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

e-mail address: josep.bonjoch@ub.edu; benbradshaw@ub.edu

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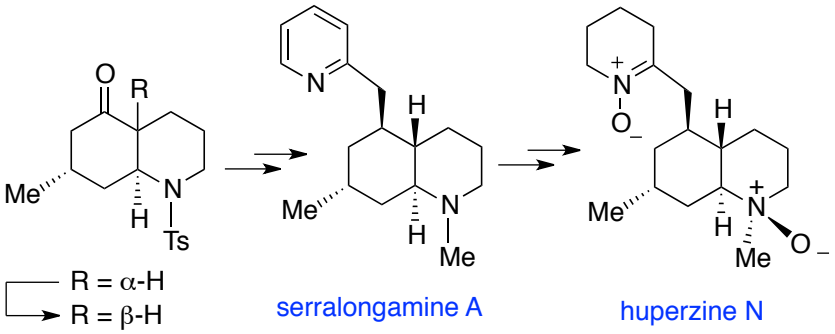
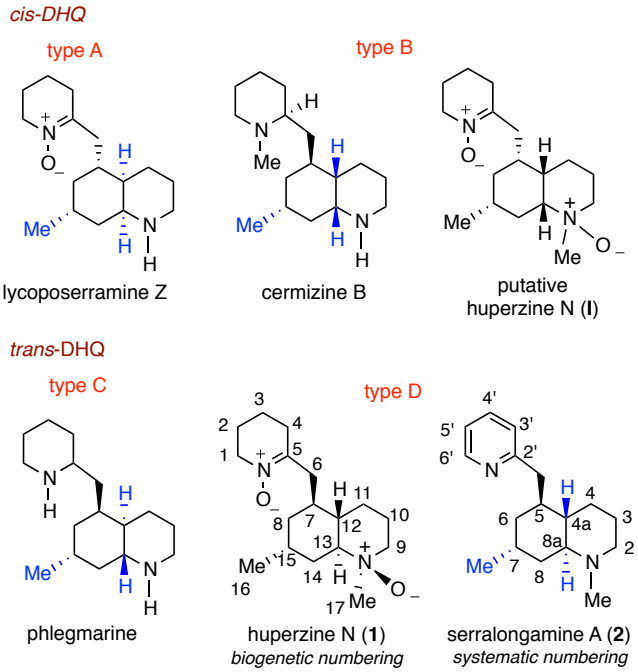


ABSTRACT: A revised structure for the *Lycopodium* alkaloid huperzine N is proposed and confirmed by synthesis. The key synthetic steps involve an epimerization of a *cis*-5-oxodecahydroquinoline to the corresponding trans isomer and a coupling followed by a diastereoselective hydrogenation using Wilkinson's 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 to D, 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).[2,3] 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.

Figure 1. Phlegmarine Alkaloids Showing the Four Different Stereoparents

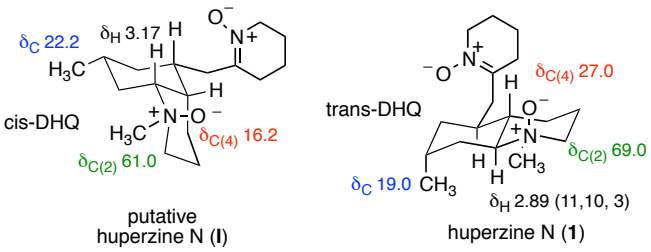


After recently describing the total synthesis of **I**, the proposed structure of huperzine N,[4] we revealed its misassignment. We here suggest an alternative structure for this natural product[5,6] (*i.e.* **1**), and confirm it by a total synthesis. Moreover, the synthesis of serralongamine A (**2**),[7] 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 N has a *trans*-decahydroquinoline ring core instead of the cis-ring fusion originally

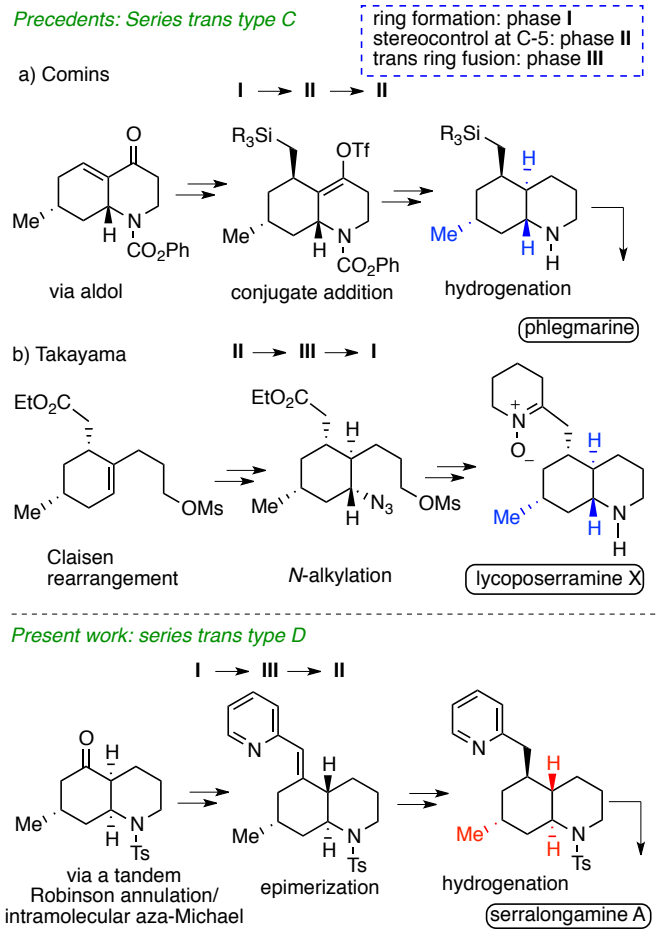
reported; (ii) the chemical shift of the methyl group at C(7), which resonates at δ 19.0 in huperzine N, but at δ 22.2 in **I**, indicates an axial disposition, which is only possible in a *trans*-decahydroquinoline with a stereoparent of type D (see Figures 1 and 2). Consequently, the NMR data reported for huperzine N can be explained by structure **1**. Building on this point of view, we synthesized **1** to confirm the new structural assignment.

Figure 2. Differential NMR Trends Between Putative and Natural Huperzine N



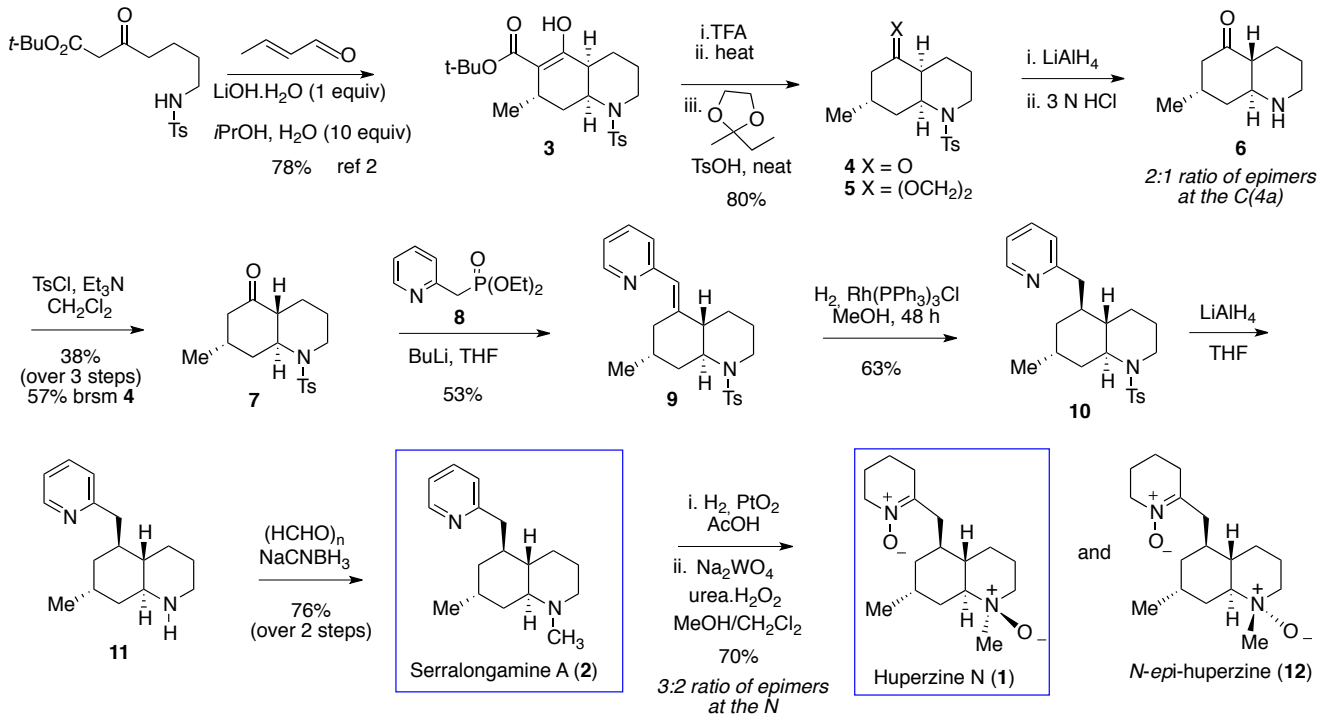
Previous trans-phlegmarine syntheses have targeted alkaloids with the type C stereoparent. The synthesis of phlegmarine itself was completed by Comins,[8] who also reported the synthesis of three related alkaloids bearing different substituents at the two nitrogen atoms, while Takayama[9] achieved lycoposerramine 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.

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



Our approach differs from the aforementioned both in 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)

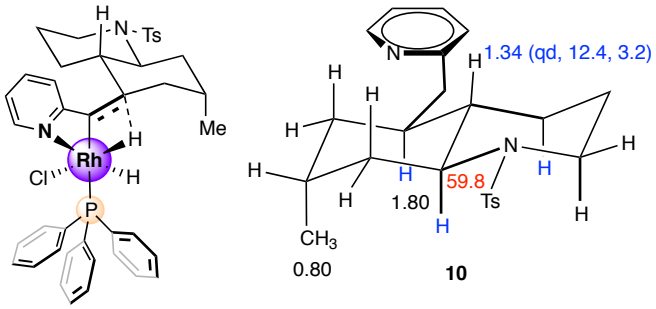


Commencing the synthesis from the easily available ketone **4**,[11] our original protocol[2] allowed the ring fusion to be changed from cis to trans, via the conversion of acetal **5** to the corresponding secondary amine and acid-induced epimerization at C(4a). Tosylation of the resulting 2:1 mixture 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 contra-steric selectivity (Figure 3).

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]

Figure 3. Transition State Leading to 10 and its Representative NMR Data



Removal of the tosyl group in **10** using $LiAlH_4$ 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).

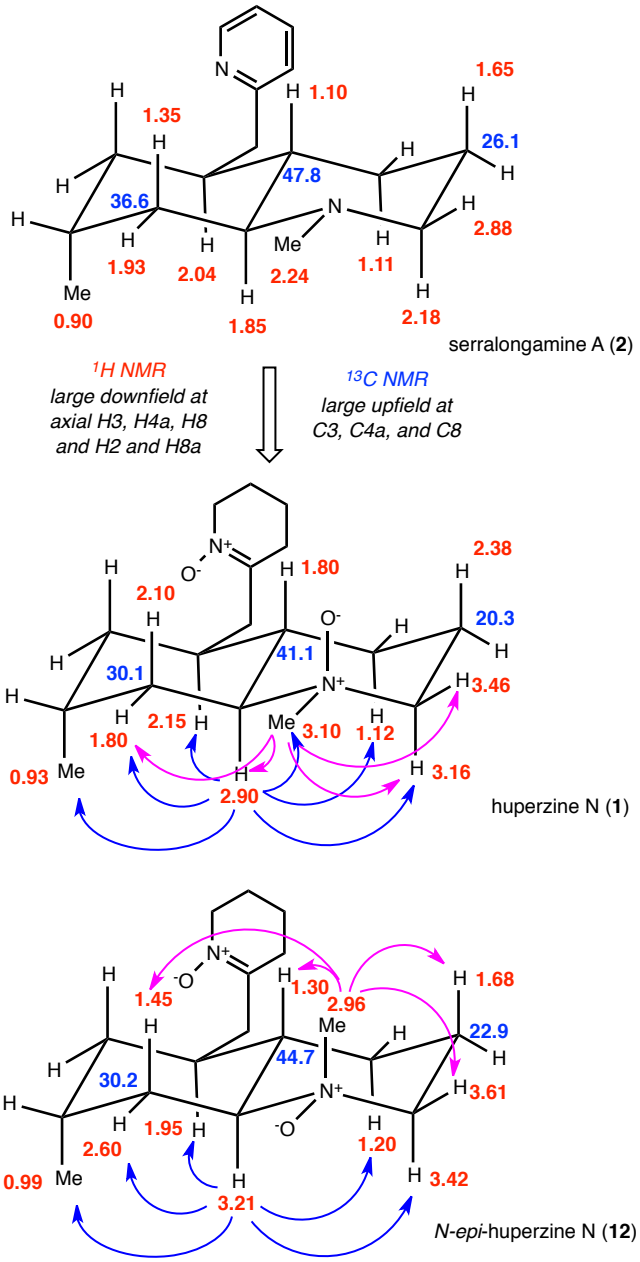
It is noteworthy that the NMR data of our synthetic **2** were clearly different from those reported for the isolated serralongamine A in CD_3OD. Since basic nitrogen atoms readily protonate, we were able to reproducibly obtain ^1H and ^{13}C NMR spectra of the free base forms of serralongamine A in CD_3OD containing $NaOCD_3$.[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 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 Na_2WO_4/

urea·H_2O_2(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 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.

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



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 (λ = 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 or/and 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_2SO_4. Chemical shifts of ^1H and ^{13}C NMR spectra are reported in ppm downfield (δ) from Me_4Si. All NMR data assignments are supported by gCOSY and gHSQC experiments.

(4a*RS*,7*RS*,8a*RS*)-7-Methyl-1-(4-methylphenylsulfonyl)-5-oxodeca-hydroquinoline 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 ºC. For NMR data, see ref. 2.

(**4a*RS*,7S*R*,8aS*R*)-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*,7S*R*,8aS*R*)-7-Methyl-5-oxo-1-(4-methylphenylsulfonyl)decahydro-quinoline (7).** To a cooled (0 ºC) stirred solution of the above mixture of **6** and

its epimer (110 mg) in CH_2Cl_2 (8 mL) was added a solution of TsCl (214 mg, 1.12 mmol, 1.1 equiv) in CH_2Cl_2 (4 mL) followed by Et_3N (0.17 mL, 1.23 mmol, 1.2 equiv). The mixture was stirred at rt for 6 h and diluted with CH_2Cl_2 (20 mL). The organics were washed with brine (2 x 5 mL), dried, concentrated, and purified by chromatography (5% to 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 ºC; ^{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_3Ar), 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 $C_{17}H_{24}NO_3S$ 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 ºC 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 ºC. The reaction mixture was stirred for 30 min at -78 ºC, 1 h at -30 ºC, and 6 h at 0 ºC, and quenched with sat. aq. NH_4Cl (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% to 40% EtOAc in hexanes) to give **9** (39 mg, 53%) as a white solid: R_f = 0.49 (50% hexane/EtOAc); mp 128 ºC; ^{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_3Ar), 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 $C_{23}H_{29}N_2O_2S$ 397.1944, found 397.1953.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)-1-(4-methylphenyl-sulfonyl)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% to 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_2Py), 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_2Py), 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_2Py), 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 $C_{23}H_{31}N_2O_2S$ 399.2101, found 399.2116.

(4a*RS*,5*RS*,7*SR*,8a*RS*)-7-Methyl-5-(pyridin-2-ylmethyl)decahydro-quinoline (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 ºC. 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_2Cl_2, filtered through a pad of Celite®, and washed thoroughly with CH_2Cl_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% to 5% MeOH in CH_2Cl_2): R_f = 0.22 (5:95 MeOH:CH_2Cl_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_2Py), 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_2Py), 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_2Py), 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)decahydro-quinoline (*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 $NaBH_3CN$ (18 mg, 0.287 mmol) at 0 ºC, and the mixture was stirred at rt for 30 min. The volatiles were evaporated and

the crude was purified on neutral alumina (CH_2Cl_2 to 5% MeOH in CH_2Cl_2) to give **2** (8.4 mg, 76% over two steps from **10**): R_f = 0.70 (5% CH_3OH in CH_2Cl_2). This sample was dissolved in CD_3OD and $NaOCD_3$ (0.1 M in CD_3OD) was added. ^1H and ^{13}C NMR spectra of the free base were obtained: ^1H NMR (400 MHz, CD_3OD, $NaOCD_3$) 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_2py), 2.88 (dm, *J* = 12.0 Hz, 1H, H-2eq), 3.19 (dd, *J* = 13.2, 4.0 Hz, 1H, CH_2py), 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_3OD, $NaOCD_3$) 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_2py), 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_3OD to the above sample of **2**: ^1H (400 MHz, CD_3OD, 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_2py), 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_2py), 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_3OD, 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_2py), 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_2Cl_2 (2 mL) before it was filtered through a pad of celite and washed through with CH_2Cl_2. The filtered solution was washed with 1 N NaOH, dried, and concentrated. To a solution of the above crude diamine in MeOH/ CH_2Cl_2 (1:1; 0.2 mL) were added in one portion UHP (30 mg, 0.31 mmol) and $Na_2WO_4 \cdot 2H_2O$ (2 mg, 0.006 mmol) and the mixture was stirred at rt for 72 h. After concentration, CH_2Cl_2 was added and the reaction mixture was filtered, concentrated and purified by chromatography (2.5 to 10% MeOH in CH_2Cl_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_2py), 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_2py), 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_2py), 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 $C_{17}H_{31}N_2O_2$ 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_2py), 2.40 (t, *J* = 6.0 Hz, 2H, H-2'), 2.60 (1H, m, H-8eq), 2.70 (m, 1H, CH_2py), 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_2py), 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 $C_{17}H_{31}N_2O_2$ 295.2380; found 295.2374.

ASSOCIATED CONTENT

Supporting Information

Tables for ^{1}H and ^{13}C NMR data of synthetic serralongamine 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**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: josep.bonjoch@ub.edu; benbradshaw@ub.edu;

Notes

The authors declare no competing financial interest.

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