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SYNTHESIS OF 7-DESMETHYL ANALOGS OF (+)- AND (−)-HUPERZINE A

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Abstract – The natural alkaloid (−)-huperzine A is an inhibitor of AChE and has been demonstrated to exert neuroprotection and to possess beneficial effects on other CNS related disorders. In this manuscript, we report the synthesis of the analogs of huperzine A in their enantiomeric form, starting from a common precursor that can be easily prepared in both the enantiomeric forms in high enantiomeric excess and at moderate costs.

INTRODUCTION

The natural compound (−)-huperzine A is a reversible inhibitor of acetylcholinesterase (AChE), and is known to exert beneficial effects such as the modification of beta-amyloid peptide processing, the attenuation of oxidative stress, and the regulation of the expression and secretion of nerve growth factor.[1-3] The capability of this molecule to slow down the onset of phenomena related to aging, makes it one of the widest spread nutraceuticals in the Chinese medicine. (−)-Huperzine A rapidly penetrates the Blood-Brain Barrier (BBB) and binds to the N-methyl-D-aspartate (NMDA) receptor, reducing glutamate and NMDA-induced toxicity.[4,5] By virtue of this action, pretreatment with (−)-huperzine A was found to have neuroprotective effects against nerve damaging agents such as soman, sarin, and VX, and the combined use of (−)-huperzine A and imidazenil has a preventing effect on diisopropyl fluorophosphate-induced neurotoxicity.[6] Although the unnatural enantiomer (+)-huperzine A is approximately three orders of magnitude less active as an AChE inhibitor, studies at the Walter Reed Army Institute of Research have demonstrated post-treatment neuroprotection effects of (+)-huperzine A against both NMDA- or diisopropyl fluorophosphate-induced seizures.[4] It might be then hypothesized that analogs of both (−)- and

(+)-huperzine A with an improved ability to interact with NMDA receptors, together with reduced AChE inhibition, will exhibit more effective neuroprotection against nerve agents. Therefore, an expedite way to synthesize analogs of both the enantiomers, preferably starting from a common easily available precursor, would be highly desirable.

RESULTS AND DISCUSSION

We have recently reported[7] the synthesis of huperzine A and its analogs **3** and **4** (Figure 1), as racemic mixture and single enantiomers, starting from intermediate **1**.[8-10]

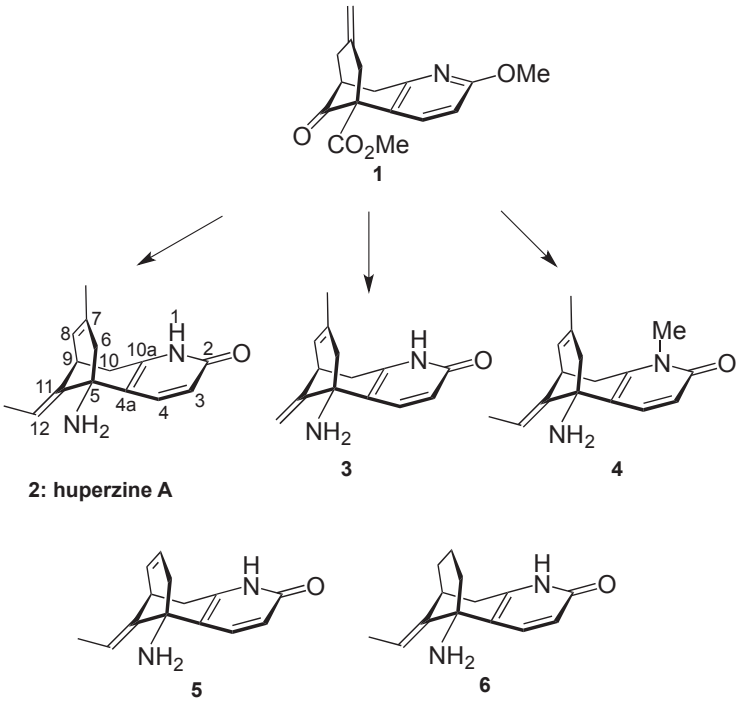


Figure 1. Derivatives prepared from common precursor **1**

This precursor has the advantage to be easily prepared in both the enantiomeric forms in high enantiomeric excess, and at moderate costs.[11] Therefore, the stereospecific synthesis of analogues can be promptly carried out. Although the huperzine A scaffold has been widely studied, defining a comprehensive Structure-Activity Relationship (SAR) with regard to its inhibitory properties of AChE, modifications at C-7 position have been only seldom investigated.[11-14] In our continuous efforts toward the preparation of huperzine A analogs, we herein report the expedited synthesis of the C-7 desmethylated derivatives **5** and **6** starting from the common precursor **1**. The products were prepared in both the enantiomeric forms (see data in the experimental part); however, the attempts to optimize some of the syntheses reported in this manuscript were performed in the racemic mixture, because of the reduced costs of producing the precursors. We envisioned that compound **8** (Figure 2), whose synthesis from **1** was earlier reported by Kozikowski,[11] would serve as a common precursor to both the desired compounds

5 and **6**. Initially we attempted synthesis of the olefin **10** by converting the hydroxyl group of **8** to a better leaving group such as the mesylate **9**, followed by elimination favored by a strong base to give the desired adduct (Scheme 1).

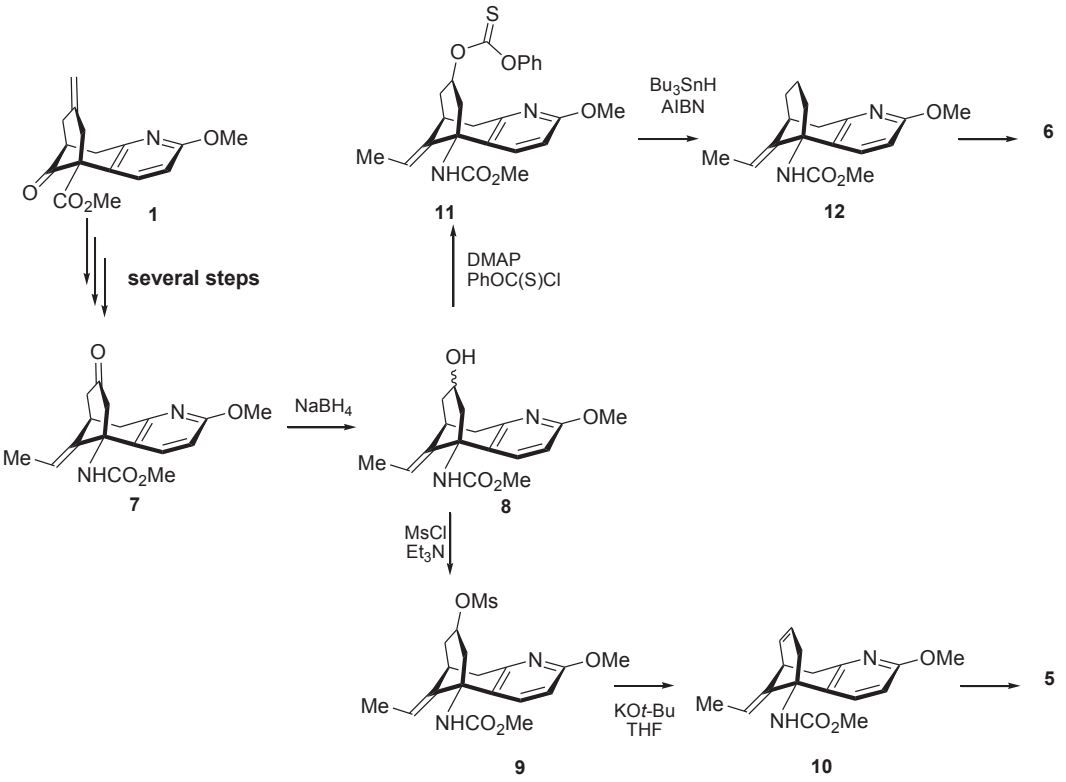
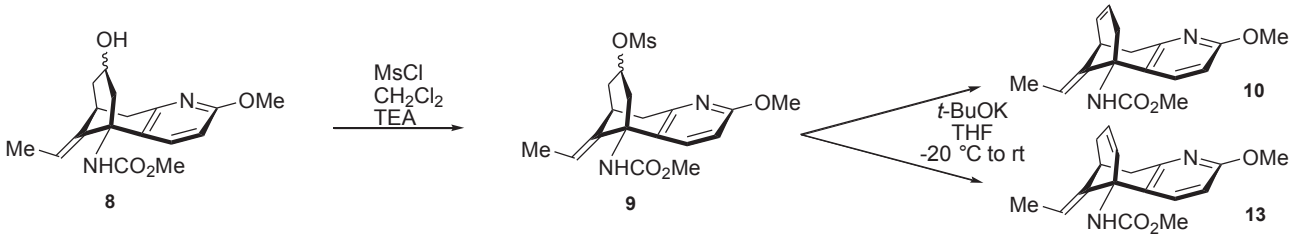
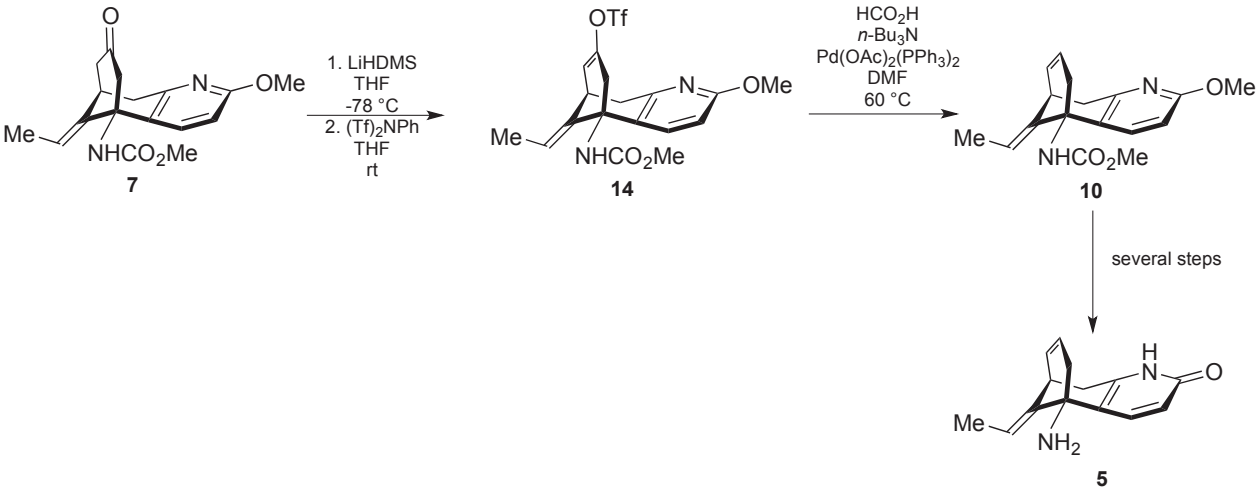


Figure 2. Planned synthesis of analogs **5** and **6**



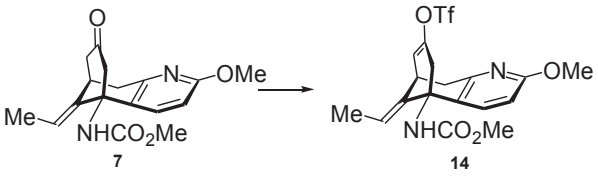
Scheme 1

However, due to the poor regioselectivity, both the isomers **10** and **13** were obtained (ca 1:1 ratio, according to HPLC), affecting the yields and leading to purification issues. Since the double bond of Huperzine A is in position 7,8, we deemed necessary to obtain only this isomer. A possible way to improve the yields would have been the isomerization of the 6,7 double bond of **13**, once obtained, with the use of thiophenol and AIBN for instance; however, since the presence of another isomerizable double bond in the molecule, this option was deemed of limited usefulness. As an alternative, we looked at the possibility of forming a vinyl triflate from intermediate **7**, that could then be removed through hydrogenation to yield compound **10** (Scheme 2).



Scheme 2

Table 1. Optimization of the triflation of compound **7**



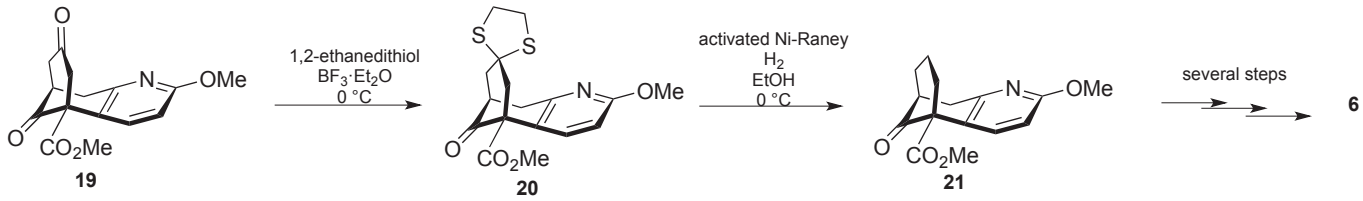
Base	Tf Source	Temp	yield
LDA	Comins' reagent	-78	no reaction
LDA	$(Tf)_2PhN$	-78	48[a]
LDA	$(Tf)_2O$	-78	20
LiHDMS	$(Tf)_2PhN$	-78	70%
t-BuOK	$(Tf)_2PhN$	0	no reaction
NaH	$(Tf)_2PhN$	0	no reaction

[a]After recovering of the starting material. Reaction does not go to consumption.

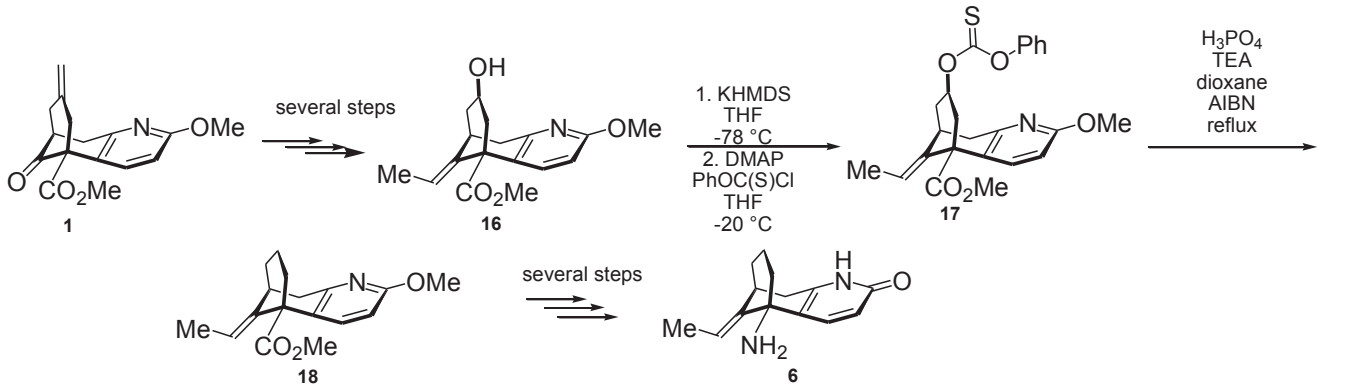
In a previous work,[11] it has been reported that isomerization of an exocyclic olefin at the C-7 position exclusively led to the most thermodynamically stable 7,8-endocyclic olefin without formation of the 6,7-isomer. Based on this, and on the fact that the stability of enolates follows the stability of underlying olefins, we reasoned that the regiochemistry of the final enol triflate is ultimately governed more by the stability of enolate rather than the site of deprotonation; therefore it was reasonable to assume that **14** would have been produced predominantly or exclusively irrespective of enolization conditions. We initially set out to investigate the reaction conditions with strong non-nucleophilic bases and the most widely used procedure in this case is the use of LDA and the Comins' reagent[15] (*N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide)) as the triflating agent, but surprisingly failed to obtain the

desired adduct. Therefore, we optimized the reaction conditions by adjusting some parameters of the reaction such as the base, the triflating agent, and the temperature (Table 1).

We found out that the best procedure to obtain derivative **14** in good yields was the use of LiHDMS in THF at -78 °C, with *N*-phenyl-bis(trifluoromethanesulfonimide) as the triflating agent.[16] It is intriguing to notice how little changes in the base (LDA *vs* LiHDMS) as well as in the triflating agent (Comins' reagent *vs* N-phenyl-bis(trifluoromethanesulfonimide) employed, could lead to such a different outcome; apparently, chemical manipulation of this heterocycle required strict control of the reaction conditions. In the attempt to give further insights into the best base to use for this reaction, bases other than the lithioamides were investigated. However, in the conditions tested, both NaH and *t*-BuOK failed to give the desired compounds. Interestingly, the 6,7 olefin was not detected by the HPLC analysis either with theromdymanic or with kinetic enolization conditions, corroborating the fact that the enol triflate formation was indeed dictated by the stability of the final enolate rather than the enolization conditions. The vinyl triflate **14** was then reacted with HCO_2H, $(nBu)_3N$, $Pd(OAc)_2(PPh_3)_2$ in DMF at room temperature,[17] obtaining in 80% yield compound **10**. This precursor, in turn, led to compound **5** after passing through the known synthetic protocol already reported.[18] For the synthesis of compound **6**, starting also in this case from **1**, we thought to exploit a straightforward synthetic procedure (Scheme 3) by preparing the dithiolane **20** from diketone **19**, that could then undergo a catalytic desulphurization using Ni-Raney and H_2, to yield the deoxygenated compound **21**.[19,20]



Scheme 3



Scheme 4

Unfortunately, the low yields, and the issues encountered in the purification of the reduced derivatives, prompted us to investigate other synthetic alternatives. Therefore, the synthesis of compound **6** relied on the formation of the thiocarbonate **17** from the 7-hydroxyl derivative **16** (Scheme 4). We initially did not find much success in obtaining the thiocarbonate by employing the most commonly used mild bases such as DMAP or pyridine. Therefore, a stronger base was used, and following a procedure reported by Danishefsky,[21] deprotonation of the alcoholic proton was made possible by using KHMDS and then adding the anion to a mixture of DMAP and PhOC(S)Cl in THF at -20 °C. Radical deoxygenation of **17** was carried out by treatment with aqueous H_3PO_4, TEA and AIBN in dioxane, according to the procedure reported by Barton.[22] Compound **18** underwent to similar reaction protocol as that reported in Scheme 1, to yield derivative **6** in ~40% overall yield starting from **16**.

In conclusion, we have reported a practical and easy route for the synthesis of intermediate **5** and **6,** in their enantiomeric forms, starting from intermediate **1.** This precursor can be easily prepared in pure enantiomers, and, as already described, has been successfully used for the preparation of several substituted huperzine derivatives.

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz, respectively, with TMS as an internal standard. Standard abbreviation indicating multiplicity was used as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, m = multiplet and br = broad. HRMS experiments were performed on Q-TOF-2TM (Micromass) and IT-TOF (Shimadzu) instruments. TLC was performed with Merck 60 F254 silica gel plates. Flash chromatography was performed using CombiFlash® Rf system with RediSep® columns or alternatively using Merck silica gel (40–60 mesh). Final compounds were purified by preparative HPLC unless otherwise stated. The preparative HPLC employed an ACE 5-AQ (21.2 mm × 150 mm) column, with detection at 254 and 280 nm on a Shimadzu SCL-10A VP detector, flow rate = 17.0 mL/min. Method 1: 50–100% MeOH/H_2O in 30 min; 100% MeOH in 5 min; 100–50% MeOH/H_2O in 4 min. Method 2: 25–100% MeOH/H_2O in 30 min; 100% MeOH in 5 min; 100–25% MeOH/H_2O in 4 min. Method 3: 15-100% MeOH/H_2O in 30 min; 100% MeOH in 5 min; 100–15% MeOH/H_2O in 4 min. Both solvents contains 0.05 vol % of trifluoroacetic acid (TFA). Purities of final compounds were established by analytical HPLC, which was carried out using the Agilent 1100 HPLC system with a Synergi 4 μm Hydro-RP 80A column, on a variable wavelength detector G1314A. Method 1: flow rate = 1.4 mL/min; gradient eluation over 20 min, from 30% MeOH-H_2O to 100% MeOH with 0.05% TFA. Method 2: flow rate = 1.4 mL/min; gradient eluation over 20 min, from 50% MeOH-H_2O to 70% MeOH with 0.05% TFA. The purity of all tested compounds was >95% as determined by the method described above.

Methyl (11-*E*-ethylidene-7,8,9,10-tetrahydro-7-(phenoxythiocarbonyl)-2-methoxy-5,9-methano-cycloocta[*b*]pyridin-5(6*H*)-yl)-carboxylate 17. To a solution of **16** (45 mg, 0.148 mmol) in THF (2 mL) was added KHMDS (0.5 M in toluene, 1.036 mmol) at -78 °C. The solution was stirred at the same temperature for 30 min and then added to a solution of of DMAP (145 mg, 1.18 mmol) and PhOC(S)Cl (0.159 mL, 1.18 mmol) in THF at -20 °C, and the resultant mixture was stirred at the same temperature for 3 h. After warming at rt, the reaction mixture was diluted with EtOAc, washed with water and brine and dried over anhydrous Na_2SO_4. Flash column cromatography (hexanes/EtOAc 0→50%) gave **17** as a dark brown oil (71%) used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 1.75 (d, *J* = 6.8 Hz, 3H), 2.10-2.40 (m, 2H), 2.52-2.69 (m, 1H), 2.70-2.72 (m, 1H), 3.10 (d, *J* = 20 Hz, 1H) 3.35-3.53 (m, 2H), 3.87 (s, 3H), 3.98 (s, 3H) 5.22 (q, *J* = 6.8 Hz, 1H), 6.72 (d, *J* = 6.8 Hz, 1H), 6.86 (d, *J* = 8 Hz, 2H) 7.20-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) 12.0, 28.6, 36.8, 41.4, 52.0, 53.2, 54.6, 54.8, 107.0, 107.4, 116.8, 118.2, 126.0, 128.5, 135.1, 135.4, 139.3, 152.6, 161.2, 173.8, 192.8. LRMS calculated for $C_{24}H_{25}NO_5S$ 440,14 $[M+H]^+$, found 440.

Methyl (11-*E*-ethylidene-7,8,9,10-tetrahydro-2-methoxy-5,9-methanocycloocta[*b*]pyridin-5(6*H*)-yl)-carboxylate 18. A solution of **17** (48 mg, 0.1 mmol), H_3PO_4 (57 μL, 0.5 mmol) and TEA (78 μL, 0.5 mmol) in dioxane (3 mL) at reflux was treated at 30 min intervals with 41 μL of a solution 4.5M of AIBN in dioxane. After consumption of the starting material (please note that the reaction is checked through analytical HPLC, as the spots on TLC are too close to see the reaction development), the solvent was evaporated and the solid dissolved in EtOAc, washed with water and dried. Column chromatography (hexanes/EtOAc 0→40%) gave **18** as a colorless semisolid in 77% yield. ^{1}H NMR ($CDCl_3$) δ 1.19-1.28 (m, 1H), 1.55-1.81 (m, 6H), 2.12-2.19 (m, 1H), 2.82-2.86 (m, 2H), 3.17-3.32 (m, 2H), 3.90 (s, 3H), 4.16 (s, 3H), 5.07 (q, *J* = 7.2 Hz, 1H), 6.32 (d, *J* = 9.2 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 12.0, 18.4, 30.4, 34.2, 38.2, 38.5, 53.0, 62.5, 63.9, 107.0, 114.1, 125.7, 137.3, 130.0, 154.4, 161.9, 175.4; LRMS calculated for $C_{17}H_{21}NO_3$ 288,15 $[M+H]^+$, found 288.

Methyl (11-*E*-ethylidene-2-methoxy-7-(trifluoromethansulfonyloxy)-5,9-methanocycloocta[*b*]-pyridine-5(6*H*)-yl)-carbamate 14. A solution of ketone **7** (210 mg, 0.66 mmol) in THF (10 mL) was added to a solution of LiHMDS (1M in THF, 2.65 mL, 2.65 mmol) at -78 °C and the mixture allowed to stir for 1 h. A solution of $(Tf)_2NPh$ (946 mg, 2.65 mmol) in THF (1 mL) was then added and the reaction was stirred overnight at rt. Please note that 4 equiv of base and $(Tf)_2NPh$ have been added, while in the reference[20] only 2 equiv were used. After evaporation of the solvent, the resultant yellow oil was purified by flash chromatography (hexanes/EtOAc 0→40%) to yield 220 mg (74%) of the enol triflate **14** as a colorless semisolid. ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 1H), 1.74-1.82 (m, 4H), 2.56 (d, *J* = 18 Hz, 1H), 2.86-3.20 (m, 2H), 3.53 (s, 3H), 3.96-4.00 (m, 4H), 5.51 (q, *J* = 6.8 Hz, 1H), 6.00 (bs, 1H), 7.07 (d, *J* =

9.2 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) 10.8, 30.7, 35.1, 43.4, 50.7, 54.7, 56.7, 99.6, 107.8, 115.4, 121.6, 130.5, 131.4, 140.4, 146.0, 149.5, 155.4, 161.6; LRMS calculated for $C_{18}H_{19}F_3N_2O_6S$ 449,0916, $[M+H]^+$, found 449.2.

Methyl (11-*E*-ethylidene-2-methoxy-5,9-methanocycloocta[*b*]pyridine-5(6*H*)-yl)-carbamate (10). A solution of **14** (220 mg, 0.49 mmol), HCO_2H (37 µL, 0.98 mmol), nBu_3N (346 µL, 1.47 mmol), $Pd(OAc)_2(PPh_3)_2$ (18 mg, 0.0245 mmol) in DMF (3 mL) was stirred at 60 °C under argon atmosphere for 3 h until consumption of the starting material monitored by analytical HPLC. The mixture was poured in ice water, and the organic phase extracted with EtOAc, washed with water and dried over brine and Na_2SO_4. The resultant oil was purified by flash chromatography (hexanes/EtOAc 0→40%) to yield derivative **10** as a white solid (135 mg, 90%). ^{1}H NMR ($CDCl_3$) δ 1.75 (d, *J* = 8 Hz, 3H) 2.36-2.41 (m, 2H), 3.00-3.20 (m, 2H), 3.54 (s, 3H), 3.84 (bs, 1H), 4.02 (s, 3H), 5.44 (bs, 1H), 5.41-5.57 (m, 2H), 5.81 (bs, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H); LRMS calculated for $C_{17}H_{20}N_2O_3$ 301,1474 $[M+H]^+$, found 301.2.

(–)-5,9-Methanocycloocta[*b*]pyridin-2(1*H*)-one, 5-amino-11-ethylidene-5,6,9,10-tetrahydro-(5*R*,9*R*,11*E*) ((–)-5): ^{1}H NMR (MeOD) δ 1.81 (d, *J* = 6.8 Hz, 1H) 2.00 (s, 1H), 2.52-2.71 (m, 3H), 2.99-3.06 (m, 3H), 3.83 (bs, 2H), 5.49 (q, *J* = 7.2 Hz, 2H), 5.65 (bs, 1H), 5.86 (bs, 1H) 6.51 (d, *J* = 9.2 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (MeOD) 10.9, 31.9, 33.8, 39.7, 56.2, 113.8, 115.7, 117.4, 123.2, 129.4, 133.1, 137.2, 144.2, 163.7; HPLC purity: 98.8%. HRMS for $C_{14}H_{16}N_2O$ ESI M-H^+ exp: 227.1189, found 227.1201. White solid. $[\alpha]_D^{20}$ =-662,2

(+)-5,9-Methanocycloocta[*b*]pyridin-2(1*H*)-one, 5-amino-11-ethylidene-5,6,9,10-tetrahydro-(5*S*,9*S*,11*E*) ((+)-5): ^{1}H NMR (MeOD) δ 1.76 (d, *J* = 6.8 Hz, 1H) 1.93 (s, 1H), 2.40-2.80 (m, 3H), 2.85-2.95 (m, 3H), 3.83 (bs, 2H), 5.41 (q, *J* = 7.2 Hz, 2H), 5.61 (bs, 1H), 5.79 (bs, 1H) 6.42 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (MeOD) 10.8, 32.0, 33.8, 39.7, 56.2, 113.7, 115.3, 117.4, 123.2, 129.4, 133.3, 136.9, 144.4, 163.5; HPLC purity: 98.8%. HRMS for $C_{14}H_{16}N_2O$ ESI M-H^+ exp: 227.1189, found 227.1201. White solid. $[\alpha]_D^{20}$ = +694,5

(–)-5,9-Methanocycloocta[*b*]pyridin-2(1*H*)-one, 5-amino-11-ethylidene-5,6,7,8,9,10-hexahydro--(5*R*,9*R*,11*E*) ((–)-6): ^{1}H NMR (MeOD) δ 1.30-2.00 (m, 9H), 2.7 (d, *J* = 20 Hz, 1H), 2.98-3.06 (m, 3H), 3.49 (s, 1H), 5.44 (q, *J* = 7.2 Hz, 1H), 6.45 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H); ^{13}C NMR (MeOD) 10.6, 18.2, 29.5, 32.1, 32.9, 38.3, 57.3, 111.2, 113.9, 117.2, 135.9, 136.2, 145.8, 163.0; HPLC purity: 98.7%. HRMS ESI for $C_{14}H_{18}N_2O$ M+H^+ exp: 231.1491, found 231.1495. White solid. $[\alpha]_D^{20}$ = -127,2

(+)-5,9-Methanocycloocta[*b*]pyridin-2(1*H*)-one, 5-amino-11-ethylidene-5,6,7,8,9,10-hexahydro--(5*S*,9*S*,11*E*) ((+)-6): ^{1}H NMR (MeOD) δ 1.30-1.95 (m, 9H), 2.7 (d, *J* = 20 Hz, 1H),

2.99-3.06 (m, 3H), 3.49 (s, 1H), 5.42 (q, J = 7.2 Hz, 1H), 6.47 (d, J = 9.2 Hz, 1H), 7.54 (d, J = 9.2 Hz, 1H); ^{13}C NMR (MeOD) 10.6, 18.2, 29.5, 32.1, 32.9, 38.3, 57.3, 113.2, 114.0, 117.2, 135.9, 136.1, 145.8, 163.2; HPLC purity: 100%. HRMS ESI for $C_{14}H_{18}N_2O$ M+H$^+$ exp: 231.1491, found 231.1495. White solid. $[\alpha]_D^{20}$ = +105,8

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