Pergamon

Tetrahedron 56 (2000) 3181–3187

TETRAHEDRON

A Formal Synthesis of (+)-Huperzine A

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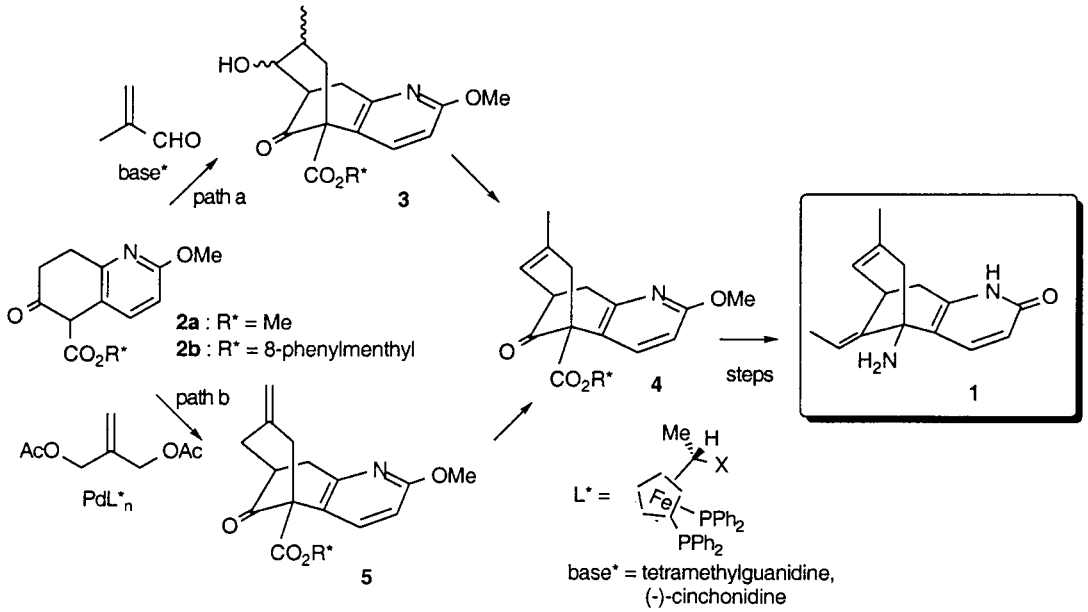
Received 14 January 2000; accepted 14 March 2000

Abstract—A new formal stereoselective synthesis of (+)-Huperzine A (**1**) was achieved using as a key step a palladium mediated annulation between 2-methylene-1,3-propanediol diacetate and (1*R*,2*S*)-2-phenylcyclohexanol derived β-ketoester **2c**.

(−)-Huperzine A (**1**) isolated from *Huperzia serrata*,[1] a plant used in Chinese folk medicine, is a very potent inhibitor of acetylcholinesterase and is currently under clinical trial for the treatment of Alzheimer's disease.[2] This particular biological activity induced several synthetic studies which culminated with two total syntheses by Qian[3] and Kozikowski.[4] In both syntheses, β-ketoester **2** is a central synthon (Scheme 1).

Two strategies have been used for the synthesis of Huperzine A (**1**), either a particular case of the Robinson annulation already used by Raphael[5] or a palladium-catalysed bicycloannulation first studied by Gravel[6] on a model system. The first synthesis of (−)-huperzine A (**1**) was described by Kozikowski[7] using the Michael-aldol annulation (path a) with a (−)-8-phenylmenthol as chiral auxiliary. A different approach using a chiral base was more recently studied by Terashima.[8]

The same group also developed an asymmetric palladium-catalysed bicycloannulation following path b.[8] A modified chiral ferrocenyl ligand previously developed by Hayashi[9]



Scheme 1.

Keywords: alkaloids; palladium; cyclisation.
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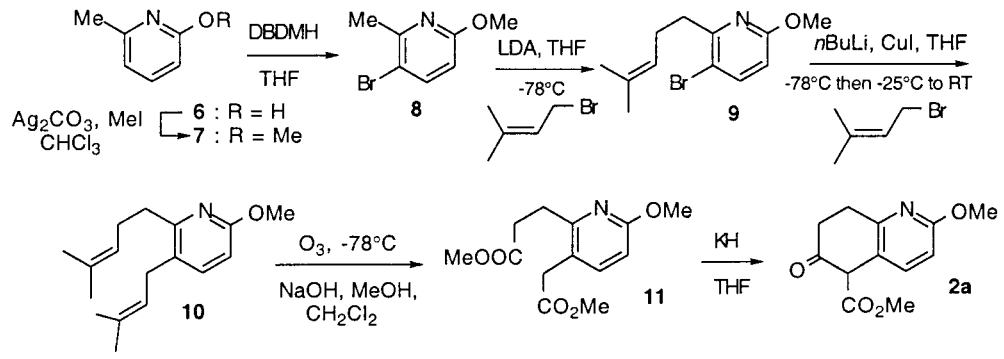


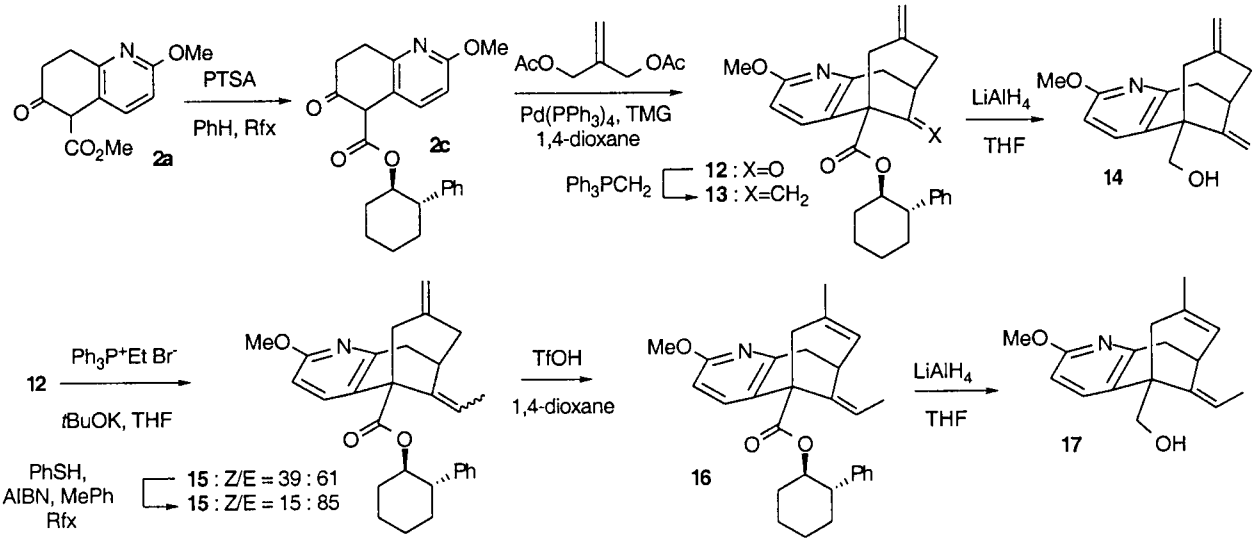
Scheme 2.

was used. A rather similar result was obtained by He and Bai.[10] The diastereo- or enantiomeric excesses of these syntheses were in a range of 52 to 80% (Scheme 1).

Herein we report as a full account[11] a new efficient formal synthesis of (+)-huperzine A (**1**). Classical *O*-alkylation of the commercially available 2-hydroxy-6-methylpyridine (**6**) afforded 2-methoxy-6-methylpyridine (**7**) in 97% yield (Scheme 2). Bromination of **7** with dibromodimethylhydantoin[12] afforded 5-bromo-2-methoxy-6-methylpyridine (**8**) in 85% yield. Deprotonation of the methyl side chain in compound **8** with lithium diisopropyl amide at low temperature followed by alkylation with 4-bromo-2-methyl-2-butene[13] gave rise to the expected pyridine derivative **9** isolated in 74% yield. Low temperature halogen–lithium exchange on the bromo pyridine derivative **9** and transmetallation with copper (I) iodide[14] followed by alkylation with 4-bromo-2-methyl-2-butene led in 72% yield to the pyridine derivative **10**.

The oxidative cleavage of the alkenyl appendages in compound **10** was in turn studied. The use of the Sharpless oxidative reagent,[15] i.e., $RuCl_3$ (catalytic), $NaIO_4$, MeCN, CCl_4, H_2O, was first examined. After diazomethane esterification of the resulting diacid intermediate, diester **11** was obtained in modest yield together with an unexpected degradation product, lacking the side chain on carbon 5. Better results were obtained with ozonolysis in alkaline medium as described by Marshall.[16] Under these conditions, the diester **11** was directly isolated in 53% yield. With the two trisubstituted double bonds on the side chains as in compound **10**, the reaction can be performed, without decomposition, on a larger scale (1.2 g) than in our previous study using monosubstituted double bonds.[13] Dieckmann cyclisation on diester **11** in the presence of potassium hydride afforded the cornerstone ketoester **2a** in 91% yield.[4b] This compound, which proved to be rather unstable, was obtained in six steps and 21% overall yield from 2-hydroxy-6-methylpyridine (**6**) (Scheme 2).

Retrosynthetic analysis and results already published in the literature reveal a potential convenient route to the huperzine A skeleton via an asymmetric palladium-catalysed annulation. In order to overcome the difficulty which is inherently present in the use of asymmetric catalysis with chiral ligands,[8,10,17] we decided to use a stoichiometric chiral auxiliary in this process. Enantiomerically pure (+)- and (−)-2-phenylcyclohexanols, both available by the use of the asymmetric Sharpless dihydroxylation reaction,[18] seemed to be good candidates for such a reaction as far as an interaction between the two aromatic moieties could be expected in the transition state.



Scheme 3.

Transesterification of ketoester **2a** with (1*R*, 2*S*)-2-phenylcyclohexanol afforded the corresponding ester **2c** in 84% yield (Scheme 3). A modification of the conditions described by Kozikowski[19] for the racemic annulation was selected. Accordingly, tetrakis(triphenylphosphine)palladium was used instead of palladium diacetate in the presence of triphenylphosphine. Annulation was performed with 0.1 equiv. of palladium catalyst and 1.1 equiv. each of 2-methylene-1,3-propanediol diacetate and tetramethylguanidine at room temperature for 18 h. Under these conditions, the expected annulated compound **12** was isolated in 75% yield.

The diastereoselectivity of this reaction was estimated after a three step sequence of reactions. Wittig olefination of compound **12** afforded the *exo* methylene derivative **13**[20] (yield: 70%) which was subsequently reduced giving rise to the primary alcohol **14** in 95% yield. Mosher ester of **14** was then prepared in the same yield. ^{19}F NMR analysis of this Mosher ester and comparison with the same ester prepared by acylation of (±)-**14** allowed to measure a diastereomeric excess of 92% for compound **14** and consequently for ketoester **12** (Scheme 3).[21] This asymmetric palladium-catalysed annulation competes favourably with the catalytic processes described previously[8,10] with regard to both yield and diastereoselectivity.

Having succeeded in the asymmetric step, the synthesis was completed as follows. Wittig olefination with ethylidenetriphenylphosphorane afforded after 4 days at room temperature compound **15** (Scheme 3) as a 39:61 mixture of *Z* and *E* isomers in 89% yield.[22] Higher temperature produced extensive degradation. According to Kozikowski,[7a] radical isomerisation was first performed with benzenethiol and AIBN in toluene at 110°C and gave rise to a 15/85 mixture of *Z* and *E* isomers of **15** after 7 days. Isomerisation of the *exo* methylene double bond was achieved in the presence of triflic acid in dioxane in a sealed tube. The resulting compound **16**, isolated in 88% yield, was in turn quantitatively reduced giving rise to the known primary alcohol **17**, a direct synthetic precursor of huperzine A (Scheme 3).[7a] It was subsequently discovered that the isomerisation of the double bonds could be conducted in a single step by reacting the 39:61 mixture of **15** with triflic acid in dioxane to afford directly compound **16** in 86% yield after 48 h. The high regio- and stereoselectivity of this process is worth noting.

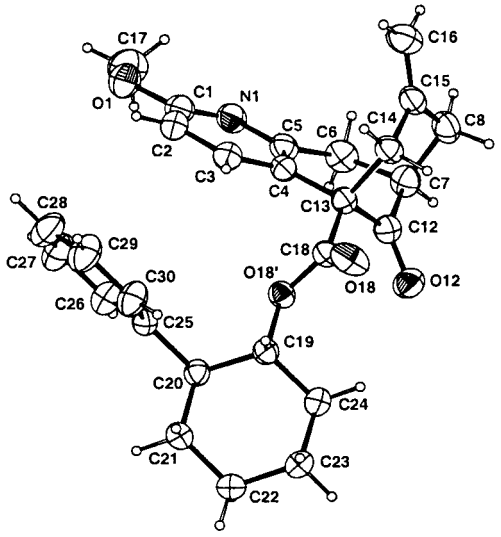


Figure 1. ORTEP drawing of **12**. (Displacement ellipsoids are drawn at 30% probability level.)

The measure of the optical rotation of alcohol **17** showed the same absolute value as the product described by Kozikowski[7a] but the reverse sign ($[\alpha]_D$=+37 (*c* 1, $CHCl_3$)) indicating that **17** is antipodal to the natural series. The use of (1*S*,2*R*)-2-phenylcyclohexanol would obviously provide an access to natural (−)-huperzine A (**1**).

Absolute configuration has also been secured by the X-ray analysis of compound **12**. The molecular structure and labelling scheme are shown in Fig. 1. The crystal structure of (−)-huperzine A (**1**) has been established by Kozikowski et al.[23] The conformations of huperzine A (**1**) and **12** are similar except for the C8–C15 bridge. In huperzine A (**1**) C8–C15 is a double bond and C16 is a methyl group while in **12** C15–C16 is a methylene group. The six membered ring C7 to C12 is chair shaped in **12** while it is a half-chair in huperzine A (**1**).[24,25]

In summary, a new efficient access to alcohol **17**, a precursor of (+)-huperzine A, has been achieved. This compound was prepared in 12 steps from 2-hydroxy-6-methylpyridine **6** in 11.5% overall yield and with an enantiomeric excess of 92%. Application of the same strategy to the synthesis of (−)-huperzine B[26] is currently under investigation.

Experimental

General

^{1}H and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, respectively unless noted otherwise. Optical rotations were recorded at 20°C. Elemental analyses were performed at the CNRS, Gif sur Yvette, France. Unless otherwise stated, chromatographic purifications were performed on a column with 230–400 mesh silica gel (Merck 9385) using the indicated solvent system. Dichloromethane was distilled from calcium hydride. Toluene, diethyl ether and THF were distilled from sodium metal/benzophenone ketyl. Methanol was distilled from magnesium.

2-Methoxy-6-methylpyridine (7). A solution of 2-hydroxy-6-methylpyridine (**6**) (80 g, M_w=109 g mol^{-1}, 734 mmol), silver carbonate (273 g, M_w=275.75 g mol^{-1}, 990 mmol, 1.35 equiv.) and iodomethane (470 mL, *d*=2.280, 1071.6 g, M_w=141.94 g mol^{-1}, 7.55 mol, 10.3 equiv.) in chloroform (2.8 L) was stirred for 60 h in the dark. The reaction mixture was then filtered through a Celite pad, and the solids were washed three times with 300 mL of ether. After evaporation at a temperature below 20°C, distillation under reduced pressure (bp=80°C/14 mmHg) gave **7** (87.6 g, M_w=123 g mol^{-1}, 712 mmol, 97%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.42 (t, 1H, *J*=8.3 Hz, C_4-H), 6.68 (d, 1H, *J*=8.3 Hz, C_5-H), 6.51 (d, 1H, *J*=8.3 Hz, C_3-H), 3.89 (s, 3H, OMe), 2.40 (s, 3H, Me).^{13}C NMR ($CDCl_3$): δ 163.7 (C_2), 156.2 (C_6), 138.6 (C_3), 115.6 (C_5), 107.0 (C_4),

53.1 (OMe), 24.1 (Me). IR (ν_{max}, cm^{-1}, film): 1585, 1462, 1420, 1295, 1040, 800. HRMS: Calculated: 123.0684, found: 123.0680, Δmmu=0.4.

5-Bromo-2-methoxy-6-methylpyridine (8). To a solution of **7** (22 g, M_w=123 g mol^{-1}, 178.8 mmol) in freshly distilled THF (1.54 L) under argon, was added 1,3-dibromo-5,5-dimethylhydantoin (51.1 g, M_w=285.93 g mol^{-1}, 178.8 mmol). The reaction mixture was stirred for 72 h in the dark. After addition to a 10% solution of $Na_2S_2O_3$ in water (1 L) diethylether was added (1 L). The aqueous phase was extracted with diethyl ether (2×500 mL). The combined organic phases were dried over $MgSO_4$, filtered, evaporated and purified by distillation to give **8** (30.6 g, M_w=202 g mol^{-1}, 151.4 mmol, 97%) as a colourless oil. Bp=95°C/18 mmHg. ^{1}H NMR ($CDCl_3$): δ 7.57 (d, 1H, *J*=8.8 Hz, C_4-H), 6.43 (d, 1H, *J*=8.8 Hz, C_3-H), 3.86 (s, 3H, OMe), 2.52 (s, 3H, Me). ^{13}C NMR ($CDCl_3$): δ 162.4 (C_2), 154.4 (C_6), 142.0 (C_3), 111.7 (C_5), 109.5 (C_4), 53.5 (OMe), 24.5 (Me). IR (ν_{max}, cm^{-1}, film): 2950, 1581, 1467, 1423, 1315, 1254, 1127, 1044, 995, 650. HRMS: Calculated: 200.9804 and 202.9786, found: 200.9789 and 202.9770, Δmmu=−1.5 and −1.6.

5-Bromo-2-methoxy-6-(4-methyl-3-pentenyl)pyridine (9). To freshly distilled diisopropylamine (22.6 mL, *d*=0.722, 16.3 g, M_w=101.19 g mol^{-1}, 161 mmol, 2.5 equiv.) in anhydrous THF (430 mL), was added under argon at 0°C, a 1.6 M solution of *n*-butyllithium in hexanes (101.4 mL, 162.2 mmol, 2.5 equiv.). The reaction mixture was stirred at 0°C for 30 min and cooled to −78°C, and a solution of **8** (13 g, M_w=202 g mol^{-1}, 64 mmol) in anhydrous THF (430 mL) was then added in 30 min. After stirring for 30 min more at −78°C, freshly distilled 4-bromo-2-methyl-2-butene (3,3-dimethylallyl bromide, prenyl bromide, 22.1 mL, *d*=1.293, 28.6 g, M_w=149.04 g mol^{-1}, 192 mmol, 3 equiv.) was added dropwise. After 1 h at −78°C, the reaction mixture was quenched at this temperature with saturated NH_4Cl (200 mL) and extracted with ether (4×600 mL). The combined organic phases were dried over $MgSO_4$, filtered, evaporated and the residue was purified by silica gel column chromatography (pentane, pentane/ethyl acetate 99/1, 98/2, 97/3, 96/4, 95/5, 94/6, 93/7, 90/10) to afford **9** (12.8 g, M_w=270 g mol^{-1}, 47.4 mmol, 74%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 1H, *J*=8.1 Hz, C_4-H), 6.43 (d, 1H, *J*=8.1 Hz, C_3-H), 5.21 (m, 1H, C=C*H*), 3.87 (s, 3H, OMe), 2.82 (m, 2H, Ar-CH_2), 2.37 (m, 2H, CH-CH_2), 1.66 and 1.56 (2s, 2×3H, 2 Me). ^{13}C NMR ($CDCl_3$): δ 162.3 (C_2), 157.1 (C_6), 142.2 (C_3), 132.2 (C_{10}), 123.5 (C_9), 111.6 (C_5), 109.4 (C_4), 66.4 (Ar-*C*H_2), 53.5 (OMe), 37.1 (CH-*C*H_2), 26.7 and 25.7 (2 Me). IR (ν_{max}, cm^{-1}, film): 2968, 2925, 2856, 1575, 1461, 1417, 1311, 1255, 1117, 1040, 1008, 819, 644. HRMS: Calculated: 269.0420 and 271.0399, found: 269.0415 and 271.0396, Δmmu=−0.5 and −0.3.

2-Methoxy-5(3-methyl-2-butenyl)-6-(4-methyl-3-pentenyl)-pyridine (10). To a solution of **9** (6.5 g, M_w=270 g mol^{-1}, 24.1 mmol) in anhydrous THF (117 mL) at −78°C under argon, was added slowly a 1.6 M solution of *n*-butyllithium in hexanes (31.2 mL, 49.9 mmol, 2.1 equiv.). The solution became red. After stirring for 5 min at −78°C, tlc with ethyl acetate/pentane (2:98) showed that the Br/Li exchange was complete. The reaction mixture was slowly (within approximately 15 min) warmed to −30°C, and copper(I) iodide (955 mg, M_w=190.44 g mol^{-1}, 5 mmol, 0.2 equiv.) was added (the solution became brown). After stirring for 5 min at −25°C, freshly distilled 4-bromo-2-methyl-2-butene (3,3-dimethylallyl bromide, prenyl bromide, 8.6 mL, *d*=1.293, 11.13 g, M_w=149.04 g mol^{-1}, 74.7 mmol, 3.1 equiv.) was added dropwise, and the reaction mixture was warmed to room temperature and finally stirred for 1 h. Quenching with saturated NH_4Cl (26 mL) and water (13 mL), followed by successive extractions with ethyl acetate (2×300 mL), ether (2×300 mL) and methylene chloride (300 mL), drying of the combined organic phases over $MgSO_4$, filtration, evaporation and purification by silica gel column chromatography (pentane, pentane/ethyl acetate 99/1, 98/2, 97/3, 96/4, 95/5, 94/6, 93/7, 90/10) afforded **10** (4.5 g, M_w=259 g mol^{-1}, 17.3 mmol, 72%) as a colourless oil. ^{1}H NMR ($CDCl_3$): δ 7.58 (d, 1H, *J*=8.1 Hz, C_4-H), 6.43 (d, 1H, *J*=8.1 Hz, C_3-H), 5.21 (m, 1H, C_9-H), 3.87 (s, 3H, OMe), 2.82 (m, 2H, 2C_7-H), 2.37 (m, 2H, 2C_8-H), 1.66 and 1.56 (2 s, 2×3H, 2 Me). ^{13}C NMR ($CDCl_3$): δ 162.3 (C_2), 157.1 (C_6), 142.2 (C_3), 132.2 (C_{10}), 123.5 (C_9), 111.6 (C_5), 109.4 (C_4), 66.4 (C_7), 53.5 (OMe), 37.1 (C_8), 26.7 and 25.7 (2Me). IR (ν_{max}, cm^{-1}, film): 2968, 2925, 2856, 1575, 1461, 1417, 1311, 1255, 1117, 1040, 1008, 819, 644. HRMS: Calculated: 269.0420 and 271.0399, found: 269.0415 and 271.0396, Δmmu=−0.5 and −0.3.

2-Methoxy-6-(2-methoxycarbonylethyl)-5-methoxycarbonylmethylpyridine (11). To a solution of **10** (1.2 g, M_w=259 g mol^{-1}, 4.63 mmol) in distilled methylene chloride (18 mL) was added a solution of NaOH (1.86 g) in distilled methanol (18 mL). At −78°C, ozone was passed slowly through the solution. After 45 min, the reaction mixture was diluted with ethyl acetate (40 mL), and water (6 mL) and saturated NH_4Cl (7 mL) were successively added. The reaction mixture was allowed to warm to room temperature. After extraction with ethyl acetate (3×100 mL) and methylene chloride (100 mL), the combined organic phases were dried over $MgSO_4$, filtered, and evaporated to give an oil. After dilution with 10 mL of methylene chloride (10 mL), treatment with a CH_2N_2 solution in ether gave after evaporation an oil which was purified by silica gel column chromatography (pentane, pentane/ethyl acetate 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1, 3/1, 2/1) to afford **11** (643 mg, M_w= 267 g mol^{-1}, 2.41 mmol, 52%). ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 1H, *J*=8.6 Hz, C_4-H), 6.55 (d, 1H, *J*=8.6 Hz, C_3-H), 3.87 (s, 3H, Ar-OMe), 3.70 and 3.68 (2 s, 2×3H, 2 OMe), 3.62 (s, 2H, Ar-CH_2-CO), 3.05 (t, 2H, *J*=7.0 Hz, Ar-CH_2), 2.85 (t, 2H, *J*=7.0 Hz, CH_2-CO). ^{13}C NMR ($CDCl_3$): δ 173.9 (C=O), 171.6 (C=O), 162.4 (C_2), 155.1 (C_6), 140.7 (C_3), 111.8 (C_5), 107.9 (C_4), 53.1 (Ar-OMe), 52.0 and 51.6 (2OMe), 36.7 (Ar-*C*H_2CO), 31.4 (*C*H_2CO), 28.7 (Ar-*C*H_2). IR (ν_{max}, cm^{-1}, film): 2952, 1734, 1598, 1582, 1477, 1437, 1297, 1200, 1159, 1038, 815. HRMS: Calculated: 267.1106, found: 267.1088, Δmmu=1.8.

5,6,7,8-Tetrahydro-2-methoxy-6-oxo-5-quinolinecarboxylic acid methyl ester (2a).[4b] To a suspension of potassium hydride (freshly washed with anhydrous pentane, 450 mg, M_w=40.11 g mol^{-1}, 11.2 mmol, 1.2 equiv.) in

freshly distilled THF (50 mL) under argon was slowly added a solution of **11** (2.5 g, M_w=267 g mol^{-1}, 9.4 mmol) in anhydrous THF (37 mL). The reaction mixture was stirred for 30 min and then saturated NH_4Cl (125 mL) and HCl 0.1 N (62 mL) were successively added. After extraction with ether (100 mL) and ethyl acetate (2×100 mL), the combined organic phases were dried on $MgSO_4$, filtered and evaporated to give a yellow oil which was purified by silica gel column chromatography (pentane/ethyl acetate 7/3) to afford **2a** (2 g, M_w=235 g mol^{-1}, 8.5 mmol, 91%), which was used rapidly for the next step. ^{1}H NMR ($CDCl_3$): δ 13.18 (s, 1H, OH), 7.91 (d, 1H, J=8.7 Hz, C_4-H), 6.57 (d, 1H, J=8.7 Hz, C_3-H), 3.91 (s, 3H, Ar-OMe), 3.90 (s, 3H, OMe), 2.95 (dd, 2H, J=9.6 Hz, J=8.2 Hz, C_7-H), 2.63 (dd, 2H, J=9.6 Hz, J=8.2 Hz, C_8-H). ^{13}C NMR ($CDCl_3$): δ Identical to the literature, see Ref. 4b. IR (ν_{max}, cm^{-1}, film): 2954, 1738, 1639, 1601, 1567, 1478, 1448, 1426, 1300, 1281, 1263, 1227, 1115, 1058, 1036, 1016, 826.

5,6,7,8-Tetrahydro-2-methoxy-6-oxo-5-quinolinecarboxylic acid, (1*R*,2*S*)-2-phenylcyclohexyl ester (2c). To a solution of **2a** (1.5 g, M_w=235 g mol^{-1}, 6.4 mmol) in freshly distilled benzene (150 mL) under argon were successively added *p*-toluenesulphonic acid monohydrate (112 mg, M_w=190.22 g mol^{-1}, 589 μmol, 9%) and (1*R*, 2*S*)-2-*trans*-phenyl–cyclohexanol (1.69 g, M_w=176.26 g mol^{-1}, 9.6 mmol, 1.5 equiv.). A Dean-Stark apparatus was used and the reaction mixture was heated under reflux for three days. After tlc check with pentane/ethyl acetate 7:3, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. The brown oil was purified by silica gel column chromatography (pentane, pentane/ethyl acetate 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1, 3/1, 2/1) to afford **2c** (2 g, M_w=379 g mol^{-1}, 5.37 mmol, 84%) as a pale yellow oil which was used rapidly for the next step. $[\alpha]_D^{20}$=−21.1° (*c* 0.7, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 200 MHz): δ 13.10 (s, 1H, OH), 7.37–7.21 (m, 5H, CAr-H), 7.06 (d, 1H, J=8.6 Hz, C_4-H), 6.34 (d, 1H, J=8.6 Hz, C_3-H), 5.23 (td, 1H, J=10.4 Hz, J=4.3 Hz, C*H*-OCO), 3.88 (s, 3H, OMe), 3.02–2.73 (m, 4H, C_7-H and C_8-H), 3.36–2.56 (m, 1H, C-H), 2.03–1.91 (m, 3H, C*H*-Ph+2C-H), 1.66–1.23 (m, 5H, C-H). ^{13}C NMR ($CDCl_3$): δ 208.0 (CO), 175.9 (CO_2), 160.9 (C_2), 150.8 (C_6), 143.2 (CAr), 136.4 (C_3), 128.6 (CAr), 127.4 (CAr), 126.7 (CAr), 119.9 (C_5), 106.9 (C_4), 98.5 (C_{10}), 77.8 (CH), 53.3 (OMe), 49.8 (*C*H-OCO), 34.7 (CH_2), 32.2 (CH_2), 29.8 (C_8), 29.0 (C_7), 25.8 (CH_2), 24.7 (CH_2). IR (ν_{max}, cm^{-1}, film): 2935, 2857, 1737, 1665, 1632, 1602, 1567, 1477, 1434, 1323, 1300, 1279, 1226, 1112, 1036, 825, 756, 700. HRMS: Calculated: 380.1850, found: 380.1862, Δmmu=1.2.

(5*S*)-7,8,9,10-Tetrahydro-2-methoxy-7-methylene-11-oxo-5,9-methanocycloocta[b]pyridine-5(6*H*)carboxylic acid, (1*R*,2*S*)-2-phenylcyclohexyl ester (12). To a solution of tetrakis(triphenylphosphine)palladium(0) (404 mg, M_w=1155.58 g mol^{-1}, 395 μmol, 12%) in freshly distilled and deoxygenated *p*-dioxane (25 mL) under argon was slowly added a solution of **2c** (1.26 g, M_w=379 g mol^{-1}, 3.32 mmol), freshly distilled 1,1,3,3-tetramethylguanidine (510 μL, *d*=0.918, 468 mg, M_w=115.18 g mol^{-1}, 4.1 mmol, 1.22 equiv.) and 2-methylenepropane-1,3-diol diacetate (630 mg, M_w=172 g mol^{-1}, 3.66 mmol, 1.1 equiv.) in freshly distilled and deoxygenated *p*-dioxane (25 mL). After stirring at room temperature for 30 min, a solution of freshly distilled 1,1,3,3-tetramethylguanidine (430 μL, *d*=0.918, 395 mg, M_w=115.18 g mol^{-1}, 3.4 mmol, 1 equiv.) in freshly distilled and deoxygenated *p*-dioxane (5 mL) was added. The reaction mixture was stirred at room temperature for 15 h. After tlc check with pentane/ethyl acetate 7:3, the reaction mixture was evaporated to dryness and purified by silica gel column chromatography (pentane, pentane/ethyl acetate 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1, 3/1, 2/1) to afford **12** (1.07 g, M_w=431 g mol^{-1}, 2.49 mmol, 75%) as a colourless oil, which crystallised slowly on standing at room temperature (mp 118–120°C). $[\alpha]_D^{20}$=−39.9° (*c* 0.8, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.34–7.21 (m, 3H, CAr-H), 7.11 (m, 1H, J=7.9 Hz, CAr-H), 7.10 (m, 1H, J=8.2 Hz, CAr-H), 5.97 (d, 1H, J=8.5 Hz, C_4-H), 5.61 (d, 1H, J=8.5 Hz, C_3-H), 5.36 (td, 1H, J=9.9 Hz, J=4.0 Hz, C*H*-OCO), 4.73 (broad d, 1H, J=1.7 Hz, C=CH_aH$_b$), 4.36 (broad d, 1H, J=1.7 Hz, C=CH$_a$$H_b$), 3.84 (s, 3H, OMe), 3.38 (dd, 1H, J=18.3 Hz, J=6.8 Hz, C_{10}-H$_a$), 3.05 (d, 1H, J=13.6 Hz, C_6-H$_a$), 3.01 (d, 1H, J=18.3 Hz, C_{10}-H$_b$), 2.89 (broad t, 1H, J=4.5 Hz, C_9-H), 2.71 (ddm, 1H, J=11.3 Hz, J=2.8 Hz, C_8-H$_a$), 2.53 (m, 2H, C_6-H$_b$+C_8-H$_b$), 2.33 (m, 2H, C*H*-Ph, C-H), 1.88 (m, 2H, C-H), 1.73 (m, 1H, C-H), 1.54-1.21 (m, 4H, C-H). ^{13}C NMR ($CDCl_3$): δ 208.5 (CO), 170.3 (CO_2), 162.2 (C_2), 150.8 (C_{10a}), 143.5 (CAr), 139.0 (C_7), 137.7 (C_3), 128.5 (CHAr), 127.5 (CHAr), 126.4 (CHAr), 124.1 (C_{4a}), 116.1 (CH_2), 109.2 (C_4), 76.9 (*C*H-OCO), 61.3 (C_5), 53.3 (OMe), 49.4 (*C*H-Ph), 47.7 (C_8), 45.7 (C_6), 44.0 (C_{10}), 40.3 (C_9), 35.3 (CH_2), 32.0 (CH_2), 25.7 (CH_2), 24.7 (CH_2). IR (ν_{max}, cm^{-1}, film): 2937, 2857, 1732, 1602, 1575, 1475, 1423, 1373, 1320, 1259, 1177, 1116, 1037, 999, 912, 874, 824, 758, 701. HRMS: Calculated: 431.2142, Found: 431.2119, Δmmu=−2.3.

(5*S*)11-Ethylidene-7,8,9,10-tetrahydro-2-methoxy-7-methylene-5,9-methanocycloocta[b]pyridine-5(6*H*)-carboxylic acid, (1*R*,2*S*)-2-phenylcyclohexyl ester (15). To ethyltriphenylphosphonium bromide (780 mg, M_w=371.26 g mol^{-1}, 2.1 mmol, 9 equiv.) (evaporated with anhydrous toluene before use) and sublimated potassium *t*-butoxide (220 mg, M_w=112.22 g mol^{-1}, 1.96 mmol, 8.5 equiv.) freshly distilled THF (14 mL) was added under argon. The reaction mixture was stirred at room temperature for 15 min. Then a solution of **12** (100 mg, M_w=431 g mol^{-1}, 232 μmol) in anhydrous THF (14 mL) was slowly added. After 4 days of stirring at room temperature, the reaction mixture was quenched with water (12 mL), extracted with ethyl acetate (4×50 mL), dried over $MgSO_4$, filtered and evaporated to dryness. Silica gel column chromatography (pentane, pentane/ethyl acetate 15/1, 12/1, 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1) gave the desired compound **15** (91 mg, M_w=443 g mol^{-1}, 206 μmol, 89%). ^{1}H NMR showed that **15** is a mixture of 61% of the *E* and 39% of the *Z* isomer. (*Z*) **15**: ^{1}H NMR ($CDCl_3$): δ 7.28–7.12 (m, 6H, CAr-H+C_4-H), 6.12 (broad d, 1H, J=8.5 Hz, C_3-H), 5.37 (q, 1H, J=7.1 Hz, C=C*H*CH$_3$), 5.02 (m, 1H, CH-OCO), 4.46 (m, 1H, C=CH_aH$_b$), 4.15 (m, 1H, C=CH$_a$$H_b$), 3.83 (s, 3H, OMe), 3.10 (dd, 1H, J=18.7 Hz, J=6.2 Hz, C_{10}-H$_a$), 2.70 (m, 1H, C_9-H), 2.60 (dd, 1H, J=18.7 Hz, J=9.6 Hz, C_{10}-H$_b$), 2.47–2.17 (m, 5H, 2C_6-H+2C_8-H+C*H*-Ph), 1.95–1.72 (m, 3H, CH), 1.57 (s,

3H, Me), 1.68–1.03 (m, 5H, CH). (*E*) **15**: ^{1}H NMR ($CDCl_3$): δ 7.37–7.07 (m, 5H, CAr-H), 5.94 (d, 1H, J=8.3 Hz, C_4-H), 5.87 (d, 1H, J=8.3 Hz, C_3-H), 5.39 (m, 1H, C=C*H*CH_3), 5.32 (m, 1H, CH-OCO), 4.53 (broad s, 1H, C=CH_aH_b), 4.17 (broad s, 1H, C=CH_aH_b), 3.82 (s, 3H, OMe), 3.29 (m, 1H, C_9-H), 3.06 (dd, 1H, J=17.7 Hz, J=5.9 Hz, C_{10}-H_a), 2.73 (dd, 1H, J=17.7 Hz, J=13 Hz, C_{10}-H_b), 2.62 (m, 1H, C_8-H_a), 2.35–2.12 (m, 4H, 2C_6-H+C_8-H_b+C*H*-Ph), 1.98–1.70 (m, 3H, CH), 1.63 (s, 3H, Me), 1.70–1.18 (m, 5H, CH).

Isomerisation of (*Z*) 15 to (*E*) 15. To a solution of **15** (*E*/*Z*=61/39, 40 mg, M_w=443 g mol^{-1}, 90.2 μmol) in anhydrous toluene (200 μL) were successively added AIBN (11 mg, M_w=164 g mol^{-1}, 67 μmol, 0.74 equiv.) and thiophenol (14 μL, d=1.073, 15 mg, M_w=110.18 g mol^{-1}, 136.3 μmol, 1.5 equiv.). The reaction mixture was then heated under reflux for 7 days. Evaporation to dryness and silica gel column chromatography (pentane, pentane/ethyl acetate 15/1, 12/1, 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1) gave **15** (33.2 mg, M_w=443 g mol^{-1}, 75 μmol, 83%, *E*/*Z*=15/85) as a colourless oil. (*E*) **15**: ^{13}C NMR ($CDCl_3$): δ 173.8 (CO_2), 161.4 (C_2), 150.3 (C_{10a}), 143.8 and 142.4 (quaternary CAr), 138.3 (C_3), 137.4 (C_7), 137.1 (C_{11}), 128.6 and 127.6 (CHAr), 126.6 (C_{4a}), 115.5 (C=*C*H_2), 112.7 (C=*C*HCH$_3$), 107.8 (C_4), 65.2 (C_5), 53.2 (OMe), 49.3 (*C*H-Ar), 48.4 (C_8), 43.0 (C_{10}), 39.3 (C_6), 35.4 (CH_2), 32.3 (C_9), 31.7, 25.7 and 24.8 (CH_2), 12.7 (C=CH*C*H$_3$). IR (ν_{max}, cm^{-1}, film): 2933, 2858, 1721, 1600, 1578, 1475, 1463, 1440, 1423, 1325, 1315, 1266, 1238, 1107, 1055, 1039, 823, 758, 700. HRMS: Calculated: 444.2541, found: 444.2539, Δmmu=−0.2.

(5*R*,9*S*)-11-Ethylidene-9,10-dihydro-2-methoxy-7-methyl-5,9-methanocycloocta[b]pyridine-5(6*H*)-carboxylic acid (1*R*,2*S*)-2-phenylcyclohexyl ester (16). To a solution of **15** (25 mg, M_w=443 g mol^{-1}, 56.4 μmol) in a resealable tube in freshly distilled *p*-dioxane (400 μL) under argon was added triflic acid (7 μL, d=1.696, 11.9 mg, M_w=150.07 g mol^{-1}, 79.1 μmol, 1.4 equiv.). The reaction mixture was stirred at 90°C for 18 h. After dilution with ether (2 mL), saturated $NaHCO_3$ (300 μL) was added. The organic phase was dried over $MgSO_4$, filtered, evaporated, and the residue was purified by silica gel column chromatography (pentane, pentane/ethyl acetate 15/1, 12/1, 10/1, 9/1, 8/1, 7/1, 6/1, 5/1, 4/1) to give **16** (22 mg, M_w=443 g mol^{-1}, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.32–7.04 (m, 5H, CAr-H), 6.02 (d, 1H, J=8.5 Hz, C_4-H), 5.92 (d, 1H, J=8.5 Hz, C_3-H), 5.34 (m, 1H, CH-OCO), 5.27 (m, 1H, C_8-H), 4.79 (q, 1H, C=C*H*CH_3), 3.81 (s, 3H, OMe), 3.46 (m, 1H, C_6-H_a), 2.94 (m, 2H, C_9-H+C_{10}-H_a), 2.70 (large d, 1H, J=15.9 Hz, C_{10}-H_b), 2.55 (dt, 1H, J=11.5 Hz, J=3.6 Hz, C_6-H_a), 2.17 (m, 1H, C*H*-Ph), 1.92–1.67 (m, 3H, CH), 1.57 (d, 3H, C=CHC*H*$_3$), 1.53 (s, 3H, CH=CC*H*$_3$), 1.48–1.16 (m, 5H, CH). ^{13}C NMR ($CDCl_3$): δ 175.9 (CO_2), 160.0 (C_2), 150.0 (C_{10a}), 143.5 (quaternary CAr), 139.2 (C_3), 138.0 (C_7), 137.3 (C_{11}), 128.5 and 127.6 (CHAr), 124.3 (C_{4a}), 121.5 (C_8), 113.5 (*C*HCH$_3$), 108.2 (C_4), 67.1 (C_5), 53.5 (OMe), 49.4 (*C*H-Ar and C_9), 45.2 (C_{10}), 39.4 (C_6), 35.4, 32.2, 25.7 and 22.8 (CH_2), 12.6 (C=CHC*H*$_3$), 10.7 (CH=CC*H*$_3$). IR (ν_{max}, cm^{-1}, film): 2932, 2857, 1717, 1600, 1577, 1476, 1423, 1323, 1309, 1257, 1075, 1029, 823, 798, 759, 701. HRMS: Calculated: 444.2540, found: 444.2539, Δmmu=−0.1.

Isomerisation of the crude mixture of **15** (*E*/*Z*=61/39) was performed under the same reaction conditions and afforded **16** in 86% yield.

(5*R*,9*S*)-11-Ethylidene-9,10-dihydro-5-(hydroxymethyl)-2-methoxy-7-methyl-5,9-methanocycloocta[b]pyridine (17). To a solution of **16** (10 mg, M_w=443 g mol^{-1}, 22.5 μmol) in freshly distilled THF (200 μL) at 0°C under argon was added lithium aluminium hydride as a 1 M solution in THF (25 μL, 23 μmol, 1 equiv.). After 5 h at room temperature, the reaction mixture was diluted with ether (1 mL) and quenched with saturated NH_4Cl (100 μL). The organic phase was dried over $MgSO_4$, filtered and evaporated to give an oil which was purified by preparative tlc (pentane/ethyl acetate 3:1) to give an analytical sample (5.8 mg, quantitative). The optical rotation ($[\alpha]_D^{20}$=+37° (*c* 1, $CHCl_3$)) confirmed that this compound has the absolute configuration of the unnatural isomer of huperzine A.

Crystal structure of 12[25]

Crystal data: $C_{27}H_{29}NO_4$, M_w=431.51, colourless crystal of 0.40×0.40×0.30 mm, orthorhombic, space group *P* 21 21 21, Z=4, a=9.531(2), b=12.145(2), c=20.487(4) Å, V=2371.5(8), d_{calc}=1.209 g cm^{-3}, F(000)=920, λ=1.54180 Å (CuK_α), μ=0.647 mm^{-1}.

3326 Reflections were collected on a Nonius CAD4 diffractometer. Theta range: 4.23–67.93°, 3045 unique (R_{int}=0.0131), 2880 observed (I>2sigma(I)). The structure was solved by direct methods (SHELXS86[24a]) and refined by full-matrix least-squares (SHELXL93[24b]), R=0.0437 for 2880 observed reflections, wR2=0.1157 for 3045 unique reflections, goodness of fit=1.095, residual electron density between −0.188 and 0.234*e* Å^{-3}. Hydrogen atoms were fitted at theoretical positions.

Acknowledgements

We thank ADIR, CNRS and Université de Paris-Sud for financial support.

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22. This yield was obtained after drying ethyltriphenylphosphonium bromide by evaporation under vacuum of a suspension of this salt in anhydrous toluene. A shorter reaction time (20 h.) afforded compound **15** (*Z*/*E* mixture of isomers) in 54% yield together with 34% of recovered starting material **12**.
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