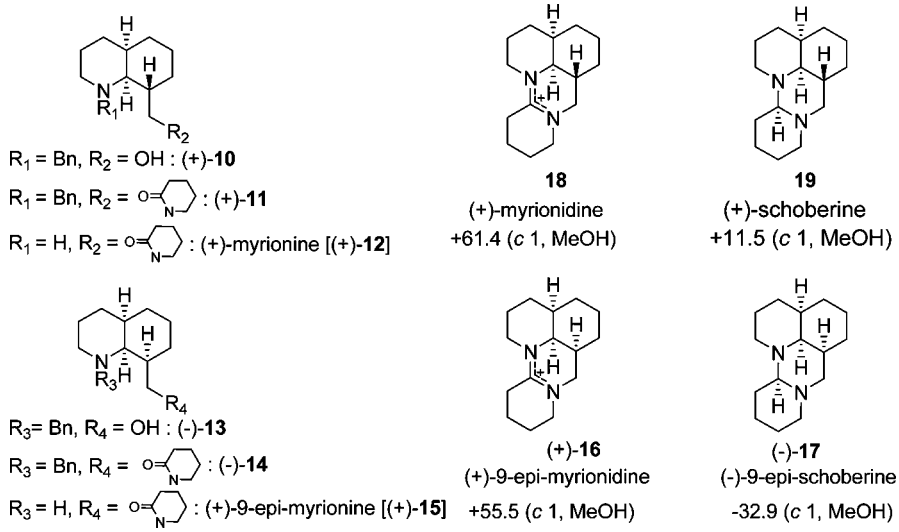
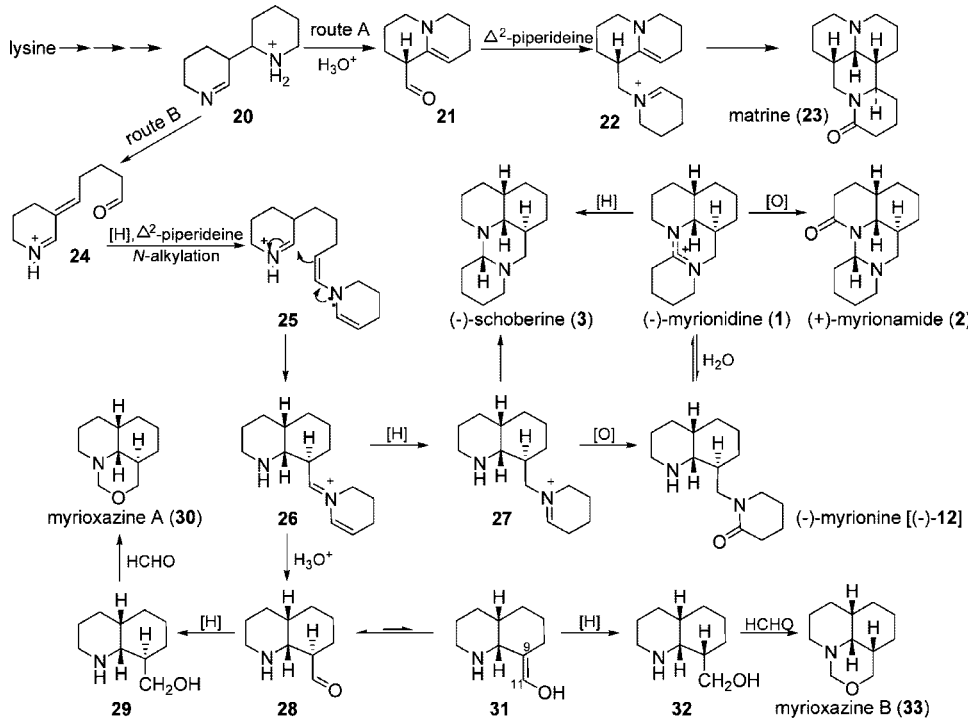


FIGURE 5. Synthetic enantiomers and 9-epimers of *Myrioneuron* alkaloids.

SCHEME 5. Proposed Biosynthesis Pathway for the *Myrioneuron* Alkaloids



activity against KB cell and antimalarial activity against *P. falciparum* (FcB1 strain) according to the previously described procedure[20−22] (Table 2). The results showed that most of these compounds were more active on *P. falciparum* than on KB cell lines, indicating the antiplasmodial activity could not be due to their cytotoxicity. The most potent compounds were the enantiomeric (−) and (+)-myrionidines (**1** and **18**), whereas their 9-epimers, (+)- and (−)-**16**, had weaker activity on both target cell lines. This suggested that the stereochemistry at C-9 in myrionidine played an important role in the bioactivity. Furthermore, as schoberine showed much lower cytotoxic and antimalarial activities than myrionidine, the iminium function probably is a significant factor for the biological activities of myrionidine.

Conclusion

This paper illustrates the structural determination, including absolute configuration, of a special class of original alkaloids from *M. nutans*. Presumably, these alkaloids are biosynthesized from L-lysine via Δ-piperideine, as described for *Lycopodium* and *Lupin* alkaloids. However, the bioformation of DHQ alkaloids of *M. nutans* was different from that of the *Lupin* alkaloids which are characterized by a quinolizidine skeleton. Furthermore, the pure enantiomers of alkaloids of *M. nutans* were obtained indicating their stereoselective biosynthesis, whereas, schoberine and nitraramine isolated from several *Nitraria* species were described as racemic mixtures. We propose the name *Myrioneuron* alkaloids for this original class of alkaloids isolated from *M. nutans*.

TABLE 2. Cytotoxic and Antimalarial Activities Expressed by IC_{50} (μg/mL)

Sample	KB cell	*P. falciparum*	Sample	KB cell	*P. falciparum*
crude alkaloid (*M. nutans*)	30	–	**6**	>100	45
(−)-myrionidine (**1**)	6	0.3	(*R*)-**7**	42	44
(+)-myrionidine (**18**)	3	0.5	(*S*)-**7**	>100	10
(+)-myrionamide (**2**)	>50	91	(−)-**8**	>100	13
(−)-schoberine (**3**)	20	4	(+)-**8**	>100	10
(+)-schoberine (**19**)	82	39	(−)-**9**	>100	9
(−)-myrionine [(−)-**12**]	50	10	(+)-**9**	>100	16
(+)-myrionine [(+)-**12**]	>100	8	(−)-**10**	23	34
(−)-9-epi-myrionine [(−)-**15**]	25	39	(+)-**10**	57	0.8
(+)-9-epi-myrionine [(+)-**15**]	87	4	(−)-**11**	>100	12
(−)-9-epi-myrionidine [(−)-**16**]	11	20	(+)-**11**	24	0.7
(+)-9-epi-myrionidine [(+)-**16**]	6	2	(−)-**13**	26	44
(−)-9-epi-schoberine [(−)-**17**]	42	44	(+)-**13**	3	13
(+)-9-epi-schoberine [(+)-**17**]	>100	3	(−)-**14**	8	2
chloroquine	–	0.03	(+)-**14**	22	4
vinblastine	0.01	–			

In order to confirm the structures of (−)-myrionidine (**1**) and (−)-schoberine (**3**) and to determine their absolute configuration, the first total asymmetric synthesis of the schoberine skeleton was performed. The absolute stereochemistry of C-9 in the intermediate **7** was deduced from X-ray analysis of its (1*S*)-(−)-camphanoyl ester **5**.

Experimental Section

(−)-Myrionidine (1). Colorless crystals, mp. 154−155 °C (MeOH), $[\alpha]_D^{20}$ −60.0 (*c* 1, MeOH); IR (KBr) ν_{cm-1}: 3217, 3035, 2940, 2874, 1626, 1517, 1392, 1316, 1245, 980, 971, 830. ESI-MS (TOF): 233.2003 (calcd. 233.2018 for $C_{15}H_{25}N_2$). ESI-MSMS on $[M]^+$: 205, 191, 177, 163, 151, 149, 135, 123, 111, 110. NMR see Table 1.

(+)-Myrionamide (2). Colorless crystals, mp. 151−152 °C (MeOH), $[\alpha]_D^{20}$ +17.0 (*c* 1, MeOH); IR (KBr) ν_{cm-1}: 2936, 2863, 1637, 1465, 1450, 1424, 1370, 1292, 1215, 1195, 1181; ESI-MS (TOF): 249.1965 $[M+H]^+$ (calcd. 249.1967 for $C_{15}H_{25}N_2O$); ESI-MSMS on $[M+H]^+$: 98, 96, 84, 70, 55. NMR see Table 1.

(−)-Schoberine (3). Colorless crystals, mp. 62−63 °C (MeOH), $[\alpha]_D^{20}$ −12.2 (*c* 1, MeOH); IR (KBr) ν_{cm-1}: 2929, 2863, 2808, 2749, 1626, 1497, 1447, 1362, 1275, 1245, 1181, 1125, 1096, 1041, 967, 850, 815, 777, 672, 605; ESI-MS (TOF): 235.2141 $[M+H]^+$ (calcd. 235.2174 for $C_{15}H_{27}N_2$); ESI-MSMS on [M+H]+: 205, 192, 184, 178, 163, 150, 136, 124, 110, 98, 83. ^{1}H NMR (400.13 MHz, $CDCl_3$, 298 K): 2.83 (dd, 9.5, 4.0, 1H, H-13), 2.81 (m, 1H, H-2_b), 2.76 (dd, 11.1 and 3.9 Hz, 1H, H-11_b), 2.73 (m, 1H, H-17_b), 2.68 (ddd, 11.5, 11.5 and 2.8 Hz, 1H, H-2_a), 2.49 (dd, 11.0 and 4.7 Hz, 1H, H-10), 2.15 (ddddd, 11.1, 11.1, 11.0, 3.9 and 3.3 Hz, 1H, H-9), 1.88 (m, 1H, H-5), 1.85 (ddd, 11.9, 11.9 and 3.4 Hz, 1H, H-17_a), 1.78 (m, 1H, H-16_b), 1.72 (m, 1H, H-6_b), 1.68 (dd, 11.1 and 11.1 Hz, 1H, H-11_a), 1.61 (m, 2H, CH_2-15), 1.57 (m, 1H, H-4_b), 1.52 (m, 2H, CH_2-14), 1.51 (m, 1H, H-3_b), 1.48 (m, 1H, H-8_b), 1.47 (m, 1H, H-6_a), 1.43 (m, 1H, H-3_a), 1.37 (m, 2H, CH_2-7), 1.30 (m, 2H, H-4_a and H-16_a), 0.79 (m, 1H, H-8_a); NMR ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 82.5 (C-13), 65.0 (C-10), 63.7 (C-11), 56.3 (C-17), 39.8 (C-2), 35.2 (C-5), 31.5 (C-14), 30.2 (C-8), 30.0 (C-15), 27.0 (C-9), 26.3 (C-6), 25.4 (C-3), 24.6 (C-16 and C-4), 20.2 (C-7).

9R-(1S-Camphanic acid)-6,7,8,9-tetrahydroquinolin-9-yl Methyl Ester (5) and (9*S*)-((1*S*)-Camphanic acid)-6,7,8,9-tetrahydroquinolin-9-yl Methyl Ester (6). To a solution of racemic **4** (15 g, 92 mmol) in dry CH_2Cl_2 (150 mL) was slowly added (1*S*)-(−)-camphanoyl chloride (20 g, 92.6 mmol) in dry CH_2Cl_2 (100 mL) and EtN_3 (20 mL) at 0 °C. The reaction mixture was then warmed to rt and stirred for 12 h. Ice water (200 mL) was added and the organic layer was separated. The aqueous solution was washed with CH_2Cl_2 (2 × 100 mL). The combined organic extracts were washed with aqueous 5% $NaHCO_3$ and then with water. The solvent was removed under diminished pressure and the residue purified by chromatography on silica gel, eluted with *n*-hexane/Et_2O/EtOH (10:1:0.5) to yield the two diastereoisomers **5** (15.2 g, 48%) and **6** (14.5 g, 46%).

5: White solid, mp. 110−110.5 °C; $[\alpha]_D^{20}$ −45 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 8.33 (m, 4.7, 1.7, 1H, H-2), 7.33 (m, 7.7, 1.7, 1H, H-4), 7.0 (dd, 7.7, 4.7, 1H, H-3), 4.63 (dd, 10.7, 8.1, 1H, H-11_a), 4.61 (dd, 10.7, 3.5, 1H, H-11_b), 3.25 (m, 1H, H-9), 2.72 (m, 2H, H-6), 2.32 (ddd, 13.3, 10.8, 4.3, 1H, H-21_a), 2.03 (m, 1H, H-8_a), 1.95 (m, 1H, H-21_b), 1.90 (m, 1H, H-7_a), 1.84 (m, 1H, H-20_a), 1.83 (m, 1H, H-8_b), 1.71 (m, 1H, H-7_b), 1.61 (ddd, 13.1, 9.3, 4.2, 1H, H-20_b), 1.03 (s, 3H, CH_3-25), 0.94 (s, 3H, CH_3-24), 0.74 (s, 3H, CH_3-23); ^{13}C ($CDCl_3$, 75.47 MHz): 178.2 (C-17), 167.3 (C-13), 155.4 (C-10), 146.9 (C-2), 136.8 (C-4), 133.2 (C-5), 121.5 (C-3), 91.2 (C-15), 68.4 (C-11), 54.6 (C-19 or C-22), 53.9 (C-22 or C-19), 40.0 (C-9), 30.4 (C-24), 28.8 (C-6, C-20), 26.1 (C-8), 20.1 (C-7), 16.6 (CH_3-21), 16.4 (CH_3-23), 9.6 (CH_3-25); ESI-MS (TOF): 344.1864 $[M+H]^+$, (calcd. 344.1862 for $C_{20}H_{26}NO_4$).

6: Colorless oil, $[\alpha]_D^{20}$ +23 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 8.33 (m, 4.7, 1.8, 1H, H-2), 7.33 (m, 7.7, 1.8, 1H, H-4), 7.0 (dd, 7.7, 4.7, 1H, H-3), 4.61 (d, 5.9, 2H, CH_2-11), 3.23 (dddd, 6.2, 6.2, 6.1, 6.0, 1H, H-9), 2.72 (dd, 6.1, 6.1, 2H, H-6), 2.30 (ddd, 13.4, 10.7, 4.3, 1H, H-21_a), 2.01 (m, 1H, H-8_a), 1.92 (m, 1H, H-21_b), 1.90 (m, 1H, H-7_a), 1.81 (m, 2H, H-20_a, and H-8_b), 1.71 (m, 1H, H-7_b), 1.59 (ddd, 13.1, 9.3, 4.3, 1H, H-20_b), 1.02 (s, 3H, CH_3-25), 0.84 (s, 3H, CH_3-24), 0.81 (s, 3H, CH_3-23); ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 178.0 (C-17), 167.1 (C-13), 155.3 (C-10), 146.8 (C-2), 136.8 (C-4), 133.1 (C-5), 121.4 (C-3), 91.1 (C-15), 68.3 (C-11), 54.5 (C-19 or C-22), 53.8 (C-22); ESI-MS (TOF): 344.1859 $[M+H]^+$, (calcd. 344.1862 for $C_{20}H_{26}NO_4$).

(*R*)-(6,7,8,9-Tetrahydroquinolin-9-yl)methanol [(*R*)-7]. A solution of **5** (8.0 g, 23.3 mmol) in MeOH (10 mL) was treated with aqueous 30% NaOH (30 mL). The reaction mixture was stirred at 50 °C for 3 h. The methanol was evaporated under diminished pressure and the aqueous solution was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with saturated aqueous solution of NH_4Cl, then with water and dried over $MgSO_4$. The solvent was removed under diminished pressure and the crude extract chromatographed on silica gel to afford (*R*)-**7** as colorless oil (3.9 g, 97%). $[\alpha]_D^{20}$ −61.5 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 8.29 (d, 4.4 Hz, 1H), 7.39 (d, 7.6 Hz, 1H), 7.05 (dd, 7.6 and 4.4 Hz, 1H), 5.58 (br.s, 1H, OH), 3.75 (br.d, 7.8 Hz, 2H), 3.01 (m, 1H), 2.72 (m, 2H), 1.95 (m, 2H), 1.71 (m, 2H); ^{13}C (75.47 MHz): 154.5, 146.8, 137.0, 133.3, 121.7, 62.9, 40.4, 28.7, 25.5, 20.2; ESI-MS (TOF): 164.1076 $[M+H]^+$, (calcd. 164.1075 for $C_{10}H_{14}NO$).

Details for compound (*S*)-**7** see the Supporting Information section.

[(5*S*,9*R*,10*R*)-Decahydroquinolin-9-yl]methanol [(−)-8] and [(5*R*, 9*R*,10*S*)-Decahydroquinolin-9-yl]methanol [(+)-9]. A solution of (*R*)-**7** (2 g, 12.27 mmol) in acetic acid (8 mL) was treated with

PtO_2 (100 mg) under hydrogen atmosphere at rt for 15 h. The solid was removed by filtration through Celite and then washed with MeOH. Methanol was eliminated by evaporation under diminished pressure and the remaining was neutralized with 10% NaOH aqueous solution to pH 8. The mixture was extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic extracts were washed with saturated aqueous solution of NH_4Cl, water and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude extract was chromatographed on silica gel column (CH_2Cl_2/MeOH/20% NH_4OH: 8/1/0.5) to provide (−)-**8** (1.3 g, 59%) and (+)-**9** (0.4 g, 18%).

(−)-**8**: White solid, mp. 110−111 °C (*n*-hexane/Et_2O); $[\alpha]_D^{20}$ −2.1 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 3.58 (dd, 10.6, 3.6, 1H, H-11_a), 3.45 (dd, 10.6, 10.6, 1H, H-11_b), 2.79 (m, 1H, H-2_{eq}), 2.77 (dd, 10.6, 2.8, 1H, H-10), 2.74 (m, 1H, H-2_{ax}), 2.10 (m, 1H, H-9), 1.73, (m, 1H, H-4_{ax}), 1.68 (m, 1H, H-5), 1.68 (m, 1H, H-3_{eq}), 1.52 (m, 1H, H-8_{eq}), 1.44 (m, 2H, H-6_{ax} and H-6_{eq}), 1.39 (m, 2H, H-7_{ax} and H-7_{eq}), 1.38 (m, 1H, H-4_{eq}), 1.36 (m, 1H, H-3_{ax}), 0.79 (m, 1H, H-8_{ax}); ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 70.6 (C-11), 60.9 (C-10), 40.0 (C-2), 37.4 (C-5), 33.4 (C-9), 31.3 (C-6), 28.3 (C-8), 27.7 (C-3), 25.1 (C-4), 19.9 (C-7); ESI-MS (TOF)**:** 170.1533 $[M+H]^+$, (calcd. 170.1545 for $C_{10}H_{20}NO$); ESI-MS/MS on $[M+H]^+$ ion: 170, 153, 135, 121, 107, 97, 93, 83, 79, 69, 67, 57, 43.

(+)-**9**: White solid, mp. 125−126 °C (EtO_2); $[\alpha]_D^{20}$ +33.2 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 3.79 (m, 1H, H −11_a), 3.52 (dd, 2.7 and 2.7 Hz, 1H, H-11_b), 3.01 (ddd, 13.0, 4.1 and 1.9 Hz, 1H, H-2_{eq}), 2.96 (dd, 2.7 and 2.7 Hz, 1H, H-10), 2.54 (ddd, 13.0, 13.0 and 3.3 Hz, 1H, H-2_{ax}), 1.78 (m, 1H, H-7_{eq}), 1.66 (m, 2H, H-4_{ax} and H-6_{ax}), 1.55 (m, 1H, H-4_{eq}), 1.48 (m, 1H, H-3_{ax}), 1.47 (m, 1H, H-5), 1.42 (m, 1H, H-9), 1.41 (m, 2H, H-8_{ax} and H-8_{eq}), 1.29 (m, 1H, H-3_{eq}), 1.28 (m, 1H, H-6_{eq}), 1.26 (m, 1H, H-7_{ax}); ^{13}C (75.47 MHz): 67.3 (C-11), 59.1 (C-10), 47.1 (C-2), 42.5 (C-9), 35.6 (C-5), 30.3 (C-4), 25.6 (C-7), 24.3 (C-6), 23.2 (C-8), 21.9 (C-3), ESI-MS (TOF): 170.1537 $[M+H]^+$, (calcd. 170.1545 for $C_{10}H_{20}NO$), ESI-MS/MS on $[M+H]^+$ ion: 170, 163, 158, 149, 140, 135, 128, 123, 121, 119, 111, 107.

Details for compounds (+)-**8** and (−)-**9** see the Supporting Information section.

[(5*S*,9*R*,10*R*)-*N*-Benzyl-decahydroquinolin-9-yl]methanol [(−)-10]. To a solution of (−)-**8** (250 mg, 1.48 mmol) in a mixture of CH_2Cl_2/ sat. Na_2CO_3 (1:1, 10 mL) was added benzyl bromide (0.26 mL, 2.22 mmol). The reaction mixture was stirred for 12 h at rt. Water (15 mL) was added and the mixture solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed under diminished pressure and the crude extract purified by chromatography over silica gel column (CH_2Cl_2/MeOH 98/2) to give 356 mg of (−)-**10** as colorless oil (93% yield). $[\alpha]_D^{20}$ −21.8 (*c* 2, MeOH); ^{1}H (400.13 MHz): 7.3 (m, 4H, H-14,15,17,18), 7.23 (m, 1H, H-16), 3.89 (s, 2H, H-12), 3.50 (dd, 10.4 and 3.2 Hz, 1H, H-11_a), 3.32 (dd, 10.4 and 104 Hz, 1H, H-11_b), 3.01 (ddd, 13.7, 13.7 and 3.1 Hz, 1H, H-2_{ax}), 2.58 (m, 1H, H-2_{eq}), 2.55 (dd, 11.1 and 4.4 Hz, 1H, H-10), 2.17 (m, 1H, H-9), 2.13 (m, 1H, H-5), 1.79 (m, 1H, H-3_{ax}), 1.76 (m, 1H, H-4_{ax}), 1.48 (m, 1H, H-6_{eq}), 1.46 (m, 1H, H-8_{eq}), 1.39 (m, 1H, H-4_{eq}), 1.38 (m, 2H, H-7_{ax} and H-7_{eq}), 1.33 (m, 1H, H-3_{eq}), 1.32 (m, 1H, H-6_{ax}), 0.68 (m, 1H, H-8_{ax}). ^{13}C (75.47 MHz): 129.0 (C-14, C-18), 128.4 (C-15, C-17), 127.2 (C-16), 138.6 (C-13), 70.7 (C-11), 66.3 (C-10), 57.1 (C-12), 44.4 (C-2), 33.7 (C-9), 31.2 (C-6), 28.7 (C-8), 28.5 (C-5), 25.4 (C-4), 19.9 (C-7), 19.7 (C-3); ESI-MS (TOF): 260.2023 $[M+H]^+$ (calcd. 260.2014 for $C_{17}H_{26}NO$); ESI-MS/MS (TOF) on $[M+H]^+$ ion: 260, 242, 168, 152, 135, 107, 91, 79, 65.

Details for compound (+)-**10** see the Supporting Information section.

1-{[(5*S*,9*S*,10*R*)-*N*-Benzyl-decahydroquinolin-9-yl]methyl}piperidin-2-one [(−)-11]. A solution containing (−)-**10** (264 mg, 1.02 mmol) in dry CH_2Cl_2 (4 mL) was treated with Et_3N (0.2 mL) and MsCl (80 μL, mmol) at −5 °C under argon atmosphere. The reaction mixture was stirred for 1 h and the solid was removed by filtration then washed with dry CH_2Cl_2. The filtrate was evaporated under diminished pressure at temperature below 25 °C. To this resulting residue was added 2-piperidinone (202 mg, 2.04 mmol) in DMSO (5 mL) and KH (90 mg, 2.25 mmol) at −5 °C. The solution mixture was stirred at at −5 °C for 3 h and then warmed to rt and stirred for additional 15 h. The reaction solution was cooled to 0 °C and ice water (20 mL) was added then the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl, then water and dried over $MgSO_4$. The solvent was removed under diminished pressure. The resulting crude extract was chromatographed on silica gel (2 to 20% MeOH in CH_2Cl_2) to afford (−)-**11** as colorless oil (260 mg, 75%). $[\alpha]_D^{20}$ −18.4 (*c* 2, MeOH); NMR spectra of (−)-**11** at 298 K showed broad signals, caused by conformational equilibrium, then spectra were recorded at 338 K. ^{1}H (400.13 MHz, C_5D_5N): 3.89 (d, 13.7, 1H, H-18_a), 3.82 (dd, 13.5, 4.6, 1H, H-11_a), 3.81 (m, 1H, H-18_b), 3.50 (dd, 13.5 and 9.7 Hz, 1H, H-11_b), 3.24 (m, 1H, H-17), 3.11 (m, 1H, H-17), 2.99 (ddd, 13.8, 11.1 and 3.0 Hz, 1H, H-2_{ax}), 2.50 (m, 1H, H-9), 2.46 (m, 1H, H-2_{eq}), 2.4 (m, 2H, CH_2-14), 2.35 (m, 1H, H-10), 2.09 (m, 1H, H-5), 1.88 (m, 1H, H-4_{eq}), 1.70 (m, 1H, H-3_{ax}), 1.69 (m, 1H, H-7_{eq}), 1.60 (m, 4H, CH_2-15, CH_2-16), 1.59 (m, 1H, H-8_{eq}), 1.42 (m, 1H, H-6_{ax}), 1.39 (m, 1H, H-6_{eq}), 1.35 (m, 2H, H-3_{eq}, H-8_{ax}), 1.30 (m, 1H, H-7_{ax}), 1.09 (m, 1H, H-4_{ax}); ^{13}C (75.47 MHz, C_5D_5N, 338 K): 169.2 (C-13), 141.5 (C-19), 129.3 (C-20, C-24), 128.7 (C-21, C-23), 127.2 (C-22), 64.2 (C-10), 58.0 (C-18), 50.9 (C-11), 49.0 (C-17), 46.2 (C-2), 33.0 (C-14), 32.9 (C-9), 31.2 (C-8), 30.2 (C-5), 29.1 (C-4), 27.1 (C-3), 23.8 (C-16), 21.9 (C-15), 21.1 (C-6), 20.9 (C-7); ESI-MS (TOF): 341.2578 $[M+H]^+$ (calcd. 341.2593 for $C_{22}H_{33}N_2O$); ESI-MSMS on $[M+H]^+$ ion: 341, 249, 242, 234, 222, 150, 135, 112, 107, 100, 91, 84, 65, 56.

Details for compound (+)-**11** see the Supporting Information section.

(−)-Myrionine [(−)-12]. To a solution of (−)-**11** (100 mg, 0.29 mmol) in AcOH (2 mL) was added 10% Pd/C (10 mg) under hydrogen atmosphere and the mixture was stirred at rt for 3 h. The solid was filtered-off and washed with MeOH. The filtrate was concentrated under diminished pressure and the residue was chromatographed on silica gel (CH_2Cl_2/MeOH: 9/1) to afford (−)-**12** (66 mg, 90%) as oil. $[\alpha]_D^{20}$ −16.8 (*c* 1, MeOH). ^{1}H (400.13 MHz, C_5D_5N, 328 K): 3.62 (dd, 13.4, 8.1, 1H, H-11_b), 3.53 (dd, 13.4, 8.1, 1H, H-11_a), 3.19 (m, 2H, CH_2-17), 2.98 (ddd, 12.0, 6.5 and 4.0 Hz, 1H, H-2_b), 2.69 (m, 1H, H-2_a), 2.68 (dd, 6.2 and 3.1 Hz, 1H, H-10), 2.38 (m, 2H, CH_2-14), 2.18 (ddddd, 8.1, 6.4, 6.2, 5.7 and 5.7 Hz, 1H, H-9), 1.90 (m, 1H, H-5), 1.85 (m, 1H, H-8_b), 1.79 (m, 1H, H-6_b), 1.67 (m, 1H, H-3_b), 1.63 (m, 2H, CH_2-16), 1.61 (m, 2H, CH_2-15), 1.57 (m, 1H, H-4_b), 1.55 (m, 1H, H-7_b), 1.46 (m, 1H, H-7_a), 1.41 (m, 1H, H-4_a), 1.35 (m, 1H, H-3_a), 1.29 (m, 1H, H-6_a), 1.20 (dddd, 12.8, 7.0, 5.7, 3.7, 1H, H-8_a); ^{13}C (75.47 MHz, C_5D_5N, 328 K): 57.9 (C-10), 49.1 (C-11), 48.3 (C-17), 44.2 (C-2), 35.6 (C-9), 33.8 (C-5), 32.8 (C-14), 29.7 (C-4), 28.3 (C-6), 26.5 (C-8), 24.2 (C-3), 23.7 (C-16), 21.7 (C-15), 21.6 (C-7); ESI-MS (TOF): 251.2136 $[M+H]^+$, (calcd. 251.2123 for $C_{15}H_{27}N_2O$); ESI-MS/MS (TOF) on $[M+H]^+$ ion: 251 $[M+H]^+$, 234, 152, 135, 112, 107, 100, 93, 84, 79, 67.

Details for compound (+)-**12** see the Supporting Information section.

[(5*S*,9*S*,10*R*)-*N*-benzyl-decahydroquinolin-9-yl]methanol [(+)-13]. According to the procedure used for (−)-**10**, compound (+)-**13** (314 mg) was obtained as an oil from (−)-**9** (250 mg, 1.48 mmol) and benzyl bromide (0.27 mL, 2.22 mmol) in 82% yield. $[\alpha]_D^{20}$ +41.8 (*c* 2, MeOH). Due to conformational equilibrium at rt, the spectra were recorded at 318 K. ^{1}H (400.13 MHz, $CDCl_3$): 7.31 (m, 2H, H-17 and 15), 7.27 (m, 2H, H-18 and H-14), 7.20 (m, 1H, H-16), 3.89 (dd,10.5 and 6.7 Hz, 1H, H-11_a), 3.88 (d, 13.0 Hz, 1H, H-12_a), 3.69 (dd, 10.5 and 7.1 Hz, 1H, H-11_b), 3.22 (d, 13.0 Hz, 1H, H-12_b), 2.78 (dd, 3.8 and 3.8 Hz, 1H, H-10), 2.68 (ddd, 11.8, 4.1 and 4.1 Hz, 1H, H-2_{eq}), 2.13 (ddd, 11.8, 11.8 and 3.5 Hz,

1H, H-2_{ax}), 1.96 (m, 1H, H-9), 1.95 (m, 1H, H-6_{ax}), 1.88 (m, 1H, H-5), 1.73 (m, 1H, H-7_{eq}), 1.69 (m, 1H, H-3_{ax}), 1.64 (m, 1H, H-8_{ax}), 1.58 (m, 2H, H-4_{ax} and H-4_{eq}), 1.50 (m, 1H, H-8_{eq}), 1.38 (m, 2H, H-3_{eq} and H-7_{ax}), 1.37 (m, 1H, H-6_{eq}); ^{13}C (75.47 MHz, $CDCl_3$): 139.8 (C-13), 128.7 (C-17 and 15), 128.3 (C-18 and 14), 126.8 (C-16), 67.7 (C-11), 63.9 (C-10), 59.3 (C-12), 50.3 (C-2), 45.2 (C-9), 36.8 (C-5), 28.6 (C-4), 28.3 (C-6), 25.7 (C-8), 23.5 (C-7), 20.7 (C-3); ESI-MS (TOF): 260.1990 $[M+H]^+$ (calcd. 260.2014 for $C_{17}H_{26}NO$); ESI-MS/MS on $[M+H]^+$ ion: 260, 242, 168, 152, 150, 135, 121, 107, 96, 91, 79, 65.

Details for compound (−)-**13** see the Supporting Information section.

1-{[(5*S*,9*R*,10*R*)-*N*-Benzyl-decahydroquinolin-9-yl]methyl}piperidin-2-one [(+)-14]. By using the similar procedure as (−)-**11**, (+)-**13** (253 mg, 0.97 mmol), MsCl (75 μL, 0.97 mmol), 2-piperidinone (144 mg, 1.45 mmol) and KH (39 mg, 0.97 mmol) afforded 247 mg of (+)-**14** as an oil (75% yield). $[\alpha]_D^{20}$ +9.6 (*c* 2, MeOH); ^{1}H (400.13 MHz, C_5D_5N, 338 K): 7.51 (br.d, 7.4 Hz, 2H, H-20 and H-24), 7.39 (m, 7.4, 7.3 and 1.5 Hz, 2H, H-21 and H-23), 7.29 (ddt, 7.3, 7.3 and 1.4 Hz, 1H, H-22), 4.10 (d, 13.0 Hz, 1H, H-18_a), 3.91 (dd, 13.1 and 9.8 Hz, 1H, H-11_a), 3.52 (dd, 13.1 and 3.5 Hz, 1H, H-11_b), 3.35 (d, 13.0 Hz, 1H, H-18_b), 3.27 (m, 1H, H-17_{ax}), 3.19 (m, 1H, H-17_{eq}), 2.81 (ddd, 11.7, 4.4 and 4.4 Hz, 1H, H-2_{eq}), 2.75 (dd, 3.0 and 3.0 Hz, 1H, H-10), 2.41 (m, 2H, CH_2-14), 2.12 (m, 1H, H-6_{ax}), 2.09 (m, 1H, H-9), 2.08 (ddd, 11.7, 11.7, 3.7 Hz, 1H, H-2_{ax}), 1.90 (m, 1H, H-7_{eq}), 1.81 (m, 1H, H-8_{ax}), 1.65 (m, 2H, CH_2-16), 1.63 (m, 2H, CH_2-15), 1.60 (m, 1H, H-3_{ax}), 1.58 (m, 1H, H-8_{eq}), 1.51 (m, 2H, CH_2-4), 1.39 (m, 1H, H-7_{ax}), 1.27 (m, 1H, H-6_{eq}), 1.25 (m, 1H, H-3_{eq}); ^{13}C (75.47 MHz, C_5D_5N, 338 K): 169.2 (C-13), 141.6 (C-19), 129.0 (C-20 and −24), 128.7 (C-21 and −23), 127.1 (C-22), 65.0 (C-10), 59.0 (C-18), 52.7 (C-11), 52.5 (C-2), 48.8 (C-17), 44.3 (C-9), 39.8 (C-5), 33.0 (C-14), 30.7 (C-4), 28.2 (C-6), 26.3 (C-8), 25.3 (C-7), 23.9 (C-16), 22.3 (C-3), 21.9 (C-15); ESI-MS (TOF): 341.2597 $[M+H]^+$ (calcd. 341.2593 for $C_{22}H_{33}N_2O$); ESI-MS/MS on $[M+H]^+$ ion: 341, 265, 251, 214, 205, 199, 183, 163, 158, 149, 140, 135, 128, 121, 111.

Details for compound (−)-**14** see the Supporting Information section.

(−)-9-Epi-myrionine [(−)-15]. By applying the procedure described above for (−)-myrionine [(−)-**12**], (+)-**14** (165 mg, 0.48 mmol) and 10% Pd/C (15 mg) provided (−)-**15** as an oil (107 mg, 89%). $[\alpha]_D^{20}$ −21.8 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 4.03 (dd, 14.3 and 11.4 Hz, 1H, H-11_a), 3.33 (m, 1H, H-2_{eq}), 3.31 (m, 1H, H-17_{eq}), 3.17 (ddd, 12.2, 8.0 and 5.1 Hz, 1H, H-17_{ax}), 2.59 (br.s, 1H, H-10), 2.55 (dd, 14.4 and 4.6 Hz, 1H, H-11_b), 2.46 (ddd, 13.0, 13.0 and 3.1 Hz, 1H, H-2_{ax}), 2.35 (m, 2H, CH_2-14), 1.93 (dddd, 12.2, 12.2, 12.2 and 4.0 Hz, 1H, H-6_{ax}), 1.83 (m, 1H, H-7_{eq}), 1.81 (m, 1H, H-3_{ax}), 1.78 (m, 2H, CH_2-16), 1.75 (m, 1H, H-9), 1.74 (m, 2H, CH_2-15), 1.59 (m, 1H, H-8_{ax}), 1.58 (m, 1H, H-5), 1.55 (m, 1H, CH_2-4), 1.39 (br.d, 14.1 Hz, 1H, H-3_{eq}), 1.26 (m, 3H, H-6_{eq}, H-7_{ax}, H-8_{eq}); ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 171.0 (C-13), 55.3 (C-10), 49.2 (C-11), 48.4 (C-17), 46.3 (C-2), 39.3 (C-9), 35.3 (C-5), 31.7 (C-14), 29.8 (C-4), 25.6 (C-7), 24.6 (C-6), 24.3 (C-8), 23.0 (C-16), 21.0 (C-15), 19.5 (C-3); ESI-MS (TOF): 251.2129 $[M+H]^+$ (calcd. 251.2123 $C_{15}H_{27}N_2O$); ESI-MS/MS on $[M+H]^+$ ion: 251, 152, 135, 121, 112, 107, 100, 96, 93, 91, 84, 81, 79, 67, 56, 44, 41.

Details for compound (+)-**15** see the Supporting Information section.

(−)-Myrionidine (1). To a solution of (−)-myrionine [(−)-**12**] (75 mg, 0.3 mmol) in dry toluene (4 mL) was added $POCl_3$ (33 μL, 0.36 mmol) and heated at reflux for 12 h. The volatile layer was removed under diminished pressure. To this residue, 10% NH_4OH (5 mL) was added and the solution was concentrated under diminished pressure to dryness. The residue was purified by repeated chromatography on Sephadex (LH-20) eluted with MeOH to afford **1** as colorless solid (72 mg, 97%). Mp 155−156 °C; $[\alpha]_D^{20}$ −60.5 (*c* 1, MeOH). NMR data were identical with those of the natural (−)-myrionidine (**1**).

Details for compound **18** see the Supporting Information section.

(−)-9-Epi-myrionidine [(−)-16]. According to the procedure described above for (−)-myrionidine (**1**), (−)-9-epi-myrionine [(−)-**15**] (87 mg, 0.34 mmol) and $POCl_3$ (49 μL, 0.4 mmol) gave [(−)-**16**] (74 mg, 92%). Mp 162−164 °C; $[\alpha]_D^{20}$ −53.2 (*c* 2, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 4.21 (br.d, 13.1, 1H, H-11_a), 3.90 (m, 2H, H-2_{eq} and H-10), 3.56 (ddd, 13.3, 5.5 and 5.4 Hz, 1H, H-17_{eq}), 3.37 (ddd, 13.2, 13.2 and 2.7 Hz, 1H, H-2_{ax}), 3.26 (ddd, 13.3, 9.0 and 4.7 Hz, 1H, H-17_{ax}), 2.99 (ddd, 17.4, 8.3 and 8.3 Hz, 1H, H-14_{ax}), 2.86 (dd, 13.1 and 1.9 Hz, 1H, H-11_b), 2.52 (ddd, 17.4, 4.8 and 4.8 Hz, 1H, H-14_{eq}), 2.05 (m, 1H, H-9), 2.01 (m, 1H, H-15_{eq}), 1.99 (m, 1H, H-16_{ax}), 1.78 (m, 3H, H-5, H-7_{eq} and H-16_{eq}), 1.74 (m, 1H, H-4_{ax}), 1.68 (m, 1H, H-3_{ax}), 1.63 (m, 1H, H-15_{ax}), 1.57 (m, 2H, H-3_{eq} and H-8_{eq}), 1.55 (m, 1H, H-4_{eq}), 1.36 (m, 1H, H-7_{ax}), 1.31 (m, 2H, CH_2-6), 1.09 (m, 1H, H-8_{ax}); ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 161.7 (C-13), 55.8 (C-10), 54.0 (C-11), 52.4 (C-17), 47.6 (C-2), 35.0 (C-5), 32.2 (C-9), 27.2 (C-14), 25.1 (C-8), 24.9 (C-6), 24.3 (C-7), 20.8 (C-16), 19.5 (C-3), 18.5 (C-15), 18.2 (C-4); ESI-MS (TOF): 233.2016 $[M]^+$ (calcd. 233.2014 for $C_{15}H_{25}N_2$); ESI-MS/MS on $[M]^+$ ion: 233, 151, 123, 111, 93, 81, 79, 67, 55, 41.

Details for compounds (+)-**16** and **19** see the Supporting Information section.

(+)-9-Epi-schoberine [(+)-17]. To a solution of (−)-9-epi-myrionidine (−)-**16** (50 mg, 0.2 mmol) in dry THF (4 mL) was treated with $LiAlH_4$ (10 mg, 0.26 mmol) at −5 °C. The reaction solution was stirred for 30 min at this temperature then warmed to rt and stirred for additional 12 h. Aqueous solution of NaOH (5%, 5 mL) was added and the solution was extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were washed with water and dried over $MgSO_4$. The solvent was removed under diminished pressure and the residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH 95/5) to afford (+)-**17** as colorless solid (51 mg, 90%). Mp 71−72 °C; $[\alpha]_D^{20}$ +32.4 (*c* 1, MeOH); ^{1}H (400.13 MHz, $CDCl_3$, 298 K): 3.15 (dd, 10.7, 3.3 and 3.3 Hz, 1H, H-2_{eq}), 2.66 (m, 1H, H-17_{eq}), 2.58 (dd 11.1 and 1.8 Hz, 1H, H-11_{eq}), 2.18 (dd, 11.1, 3.7, 1H, H-11_{ax}), 2.05 (m, 2H, H-8_{ax} and H-10), 2.03 (m, 1H, H-14_{eq}), 1.90 (dd, 11.8 and 3.1 Hz, 1H, H-13), 1.89 (m, 1H, H-17_{ax}), 1.86 (m, 1H, H-6_{ax}), 1.78 (m, 1H, H-7_{eq}), 1.77 (m, 1H, H-15_{eq}), 1.73 (m, 1H, H-3_{ax}), 1.57 (m, 1H, H-2_{ax}), 1.55 (m, 1H, H-16_{ax}), 1.52 (m, 1H, H-5), 1.46 (m, 1H, H-16_{eq}), 1.40 (m, 1H, H-9), 1.38 (m, 1H, H-3_{eq}), 1.32 (m, 1H, H-8_{eq}), 1.29 (m, 1H, H-7_{ax}), 1.24 (m, 1H, H-14_{ax}), 1.20 (m, 1H, H-15_{ax}), 1.14 (m, 1H, H-6_{eq}); ^{13}C (75.47 MHz, $CDCl_3$, 298 K): 85.7 (C-13), 64.1 (C-10), 61.9 (C-11), 56.3 (C-17), 50.3 (C-2), 37.7 (C-5 and 9), 30.5 (C-4), 28.9 (C-14), 27.0 (C-8), 26.5 (C-7), 25.9 (C-6), 25.0 (C-16), 24.1 (C-15), 21.5 (C-3); ESI-MS (TOF): 235.2179 $[M+H]^+$ (calcd. 235.2174 $C_{15}H_{27}N_2$); ESI-MS/MS, on $[M+H]^+$ ion: 235, 152, 150, 121, 98, 79, 70, 67, 55, 41.

Details for compound (−)-**17** see the Supporting Information section.

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Supporting Information Available: ESI-MS and NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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