Synthesis of (±)-Serralongamine A and the Revised Structure of Huperzine N

Gisela V. Saborit,[†] Caroline Bosch,[†] Teodor Parella,[‡] Ben Bradshaw,*[,†] and Josep Bonjoch*[,†]

[†]Laboratori de Química Orgànica, Facultat de Farmàcia, IBUB, Universitat de Barcelona, Av. Joan XXIII s/n, 08028-Barcelona, Spain
[‡]Servei de Ressonància Magnètica Nuclear, Universitat Autònoma de Barcelona, 08193-Bellatera, Barcelona, Spain

S *Supporting Information*

ABSTRACT: A revised structure for the *Lycopodium* alkaloid huperzine N is proposed and confirmed by synthesis. The key synthetic steps involve an epimerization of a *cis*-5-oxodecahydroquinoline to the corresponding trans isomer and a coupling, followed by a diastereoselective hydrogenation using Wilkinson's catalyst to incorporate the pyridylmethyl moiety. This route allowed the alkaloid serralongamine A to be synthesized for the first time, and two additional steps led to the revised structure of huperzine N, both products bearing an unusual decahydroquinoline stereostructure.
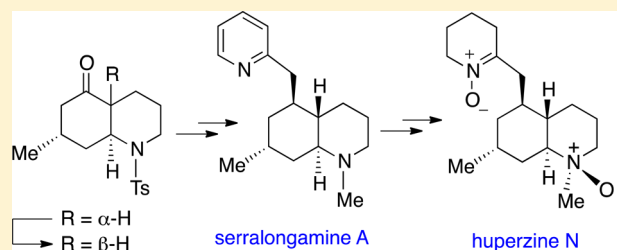
The phlegmarine alkaloids are structurally characterized by a 5,7-disubstituted decahydroquinoline ring and a $C_{16}N_2$ skeleton.[1] They can be classified in four types, designated here as A−D,[2] according to the relationship of the ring fusion hydrogens (H-4a and H-8a) with the H-7 in the decahydroquinoline ring (DHQ) (Figure 1).[3] Moreover, the phlegmarine substitution pattern involves a (2-piperidyl)methyl side chain at
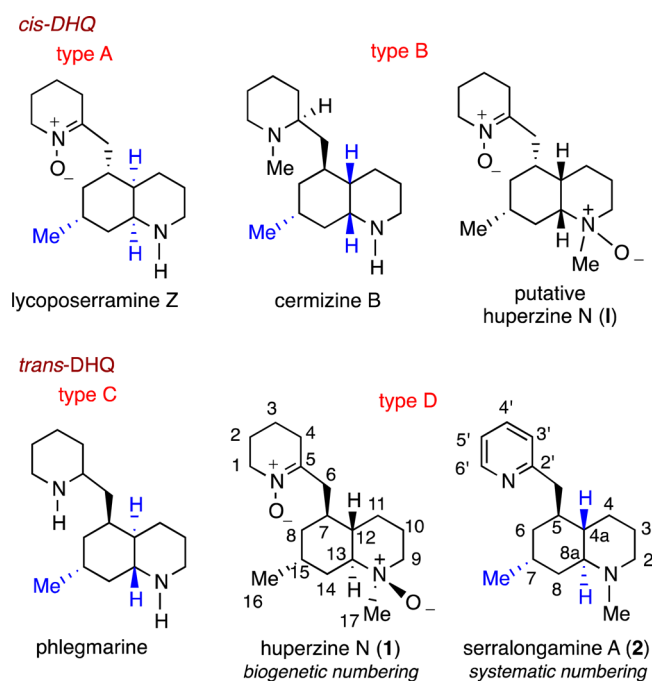
C-5, which can be partially (as in nitrone) or fully oxidized (as in pyridine), thus increasing the stereochemical variation.

After recently describing the total synthesis of I, the proposed structure of huperzine N,[4] we revealed its misassignment. We here suggest an alternative structure for this natural product[5,6] (i.e., 1) and confirm it by a total synthesis. Moreover, the synthesis of serralongamine A (2),[7] featuring a pyridine instead of the usual piperidine ring system, is also reported.

The putative (I) and natural huperzine (1) are clearly differentiated by their ^{13}C NMR data: (i) The chemical shifts of C(2) and C(4) are more deshielded (8 and 11 ppm, respectively) in 1 (Figure 2). These data suggest that huperzine
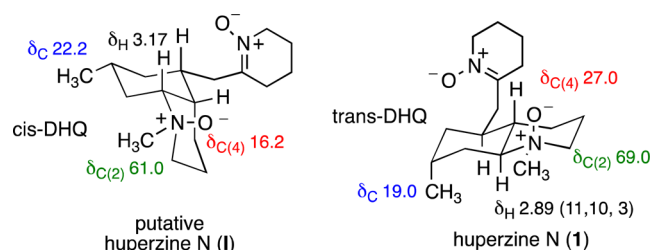

Figure 1. Phlegmarine alkaloids showing the four different stereoparents.

Figure 2. Differential NMR trends between putative and natural huperzine N.

N has a *trans*-decahydroquinoline ring core instead of the cis-ring fusion originally reported. (ii) The chemical shift of the methyl group at C(7), which resonates at δ 19.0 in huperzine N, but at δ 22.2 in I, indicates an axial disposition, which is only possible in a *trans*-decahydroquinoline with a stereoparent of type D (see Figures 1 and 2). Consequently, the NMR data reported for

## Scheme 1. Synthesis of Phlegmarines with a *trans*-Decahydroquinoline Core

Precedents: Series trans type C

a) Comins

ring formation: phase **I**
stereocontrol at C-5: phase **II**
trans ring fusion: phase **III**

I → II → II

via aldol

conjugate addition

hydrogenation

phlegmarine

b) Takayama

II → III → I

Claisen rearrangement

N-alkylation

lycoposerramine X

Present work: series trans type D

I → III → II

via a tandem Robinson annulation/ intramolecular aza-Michael

epimerization

hydrogenation

serralongamine A

huperzine N can be explained by structure **1**. Building on this point of view, we synthesized **1** to confirm the new structural assignment.

Previous *trans*-phlegmarine syntheses have targeted alkaloids with the type C stereoparent. The synthesis of phlegmarine itself was completed by Comins,[8] who also reported the synthesis of three related alkaloids bearing different substituents at the two nitrogen atoms, while Takayama[9] achieved lycoposerramine X. The key challenges in the synthesis of these alkaloids are the generation of the *trans*-decahydroquinoline core and the stereocontrol in the genesis of the stereocenter at C-5 where the pyridylmethyl backbone is attached (Scheme 1). The two different approaches to construct the *trans*-decahydroquinoline ring with the required stereochemistry in the four stereogenic centers are summarized in Scheme 1. Comins, applying his methodolgy based on pyridinium salts, prepared a polysubstituted piperidine that furnished the bicyclic ring by an aldol reaction. Stereoselective conjugated addition, followed by a hydrogenation process, allowed a stereochemical control at C-5 and in the ring fusion, respectively. In contrast, the Takayama approach involved the elaboration of a polyfunctionalized cyclohexane compound in which the four stereogenic centers were established before the cyclization, leading to the decahydroquinoline ring.

Our approach differs from the aforementioned in both its synthetic strategy and the targeted compounds, which have a decahydroquinoline core with a type D stereoparent.[10] The synthetic plan involved the same building block used in our previous synthesis of *cis*-phlegmarines and the epimerization of the stereogenic center at C-4a to achieve a ketone with a *trans*-decahydroquinoline ring, which would allow access to phlegmarine alkaloids with a new stereochemical pattern. Control of the stereochemistry at C5 through a substrate-directable hydrogenation process would be crucial in this synthetic proposal (Scheme 2).

Scheme 2. Synthesis of (±)-Serralongamine A (2) and (±)-Huperzine N (1)
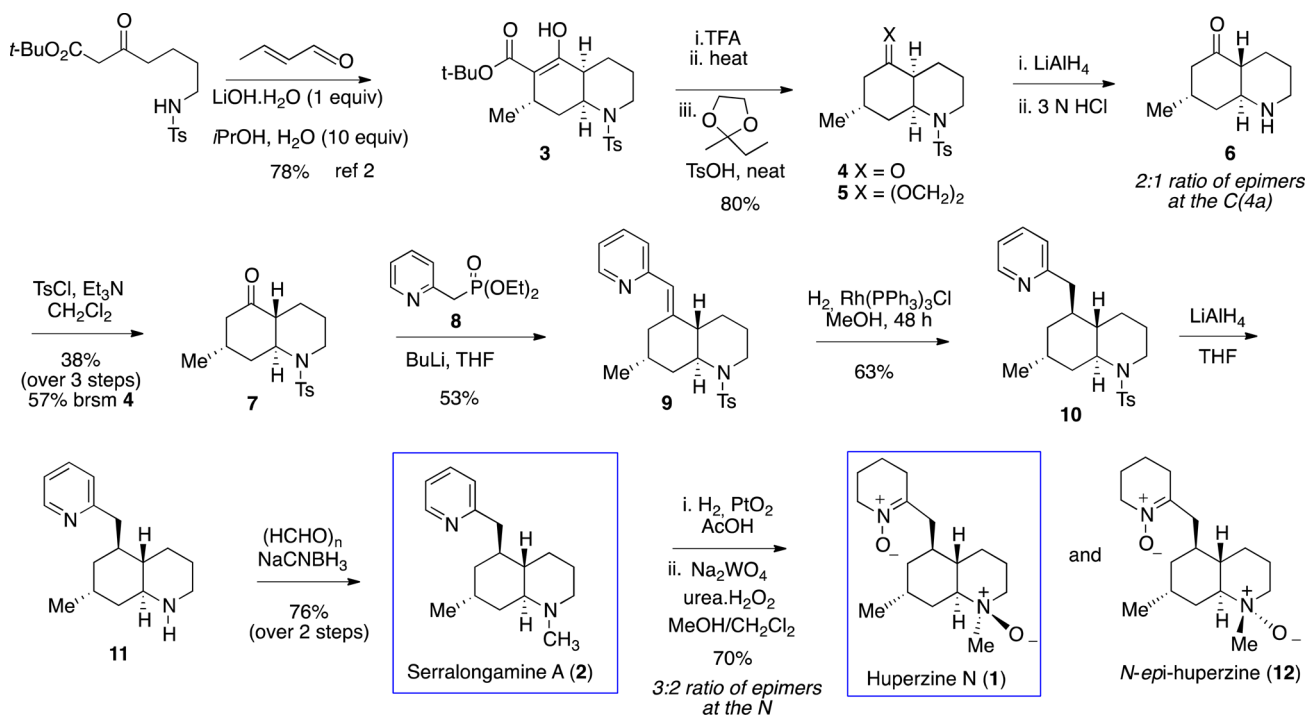
Commencing the synthesis from the easily available ketone **4**,[11] our original protocol[2] allowed the ring fusion to be changed from cis to trans, via the conversion of acetal **5** to the corresponding secondary amine and acid-induced epimerization at C(4a). Tosylation of the resulting 2:1 mixture of ketones **6** and its C4a-epimer furnished the required decahydroquinoline **7** with a trans ring fusion[12] as a single isomer after chromatographic separation. This ketone reacted with a solution of the lithium anion of phosphonate **8**[13] to give vinylpyridine derivative **9** in 53% yield, diastereoselectively providing the *E* isomer.[14] Hydrogenation of vinylpyridine **9** using Wilkinson's catalyst allowed the hydrogen to be delivered exclusively from the bottom face. Thus, a pyridine-directed hydrogenation provided access to the valuable intermediate **10** with a contrasteric selectivity (Figure 3).
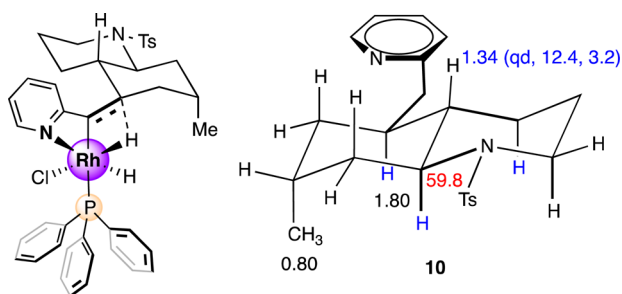

Figure 3. Transition state leading to **10** and its representative NMR data.

The stereoselectively formed decahydroquinoline **10** showed the same relative configuration in its four stereogenic centers as the target **1** and serralongamine A (**2**). The configuration at C-5 was ascertained considering the multiplicity of the signal corresponding to H-4a, which implies a trans relationship between H-4a and H-5, both in an axial disposition. Moreover, the chemical shift for C-8a (δ 59.8) did not differ from that observed in the precursors **7** (δ 60.3) and **9** (δ 60.6), indicating that the pyridylmethyl side chain is not axially located (Figure 3).[15]

Removal of the tosyl group in **10** using LiAlH4, followed by reductive *N*-methylation of **11**, gave serralongamine A (**2**) in 76% yield for the two steps, which constitutes the first synthetic entry to a phlegmarine alkaloid embodying its decahydroquinoline stereoparent. The *trans*-decahydroquinoline serralongamine A differs from phlegmarine itself in the stereochemical relationship between the configuration at C7 and the trans ring fusion carbons, C4a and C8a (Figure 1).

It is noteworthy that the NMR data of our synthetic **2** were clearly different from those reported for the isolated serralongamine A in CD3OD. Since basic nitrogen atoms readily protonate, we were able to reproducibly obtain ^{1}H and ^{13}C NMR spectra of the free base forms of serralongamine A in CD3OD containing NaOCD3.[16] We surmised that the natural isolate corresponded to its ditrifluoroacetate salt. Thus, the NMR spectra of synthetic serralongamine A was examined by titrating a sample of the free base with TFA. For a comparison of NMR data for natural and synthetic serralongamine A (**2**) as the double TFA salt, see the Supporting Information. As reproduced in Figure S1, NMR spectra identical to those reported for the natural product were obtained.

Having achieved **2**, we were two steps from completing the new structure proposed for huperzine N (**1**). Toward this end,

reduction of the pyridine ring in B gave the corresponding piperidine, which, after oxidation with Na2WO4/urea· H2O2(UHP),[3] led to **1** by formation of both the amine *N*-oxide and nitrone functionalities, which were further confirmed by ^{15}N chemical shift NMR data. The spectroscopic data of the synthetic sample were identical in all respects to those reported for the natural product,[5] although a side product purified together with huperzine N was also formed. Two-dimensional NMR spectroscopy of the mixture identified the minor product as the *N*-oxide epimer of huperzine N. Although the oxidation of cyclic tertiary amines normally takes place axially,[17] the presence of an equatorial substituent increases the equatorial oxidation,[18] as occurred in our substrate (C8−C8a bond). Thus, the reaction did not work diastereoselectively and epimeric *N*-oxide **12** was also formed. The stereostructure and the complete ^{1}H, ^{13}C, and ^{15}N chemical shifts assignment of both epimers **1** and **12** (Figure 4) and also their protonated forms[19] (see the Supporting
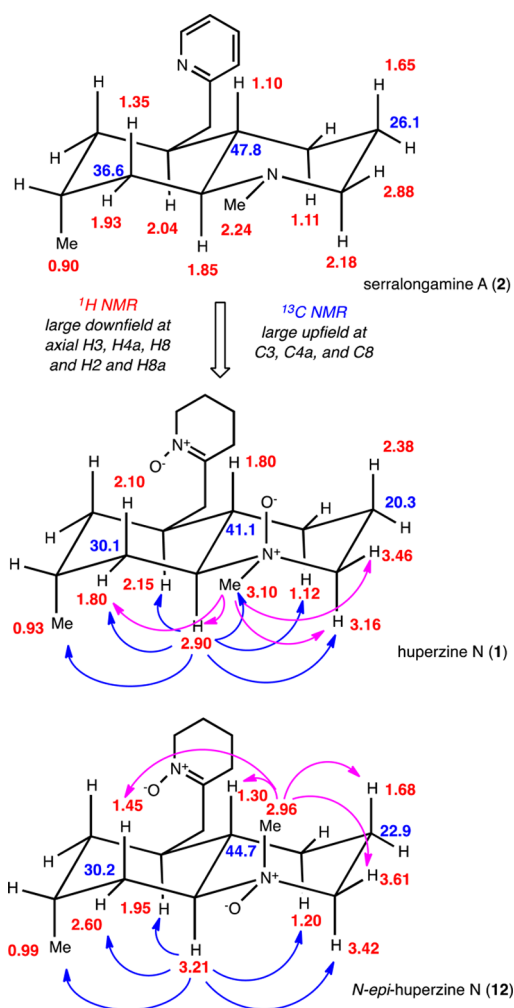

Figure 4. Characteristic NMR data and selected NOEs of huperzine N (**1**), *N-epi*-huperzine N (**12**), and serralongamine A (**2**).

Information for details) were performed from the analysis of COSY, ROESY,[20] HSQC, HMBC, and TOCSY correlation spectra of the mixture.

The configuration of the new stereogenic center at the nitrogen atom in huperzine N was corroborated as *R*, on the basis of ^{1}H and ^{13}C chemical shift NMR analysis of **1** and its *N*-epimer **12**. Thus, a clear upfield shift for C(3), C(4a), and C(8) was

observed, due to the 1,3-cis relationship between the N→O bond and the axial C−H bond of these carbon atoms (Figure 4), compared with either the free amine base nucleus (e.g., in **2**) or the *N*-epimeric *N*-oxide with the oxygen atom in an equatorial disposition (i.e., **12**).[21] The NMR data of synthetic huperzine N matched those described for the natural product, thus establishing its configuration as 1*R*,4a*S*,5*S*,7*R*,8a*S*. Although we have reported the racemic form, the phlegmarine alkaloids have always shown an *R* absolute configuration in the carbon bonded to the methyl group in the decahydroquinoline ring. Thus, the relative configuration allowed the absolute configuration to be proposed.

In summary, in this work on the phlegmarine subset of *Lycopodium* alkaloids, the first total synthesis of serralongamine A and the revised structure of huperzine N have been accomplished. The absolute configuration of the huperzine N was established, and the NMR data of the serralongamine A in its free base form are reported for the first time.

■ EXPERIMENTAL SECTION

General. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. All product mixtures were analyzed by thin-layer chromatography using TLC silica gel plates with a fluorescent indicator ($\lambda = 254$ nm). Analytical thin-layer chromatography was performed on SiO$_2$ (Merck silica gel 60 F$_{254}$), and the spots were located by UV light and/or a 1% KMnO$_4$ aqueous solution or hexachloroplatinate reagent. Chromatography refers to flash chromatography and was carried out on SiO$_2$ (silica gel 60 ACC, 230−240 mesh). Drying of organic extracts during the reaction workup was performed over anhydrous Na$_2$SO$_4$. Chemical shifts of ^{1}H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me$_4$Si. All NMR data assignments are supported by gCOSY and gHSQC experiments.

(4a*RS*,7*RS*,8a*RS*)-7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodecahydroquinoline Ethylene Acetal (5). From crystallized keto ester **3** (536 mg, 1.27 mmol), following the procedure previously described,[11] ketone **4** was obtained and used in the next step without purification. After acetalization[2] of **4** and the purification step by chromatography (5% to 25% EtOAc in hexanes), **5** (373 g, 80%) was obtained as a white solid: R_f = 0.71 (1:1 EtOAc/hexanes); mp 100 °C. For NMR data, see ref 2.

(4a*RS*,7*SR*,8a*SR*)-7-Methyl-5-oxodecahydroquinoline (6). Operating as previously described,[2] starting from **5** (373 mg, 1.02 mmol), **6**, a 2:1 mixture of epimers at C(4a), was obtained (110 mg) as a colorless oil, which was used directly in the next step. For NMR data, see ref 2.

(4a*RS*,7*SR*,8a*SR*)-7-Methyl-5-oxo-1-(4-methylphenyl-sulfonyl)decahydroquinoline (7). To a cooled (0 °C) stirred solution of the above mixture of **6** and its epimer (110 mg) in CH$_2$Cl$_2$ (8 mL) was added a solution of TsCl (214 mg, 1.12 mmol, 1.1 equiv) in CH$_2$Cl$_2$ (4 mL), followed by Et$_3$N (0.17 mL, 1.23 mmol, 1.2 equiv). The mixture was stirred at rt for 6 h and diluted with CH$_2$Cl$_2$ (20 mL). The organics were washed with brine (2 × 5 mL), dried, concentrated, and purified by chromatography (5−25% EtOAc in hexanes) to yield successively **4** (59 mg) and **7** (121 mg, 38% in three steps, 57% brsm) as a white solid: R_f = 0.35 (25% EtOAc/hexanes); mp 108 °C; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 0.81 (d, J = 7.2 Hz, 3H, CH$_3$), 1.32 (m, 1H, H-4ax), 1.64 (m, 1H, H-3ax), 1.76 (m, 1H, H-3eq), 2.00 (dd, J = 12.8, 3.6 Hz, 1H, H-4eq), 2.15 (dt, J = 13.6, 2.4 Hz, 1H, H-6ax), 2.23 (dm, J = 12.4 Hz, 1H, H-8eq), 2.33 (td, J = 13.6, 4.6 Hz, 1H, H-8ax), 2.40 (masked, H-7), 2.42 (s, 3H, CH$_3$Ar), 2.46 (qd, 1H, J = 11.4, 3.2 Hz, H-4a), 2.56 (dd, J = 11.6, 4.0 Hz, 1H, H-6eq), 2.66 (td, J = 11.2, 3.2, 1.6 Hz, 1H, H-2ax), 2.89 (td, J = 11.4, 4.0 Hz, 1H, H-8a), 4.13 (dtd, J = 12.8, 4.0, 1.2 Hz, 1H, H-2eq), 7.30 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.68 (d, J = 8.4 Hz, 2H, *m*-Ts); ^{13}C NMR (100 MHz, CDCl$_3$) δ 18.9 (CH$_3$), 21.6 (ArCH$_3$), 23.5 (C-4), 24.4 (C-3), 28.5 (C-7), 36.1 (C-8), 47.3 (C-6), 49.3 (C-2), 53.1 (C-4a), 60.3 (C-8a), 127.3 (*m*-Ts), 129.8 (*o*-Ts), 137.1 (*ipso*-Ts), 143.6 (*p*-Ts); 209.1 (C-5). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{17}$H$_{24}$NO$_3$S 322.1471, found 322.1464.

(*E*)-(4a*RS*,7*SR*,8a*RS*)-7-Methyl-1-(4-methylphenylsulfonyl)-5-(pyridin-2-ylmethylene)decahydroquinoline (9). Both the pyridine phosphonate **8** and decahydroquinoline **7** were previously dried by azeotroping with benzene. To a stirred solution of phosphonate **8** (227 mg, 1 mmol, 5 equiv) in THF (3 mL) at −78 °C was added *n*-BuLi (1.6 M in hexanes, 0.52 mL, 0.84 mmol, 4.5 equiv). The resulting dark red solution was stirred for 30 min at rt before a solution of the decahydroquinoline **7** (60 mg, 0.187 mmol) in THF (1.2 mL) was added dropwise via syringe at −78 °C. The reaction mixture was stirred for 30 min at −78 °C, 1 h at −30 °C, and 6 h at 0 °C, and quenched with sat. aq. NH$_4$Cl (1 mL) and water (1 mL). The mixture was extracted with EtOAc (2 × 3 mL), and the combined organic extracts were dried, concentrated, and purified by chromatography (5−40% EtOAc in hexanes) to give **9** (39 mg, 53%) as a white solid: R_f = 0.49 (50% hexane/EtOAc); mp 128 °C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.77 (d, J = 7.2 Hz, 3H, CH$_3$), 1.31 (qd, 1H, J = 12.4, 2.0 Hz, H-4ax), 1.68 (m, 1H, H-3), 1.82 (m, 1H, H-3), 1.95 (dm, J = 13.2 Hz, 1H, H-4eq), 2.03 (dd, J = 12.6, 4.4 Hz, 1H, H-8eq), 2.12 (m, 1H, H-6ax), 2.15 (m, 1H, H-7), 2.19 (m, 1H, H-8ax), 2.24 (brt, J = 12.0 Hz, 1H, H-4a), 2.42 (s, 3H, ArCH$_3$), 2.91 (ddd, J = 13.2, 8.8, 4.4 Hz, 1H, H-8a), 2.94 (td, 1H, J = 12.8, 5.2 Hz, H-2ax), 3.07 (dt, J = 13.2, 2.0 Hz, 1H, H-6eq), 3.97 (dt, J = 12.8, 5.2 Hz, 1H, H-2eq), 6.31 (s, 1H, C=CH), 7.07 (dd, J = 7.6, 4.8 Hz, 1H, H-5 py), 7.13 (d, J = 8.0 Hz, 1H, H-3 py), 7.28 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.59 (td, J = 7.6, 2.0 Hz, 1H, H-4 py), 7.69 (d, J = 8.4 Hz, 2H, *m*-Ts), 8.54 (dm, J = 4.8 Hz, 1H, H-6 py); ^{13}C NMR (100 MHz, CDCl$_3$, HSQC) δ 18.2 (CH$_3$), 21.7 (CH$_3$Ar), 24.5 (C-3), 25.8 (C-4), 29.3 (C-7), 35.2 (C-6), 38.1 (C-8), 46.3 (C-4a), 46.8 (C-2), 60.6 (C-8a), 121.2 (C-5 py), 124.0 (C-3 Py), 124.1 (=CH), 127.3 (*o*-Ts), 129.7 (*m*-Ts), 136.0 (C-4 Py), 137.3 (*p*-Ts), 143.3 (*ipso*-Ts), 144.7 (C-5), 149.3 (C-6 Py), 157.3 (C-2 Py). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{23}$H$_{29}$N$_2$O$_2$S 397.1944, found 397.1953.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)-1-(4-methylphenylsulfonyl)decahydroquinoline (10). To a stirred solution of **9** (27 mg, 0.068 mmol) in MeOH (7 mL) was added Wilkinson's catalyst RhCl(PPh$_3$)$_3$ (16 mg, 0.017 mmol, 25 mol %) at rt. The resulting mixture was rapidly evacuated and backfilled with H$_2$ three times and then stirred under an atmosphere of H$_2$ for 72 h. The mixture was concentrated, and purified by chromatography (5−25% EtOAc in cyclohexane) to give **10** (17 mg, 63%): R_f = 0.5 (1:1 EtOAc/cyclohexane): ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.80 (d, J = 7.2 Hz, 3H, CH$_3$), 0.91 (qd, J = 12.4, 6.2 Hz, 1H, H-4ax), 1.20 (m, 2H, H-6), 1.34 (qd, J = 12.4, 3.2, 1H, H-4a), 1.65 (m, 2H, H-3), 1.80 (m, 1H, H-5), 1.86 (td, J = 12.4, 4.8 Hz, 1H, H-8ax), 1.94 (dm, J = 12.4 Hz, 1H, H-8eq), 2.00 (m, 1H, H-7), 2.12 (dm, J = 12.0 Hz, 1H, H-4eq), 2.30 (dd, J = 13.4, 8.8 Hz, 1H, CH$_2$Py), 2.42 (s, 3H, ArCH$_3$), 2.94−3.00 (m, 2H, H-2ax, H-8a), 3.11 (dd, J = 13.4, 4.0 Hz, 1H, CH$_2$Py), 3.97 (dt, J = 13.2, 5.6 Hz, 1H, H-2eq), 7.04 (d, J = 8.0 Hz, 1H, H-3 Py), 7.08 (m, 1H, H-5 Py), 7.28 (d, J = 8.4 Hz, 2H, *o*-Ts), 7.55 (td, J = 7.6, 1.6 Hz, 1H, H-4 Py), 7.68 (d, J = 8.0 Hz, 2H, *m*-Ts), 8.50 (dm, J = 4.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, CDCl$_3$, HSQC) δ 18.3 (CH$_3$), 21.6 (ArCH$_3$), 25.1 (C-3), 27.4 (C-4), 27.5 (C-7), 36.8 (C-6), 37.1 (C-8), 37.3 (C-5), 42.3 (CH$_2$Py), 45.6 (C-4a), 47.3 (C-2), 59.8 (C-8a), 121.1 (C-5 Py), 124.0 (C-3 Py), 127.2 (*o*-Ts), 129.7 (*m*-Ts), 136.2 (C-4 Py), 138.4 (*p*-Ts), 143.0 (*ipso*-Ts), 149.4 (C-6 Py), 161.1 (C-2 Py). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{23}$H$_{31}$N$_2$O$_2$S 399.2101, found 399.2116.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (11). A solution of sulfonamide **10** (17 mg, 0.043 mmol) in anhydrous THF (1 mL) was added to a stirred suspension of LiAlH$_4$ (16 mg, 0.43 mmol) in THF (1 mL) at 0 °C. The reaction was stirred overnight at rt and quenched by addition of one drop of water, another of aqueous 15% NaOH, and three drops of water. The mixture was diluted with CH$_2$Cl$_2$, filtered through a pad of Celite, and washed thoroughly with CH$_2$Cl$_2$. Evaporation of the solvent gave **11**, which was pure enough to be used in the following step. An analytical sample of secondary amine **11** was obtained by chromatography on alumina (1−5% MeOH in CH$_2$Cl$_2$): R_f = 0.22 (5:95 MeOH:CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.91 (d, J = 7.2 Hz, 3H, CH$_3$), 0.92 (qd, J = 12.0, 3.2 Hz, 1H, H-4a), 1.09 (qd, J = 12.0, 4.0 Hz, 1H, H-4ax), 1.20−1.25 (m, 2H, 2H-6), 1.44 (td, J = 12.0, 4.2 Hz, 1H, H-8ax), 1.52 (dt, J = 12.4, 2.0 Hz, 1H, H-8eq), 1.53 (m, 1H, H-3eq), 1.71 (tt, J = 13.2, 3.2 Hz,

1H, H-3ax), 1.82 (m, 1H, H-5), 2.01 (m, 1H, H-7eq), 2.14 (dd, *J* = 13.0, 3.0 Hz, 1H, H-4eq), 2.30 (dd, *J* = 13.2, 10.0 Hz, 1H, CH$_2$Py), 2.47 (ddd, 1H, *J* = 11.2, 10.0, 4.0 Hz, H-8a), 2.66 (td, 1H, *J* = 12.2, 3.0 Hz, H-2ax), 3.07 (dm, *J* = 12.0 Hz, 1H, H-2eq), 3.14 (dd, *J* = 13.2, 4.0 Hz, 1H, CH$_2$Py), 7.06−7.09 (m, 2H, H-3 Py, H-5 Py), 7.55 (td, *J* = 8.0, 1.6 Hz, 1H, H-4 Py), 8.52 (dd, *J* = 5.2, 2.0 Hz, 1H, H-6 Py); ^{13}C NMR (100 MHz, CDCl$_3$) δ 19.2 (CH$_3$), 27.2 (C-3), 27.5 (C-7), 28.8 (C-4), 36.4 (C-5), 37.6 (C-6), 39.4 (C-8), 41.9 (CH$_2$Py), 47.0 (C-2), 48.4 (C-4a), 56.2 (H-8a), 120.9 (C-5 Py), 123.9 (C-3 Py), 136.1 (C-4 Py), 149.4 (C-6 Py), 161.8 (C-2 Py). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{16}$H$_{24}$N$_2$ 245.2012, found 245.2009.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-1,7-Dimethyl-5-(pyridin-2-ylmethyl)-decahydroquinoline (*rac*-Serralongamine A, 2). To a solution of the above crude amine **11** (10 mg, 0.043 mmol) in MeOH (2.3 mL) was added 37% aqueous formaldehyde (24 mL, 0.328 mmol) and NaBH$_3$CN (18 mg, 0.287 mmol) at 0 °C, and the mixture was stirred at rt for 30 min. The volatiles were evaporated, and the crude was purified on neutral alumina (CH$_2$Cl$_2$ to 5% MeOH in CH$_2$Cl$_2$) to give **2** (8.4 mg, 76% over two steps from **10**): *R$_f$* = 0.70 (5% CH$_3$OH in CH$_2$Cl$_2$). This sample was dissolved in CD$_3$OD, and NaOCD$_3$ (0.1 M in CD$_3$OD) was added. ^{1}H and ^{13}C NMR spectra of the free base were obtained: ^{1}H NMR (400 MHz, CD$_3$OD, NaOCD$_3$) δ 0.90 (d, *J* = 7.6 Hz, 3H, CH$_3$), 1.10−1.15 (masked, 1H, H-4a), 1.11 (br q, *J* = 12.0 Hz, 1H, H-4ax), 1.15 (br d, *J* = 12 Hz, 1H, H-6eq), 1.25 (td, *J* = 12.4, 4.4 Hz, 1H, H-6ax), 1.35 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.65−1−75 (m, 2H, 2H-3), 1.80−1.92 (m, 2H, H-5 and H-8a), 1.93 (dm, *J* = 12.0 Hz, 1H, H-8eq), 2.03 (m, 1H, H-7), 2.16 (dm, *J* = 11.8 Hz, 1H, H-4eq), 2.18 (td, *J* = 12.8, 3.2 Hz, 1H, H-2ax), 2.24 (s, 3H, CH$_3$), 2.30 (dd, *J* = 13.2, 10.4 Hz, 1H, CH$_2$py), 2.88 (dm, *J* = 12.0 Hz, 1H, H-2eq), 3.19 (dd, *J* = 13.2, 4.0 Hz, 1H, CH$_2$py), 7.24 (dd, *J* = 7.6, 4.8 Hz, 1H, H-5 py), 7.25 (t, *J* = 7.4 Hz, 1H, H-3 py), 7.73 (tt, *J* = 7.6, 1.6 Hz, 1H, H-4 py), 8.42 (dm, *J* = 4.8, 1H, H-6 py). ^{13}C NMR (100 MHz, CD$_3$OD, NaOCD$_3$) δ 19.5 (CH$_3$), 26.1 (C-3), 28.5 (C-7), 29.6 (C-4), 36.6 (C-8), 37.8 (C-5), 38.0 (C-6), 42.6 (CH$_2$py), 43.1 (NCH$_3$), 47.8 (C-4a), 58.5 (C-2), 64.8 (C-8a), 122.7 (C-3 py), 125.7 (C-5 py), 138.4 (C-4 py), 149.5 (C-6 py), 162.6 (C-2 py). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{17}$H$_{27}$N$_2$ 259.2168, found 259.2169.

Spectra matching the reported spectra of (−)-serralongamine A[6] were obtained after the addition of TFA in CD$_3$OD to the above sample of **2**: ^{1}H (400 MHz, CD$_3$OD, TFA) δ 0.95 (d, *J* = 7.6 Hz, 3H, CH$_3$), 1.15 (br d, *J* = 13.2 Hz, 1H, H-6eq), 1.41 (td, *J* = 12.8, 4.8 Hz, 1H, H-6ax), 1.44 (td, *J* = 12.4, 4.4 Hz, 1H, H-4ax), 1.53 (qd, *J* = 12.0, 2.8 Hz, 1H, H-4a), 1.64 (td, *J* = 12.4, 4.8 Hz, 1H, H-8ax), 1.88 (qt, *J* = 12.4, 4.0 Hz, 1H, H-3ax), 2.00−2.09 (m, 2H, H-3eq, H-5ax), 2.15 (br d, *J* = 12.4 Hz, 1H, H-8eq), 2.22 (br d, *J* = 12.0 Hz, 1H, H-7eq), 2.24 (m, 1H, H-4eq), 2.72 (dd, *J* = 14.4, 10.4 Hz, 1H, CH$_2$py), 2.86 (s, 3H, NCH$_3$), 3.12 (td, *J* = 13.0, 3.2 Hz, 1H, H-2ax), 3.15 (td, *J* = 12.2, 4.0 Hz, 1H, H-8a), 3.52 (br, *J* = 13.0 Hz, 1H, H-2eq), 3.56 (dd, *J* = 14.4, 4.0 Hz, 1H, CH$_2$py), 7.85 (ddd, *J* = 7.2, 5.6, 0.8 Hz, 1H, H-5py), 7.88 (d, *J* = 8.0 Hz, 1H, H-3py), 8.54 (td, *J* = 8.0, 1.6 Hz, 1H, H-4py), 8.77 (d, *J* = 5.6 Hz, 1H, H-6py); ^{1}C NMR (100 MHz, CD$_3$OD, TFA) δ 18.3 (CH$_3$), 24.0 (C-3), 27.1 (C-4), 28.1 (C-7), 33.8 (C-8), 36.8 (C-6), 37.5 (C-5), 37.9 (CH$_2$py), 41.4 (NCH$_3$), 46.3 (C-4a), 57.4 (C-2), 66.0 (C-8a), 126.3 (C-5py), 129.4 (C-3py), 142.8 (C-6py), 147.8 (C-4py), 157.7 (C-2py).

(1*RS*,4a*SR*,5*SR*,7*RS*,8a*SR*)-1,7-Dimethyl-5-(2,3,4,5-tetrahydropyridine 1-oxide)decahydroquinoline *N*-Oxide (Huperzine N, 1). To a stirred solution of **2** (8 mg, 0.031 mmol) in AcOH (0.25 mL) was added PtO$_2$ (20% w/w, 2 mg) at rt. The resulting mixture was evacuated and backfilled with hydrogen 3 times and then stirred under an atmosphere of H$_2$ for 16 h. The mixture was diluted with CH$_2$Cl$_2$ (2 mL) before it was filtered through a pad of Celite and washed through with CH$_2$Cl$_2$. The filtered solution was washed with 1 N NaOH, dried, and concentrated. To a solution of the above crude diamine in MeOH/CH$_2$Cl$_2$ (1:1; 0.2 mL) were added in one portion UHP (30 mg, 0.31 mmol) and Na$_2$WO$_4$·2H$_2$O (2 mg, 0.006 mmol), and the mixture was stirred at rt for 72 h. After concentration, CH$_2$Cl$_2$ was added and the reaction mixture was filtered, concentrated, and purified by chromatography (2.5−10% MeOH in CH$_2$Cl$_2$ and then 85/15/1.5 CHCl$_3$/MeOH/NH$_3$) to give **1** and its epimer **12** (6 mg, 66%, 3:2 ratio) as a

colorless oil, which solidified on standing: *R$_f$* = 0.20 (80/20/2 CHCl$_3$/MeOH/NH$_3$).

Data for Huperzine N (1). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.93 (d, *J* = 7.2 Hz, 3H, CH$_3$), 1.12 (qd, *J* = 12.0, 3.0 Hz, 1H, H-4ax), 1.28 (masked, 1H, H-6eq), 1.40 (td, *J* = 12.0, 4.0 Hz, 1H, H-6ax), 1.58 (br d, *J* = 13.0 Hz, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.80 (m, 2H, H-4a, H-8ax), 1.88 (m, 2H, H-5′), 1.88 (masked, 1H, CH$_2$py), 2.05 (m, 1H, H-4eq), 2.10 (1H, m, H-8eq), 2.21 (m, 1H, H-5), 2.38 (masked, 1H, H-3ax), 2.40 (t, *J* = 6.0 Hz, 2H, H-3′), 2.98 (dd, *J* = 12.0, 3.0 Hz, 1H, CH$_2$py), 2.90 (td, *J* = 11.5, 3.2 Hz, 1H, H-8a), 3.10 (s, 3H, NCH$_3$), 3.14 (ddd, *J* = 12.0, 11.0, 3.0 Hz, 1H, H-2ax), 3.46 (br d, *J* = 12.0 Hz, 1H, H-2eq), 3.75 (t, *J* = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.9 (C-4′), 19.0 (CH$_3$), 20.3 (C-3), 23.3 (C-5′), 27.0 (C-4), 27.1 (C-7), 29.9 (C-3′), 30.1 (C-8), 32.4 (C-5), 36.7 (CH$_2$py), 36.8 (C-6), 41.1 (C-4a), 57.6 (NCH$_3$), 58.5 (C-6′), 69.1 (C-2), 73.8 (C-8a), 148.0 (C-2′); ^{15}N (50 MHz, deduced from ^{1}H−^{15}N HMBC correlations) δ 114.7 (*N*-oxide), 271.7 (nitrone). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{17}$H$_{31}$N$_2$O$_2$ 295.2380; found 295.2374.

Data for N-epi-Huperzine N (12). ^{1}H NMR (400 MHz, CDCl$_3$) δ 0.99 (d, *J* = 7.2 Hz, 3H, CH$_3$), 1.20 (masked, 1H, H-4ax), 1.30 (m, 1H, H-4a), 1.35 (m, 1H, H-6), 1.40 (m, 1H, H-6), 1.45 (td, *J* = 12.0, 3.0 Hz, 1H, H-8ax), 1.68 (m, 1H, H-3eq), 1.68 (m, 2H, H-4′), 1.87 (m, 2H, H-5′), 1.87 (masked, 1H, H-3ax), 1.95 (m, 1H, H-5), 2.05 (m, 1H, H-4eq), 2.35 (masked, 1H, CH$_2$py), 2.40 (t, *J* = 6.0 Hz, 2H, H-2′), 2.60 (1H, m, H-8eq), 2.70 (m, 1H, CH$_2$py), 2.96 (s, 3H, NCH$_3$), 3.21 (br t, *J* = 12.0 Hz, 1H, H-8a), 3.42 (td, *J* = 12.0, 3.0 Hz, 1H, H-2ax), 3.61 (br d, *J* = 12.0 Hz, 1H, H-2eq), 3.72 (t, *J* = 6.4 Hz, 2H, H-6′); ^{13}C NMR (100 MHz, HSQC) δ 18.2 (CH$_3$), 19.2 (C-4′), 22.9 (C-3), 23.3 (C-5′), 27.1 (C-4), 27.2 (C-7), 29.9 (C-3′), 30.2 (C-8), 34.6 (C-5), 35.5 (CH$_2$py), 37.5 (C-6), 44.7 (C-4a), 48.0 (NCH$_3$), 58.6 (C-6′), 71.1 (C-2), 75.9 (C-8a), 147.2 (C-2′); ^{15}N (50 MHz, deduced from ^{1}H−^{15}N HMBC correlations) δ 113.8 (*N*-oxide), 271.0 (nitrone). HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{17}$H$_{31}$N$_2$O$_2$ 295.2380; found 295.2374.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00025.

> Tables for ^{1}H and ^{13}C NMR data of synthetic serralong-amine A (**2**, free base and diprotonated sample) and huperzine N (**1**) as well as NMR data of isolated alkaloids; copies of ^{1}H and ^{13}C NMR spectra of new compounds; COSY, TOCSY, ROESY, HSQC, HMBC, and ^{1}H−^{15}N HMBC spectra of huperzine N (**1**) and its epimer **12** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors
*E-mail: josep.bonjoch@ub.edu (J.B.).
*E-mail: benbradshaw@ub.edu (B.B.).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Ma, X.; Gang, D. R. *Nat. Prod. Rep.* **2004**, *21*, 752−772. (b) Siengalewicz, P.; Mulzer, J.; Rinner, U. *Alkaloids* **2013**, *72*, 1−152.
(2) Bradshaw, B.; Luque-Corredera, C.; Saborit, G.; Cativiela, C.; Dorel, R.; Bo, C.; Bonjoch, J. *Chem.—Eur. J.* **2013**, *19*, 13881−13892.

(3) Systematic numbering is used throughout this paper. In the Supporting Information, the biogenetic numbering is included in all tables to facilitate the comparison of the NMR data reported for phlegmarine alkaloids with those recorded from a synthetic source (compounds **1** and **2**).

(4) Bosch, C.; Fiser, B.; Gómez-Bengoa, E.; Bradshaw, B.; Bonjoch, J. *Org. Lett.* **2015**, *17*, 5084−5087.

(5) For isolation of huperzine N, see: Gao, W. Y.; Li, Y. M.; Jiang, S. H.; Zhu, D. Y. *Helv. Chim. Acta* **2008**, *91*, 1031.

(6) Initially, after the synthesis of putative huperzine N, we indicated that the configuration of the natural product should be trans (ref 4), but we depicted a structure of type C instead of type D as proposed here.

(7) For isolation of serralongamine A: Jiang, W.-P.; Ishiuchi, K.; Wu, J.-B.; Kitanaka, S. *Heterocycles* **2014**, *89*, 747−752.

(8) Wolfe, B. H.; Libby, A. H.; Al-awar, R. S.; Foti, C. J.; Comins, D. L. *J. Org. Chem.* **2010**, *75*, 8564−8570.

(9) Tanaka, T.; Kogure, N.; Kitajima, M.; Takayama, H. *J. Org. Chem.* **2009**, *74*, 8675−8680.

(10) For a synthetic approach to 5-oxo-*trans*-decahydroquinoline used in the synthesis of the lycopodium alkaloid lycoperine, see: Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2010**, *12*, 72−75.

(11) Bradshaw, B.; Luque-Corredera, C.; Bonjoch, J. *Org. Lett.* **2013**, *15*, 326−329.

(12) The coupling constants of H-4a (11.4, 11.4, 11.4, 3.2 Hz) and H-8a (11.4, 11.4, 4.0 Hz) would allow the trans-ring fusion in **7** to be clearly established.

(13) Gan, X.; Binyamin, I.; Rapko, B. M.; Fox, J.; Duesler, E. N.; Paine, R. T. *Inorg. Chem.* **2004**, *43*, 2443−2448.

(14) The downfield shift of the H-6eq (δ 3.07) and the upfield shift at C-6 (δ 35.2) agree with a steric crowding of the pyridyl ring upon H-6eq associated with the *E* configuration of the exocyclic double bond. For comparison of NMR data in a related system, see ref 11.

(15) For the influence of the steric compression effect on NMR chemical shifts, see: (a) Katakawa, K.; Kitajima, M.; Yamaguchi, K.; Takayama, H. *Heterocycles* **2006**, *69*, 223−229. (b) Kolocouris, A. *Tetrahedron Lett.* **2007**, *48*, 2117−2122.

(16) For a similar NMR protocol to measure the free base and its TFA salt spectra in alkaloid synthesis, see: (a) Altman, R. A.; Nilsson, B. L.; Overman, L. E.; Read de Alaniz, J.; Rohde, J. M.; Taupin, V. *J. Org. Chem.* **2010**, *75*, 7519−7534. (b) Lee, A. S.; Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2014**, *136*, 13442−13452.

(17) Shvo, Y.; Kaufman, E. D. *J. Org. Chem.* **1981**, *46*, 2148−2152.

(18) Kawazoe, Y.; Tsuda, M. *Chem. Pharm. Bull.* **1967**, *15*, 1405−1410.

(19) In **1** and **12**, the protonation of the *N*-oxide function leads to a deshielding of the α-hydrogens (Table S3). It should be noted that the protons in a 1,3-diaxial relationship with the *N*-oxide function are not affected or even slightly shielded upon protonation (e.g., H-10, H-12, and H-14 in huperzine N). For NMR studies in this field, see: Lebrun, B.; Braekman, J. C.; Daloze, D. *Magn. Reson. Chem.* **1999**, *37*, 60−64.

(20) When huperzine N was originally isolated (ref 5), NOE correlations were established between the putative H-12 proton and signals at *N*-Me and H-13. However, according to our ROESY NMR spectrum of **1**, which allowed the revised trans configuration to be established, these cross-peaks were due to H-14eq. This error is attributed to the ^{1}H chemical shift degeneracy between H-12 and H-14eq in **1**. This observation is fully confirmed by the NOE contacts observed in the related epimer (**12**) (Figure 4) and protoned *N*-oxide (see Figure S2) derivatives, as well as of the characteristic multiplet *J* pattern of H-12 and H-13.

(21) For NMR studies in *N*-oxide piperidine compounds, see: (a) Potmischil, F.; Cimpeanu, V.; Herzog, H.; Buddrus, J.; Duddeck, H. *Magn. Reson. Chem.* **2003**, *41*, 554−556. (b) Budesinsky, M.; Vanek, V.; Dracinsky, M.; Pohl, R.; Postova-Slavetinska, L.; Sychrovsky, V.; Picha, J.; Cisarova, I. *Tetrahedron* **2014**, *70*, 3871−3886.