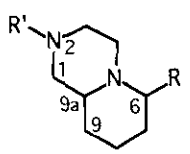
ASYMMETRIC SYNTHESIS OF OCTAHYDRO-2*H*-PYRIDO[1,2-*a*]-PYRAZINES

Olivier Froelich, Françoise Cossart, Martine Bonin, Jean-Charles Quirion*§, and Henri-Philippe Husson*

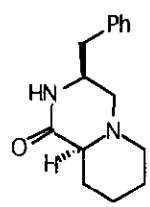
Laboratoire de Chimie Thérapeutique Associé au C.N.R.S.
Faculté des Sciences Pharmaceutiques et Biologiques. Université R. Descartes,
4, Avenue de l'Observatoire, 75270 Paris, Cedex 06. France
§ Laboratoire d'Hétérochimie Organique Associé au C.N.R.S.
IRCOF-INSA de Rouen, Place E. Blondel, BP 08
76131 Mont-Saint-Aignan Cedex. France

Abstract - A series of optically pure octahydro-2*H*-pyrido[1,2-*a*]pyrazines has been prepared from (-)-2-cyano-6-phenyloxazolopiperidine (**4**). 2*H*-Pyrido[1,2-*a*]pyrazin-3-(4*H*)-one (**7**) and octahydro-2*H*-pyrido[1,2-*a*]pyrazine (**14**) were obtained from diamino alcohol (**5**) by cyclization of bromo- or chloroamides (**6**) and (**10**). (4*R*, 9a*S*)-1,1,4-Triphenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazine (**16**) was synthesized by cyclization of amino alcohol (**15c**). The formation of cyclic urea (8a*S*)-diphenyl-3-oxooctahydroimidazo[1,5-*a*]pyridine (**18**) was observed during the hydrogenolysis of the corresponding carbamate (**17**).

Octahydro-2H-pyrido[1,2-a]pyrazine (**1a**) *is a non-common* skeleton encountered in some natural products such as verruculotoxin (**2**), a toxic metabolite isolated from *Penicillium verruculosum*.[1] Synthetic derivatives such as **1b** or **1c** have been claimed to possess hypotensive properties.[2] More recently 2-aryl-4-oxo derivative (**3**) has been synthesized and exhibited an interesting psychotropic activity.[3,4]



1a : R = R' = H
1b : R = Me, R' = $CH(C_6H_5)_2$
1c : R = Me, R' = $(CH_2)_2NH_2$



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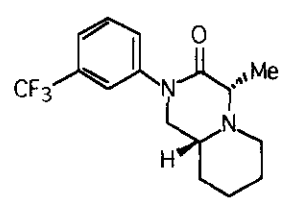

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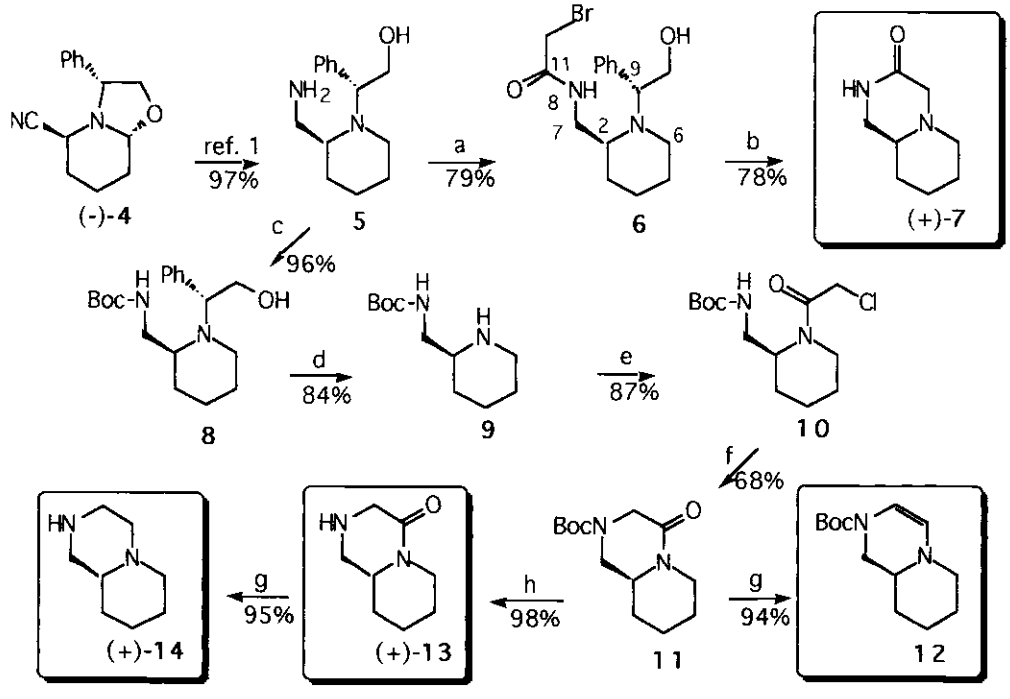
These bicyclic compounds also found new applications as ligands of the σ receptors[5] and as piperazine[6] or peptides[7] restricted analogues. Only one report[4] dealt with asymmetric synthesis of such compounds. In connexion with our work on preparation of optically pure 2-aminomethylpiperidine derivatives[8] we herein present their use to the synthesis of various substituted octahydro-2*H*-pyrido[1,2-*a*]pyrazines. In a first attempt we decided to prepare compounds (**7**, **13** and **14**) (Scheme 1) from the common intermediate (**5**) obtained by diastereoselective reduction of synthon ((-)-**4**) with $LiAlH_4$ (Y = 97%).[8,9] Acylation of 5 with bromoacetyl chloride furnished amide (**6**) which cyclized to quaternary ammonium salt in refluxing methanol. This crude material was directly hydrogenolyzed (H_2, 10% Pd/C) to give bicyclic lactam ((+)-**7**) in 78% yield. Racemic lactam (**7**) has been previously synthesized by Schmidt reaction on 1-azabicyclo[4.3.0]nonan-4-one.[10]



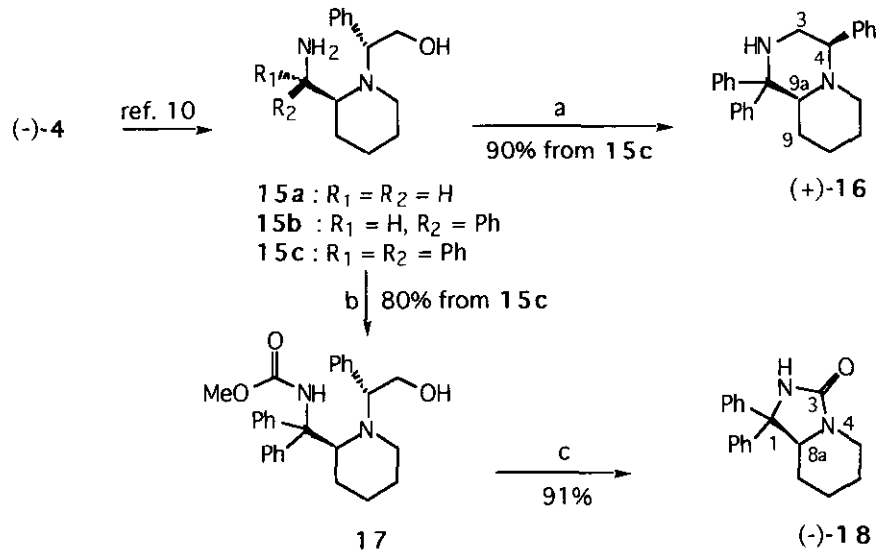
Scheme 1 : (a) $BrCH_2COCl$, NaOH, CH_2Cl_2, rt, 2 h; (b) MeOH, reflux, 2 h then H_2, 10% Pd/C, MeOH, 2 h; (c) Boc_2O, dioxane-H_2O, rt, 15 min; (d) H_2, 10% Pd/C, MeOH, 4 h; (e) $ClCH_2COCl$, aq. 15% NaOH, CH_2Cl_2, rt, 3 h; (f) NaH, THF, rt, 3 h; (g) $LiAlH_4$, Et_2O, rt, 2 h; h) MeOH-HCl, rt, 30 min

Preparation of isomeric lactam ((+)-**13**) required protection of primary amine (**5**) as a Boc-carbamate (**8**) prior to removing the chiral auxiliary, (H_2, 10% Pd/C). Pure amine (**9**) was then reacted with chloroacetyl chloride to furnish amide (**10**) in 70 % yield from compound (**5**). Cyclization of compound (**10**) was performed in THF in the presence of NaH at room temperature to give bicyclic lactam (**11**) as a crystalline product.

Surprisingly, reduction of lactam (**11**) with $LiAlH_4$ in Et_2O did not furnish the expected reduction product, instead, only enamine (**12**) was isolated in 94 % yield. This product was characterized in ^1H

NMR by the presence of two coupled olefinic protons (δ : 5.05 and 5.82 ppm, d, J = 6.5 Hz) and in ^{13}C NMR by two olefinic carbons (δ : 104.1 and 120.8 ppm). Deprotection of **11** afforded, compound (**13**) in 98 % yield. To the best of our knowledge this is the first report of the preparation of this simple bicyclic lactam. Reduction of the carbonyl group was then performed with $LiAlH_4$ in Et_2O leading to (9a-*S*)-2*H*-octahydropyrido[1,2-*a*]pyrazine (**14**), ($[\alpha]^{20}_D$: + 4° ; c = 1.4, MeOH), whose ^1H NMR spectrum was identical to that of the previously described racemic form.[5]

At this point of our study we decided to investigate the possibility of preparing some 1-substituted derivatives, (Scheme 2). Particularly attractive was the possibility of taking advantage of the primary hydroxyl function in the chiral appendage to achieve the cyclization of α-substituted primary amines (**15a-c**) prepared from synthon (**4**) as previously described.[8]



Scheme 2 : (a) MsCl, Et_3N, CH_2Cl_2, rt, 1 h; (b) $ClCO_2Me$, aq. 15% NaOH, $CHCl_3$, rt, 3 h; (c) H_2, 10% Pd/C, MeOH, 12 h

Using **15a** and **15b** as starting materials, none of the methods used (PPh_3, CCl_4; PPh_3, DEAD; MsCl, Et_3N; H_2SO_4) allowed the formation of the attempted cyclized products. But when diphenylaminomethylpiperidine (**15c**) was treated with mesyl chloride in the presence of triethylamine, bicyclic compound (**16**) was isolated in 90% yield. In this case, the presence of two aromatic rings α to the primary amine prevented the formation of *N*-mesyl derivative and favored *O*-mesylation; cyclization can then occur smoothly. Triphenyl bicyclic compound (**16**) was then characterized by ^1H NMR analysis; H-4 and H-9a were in an axial position as indicated by coupling constants ($J_{4\text{-}3ax}$ = 10.8 Hz, $J_{9a\text{-}9}$ = 11.9 and 2.8 Hz).

In an attempt to prepare different substituted products we protected primary amino function of coumpound (**15c**) as a methyl carbamate (**17**). When this compound was hydrogenolyzed (H_2, 10% Pd/C) a spontaneaous cyclization resulting from the attack of secondary amine on the carbamate function occurred furnishing octahydroimidazo[1,5-*a*]pyridine derivative (**18**) in 91% yield. This product was

characterized by MS spectrometry with a peak at m/z 292. In ^{1}H NMR the disappearance of phenylethanol chain and methoxy was observed. In ^{13}C NMR a carbonyl group was observed at δ 160.1 ppm.
In conclusion we have been able to prepare a series of substituted octahydropyridopyrazines related to biologically active compounds. The preparation of different lactams is particulary interesting as it allows further introduction of substituents α to the carbonyle group.

EXPERIMENTAL

Bromoacetamide (6) : To a solution of primary amine (5) (0.85 g, 3.63 mmol) in CH_2Cl_2 (20 mL) was added bromoacetyl chloride (325 µL, 4.46 mmol) in CH_2Cl_2 (3 mL). A 15 % aqueous solution of NaOH (2 mL) was then added. The resulting mixture was vigourously stirred for 2 h, then treated with a sat. aqueous solution of NH_4Cl, and extracted with AcOEt. Organic layers were washed with water, then dried over $MgSO_4$. Evaporation of the solvent under reduced pressure furnished an oil which was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 98/2) to give bromoacetamide (**6**) as a yellow oil (1.02 g) in 79% yield. $[\alpha]^{20}_D$: - 33° (c = 2.0, $CHCl_3$) ; IR (cm^{-1}) : 3424, 2934, 2856, 1662, 1434. MS (EI) : 354, 356 (1), 323, 325 (5), 204 (100). ^{1}H NMR ($CDCl_3$) δ 1.3-1.8 (m, 6H), 2.68 (td, J = 11.4, 2.2, H-6ax), 2.68 (m, H-2), 2.96 (dt, J = 11.4, 3.6, H-6eq), 3.60-3.68 (m, 3H, 2xH-7 and H-9), 3.94 (m, 2xH-12), 4.07 (t, J = 10.0 Hz, H-10), 4.21 (dd, J = 10.0, 4.7 Hz, H-10), 7.10-7.40 (m, 5 H Ar). ^{13}C NMR δ ($CDCl_3$) : δ : 23.4, 25.3, 29.4, 29.9, 41.6 (C-6), 45.3 (C-7), 56.0 (C-2), 61.0 (C-10), 62.2 (C-9), 128.1, 128.4, 129.0, 135.3 (Cq Ar), 166.3 (C-11).

(9a-*S*)-2*H*-Pyrido[1,2-*a*]pyrazin-3-(4*H*)-one (7) : A solution of **6** (220 mg, 0.62 mmol) in MeOH (3 mL) was refluxed for 2 h. After cooling, CH_2Cl_2 (20 mL) was added. The precipitated ammonium salt was filtered, washed twice with CH_2Cl_2 then dried under vacuum. A solution of this salt in MeOH (10 mL) was then hydrogenolized in the presence of 10% Pd/C (50 mg) (2 h). After filtration over celite, solvant was evaporated. Crude material was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 90/10) furnishing **7** as a colourless oil in 78 % yield (74 mg). $[\alpha]^{20}_D$: + 44° (c = 2.1, $CHCl_3$) ; IR (cm^{-1}) : 3422, 2945, 1653, 1453. MS (CI) : 155 (MH^+), 97, 70. ^{1}H NMR ($CDCl_3$) δ 1.1-1.9 (m, 6H), 1.98 (td, J = 11.9, 2.9 Hz, H-6 ax), 2.22 (tt, J = 10.1, 4.1 Hz, H-9a), 2.91 (br d, J = 11.9 Hz, H-6 eq), 3.11 (m, 2 x H-4), 3.13 (m, 2 x H-1), 6.62 (s, NH). ^{13}C NMR ($CDCl_3$) δ 23.5, 25.1, 29.5, 47.7 (C-6), 55.3 (C-1), 56.5 (C-9a), 58.3 (C-4), 169.4 (C-3). Anal. Calcd for $C_8H_{14}N_2O$: C : 62.31, H : 9.15, N : 18.17 . Found C : 62.59, H : 9.16 , N : 18.01.

***N*-Boc-amino alcohol (8)** : To a solution of 5 (0.87 g, 3.71 mmol) in dioxane (5 mL) and water (1.5 mL) was added a solution of Boc_2O (0.81 g, 3.71 mmol) in dioxane (5 mL). After stirring for 15 min at rt, mixture was treated with a sat. aqueous solution of NH_4Cl, then extracted with CH_2Cl_2 (2 x 35 mL). After usual work-up, the crude residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH : 95/5). Compound (**8**) (1.19 g, 96 %) was obtained as a yellow oil. $[\alpha]^{20}_D$: - 47° (c = 1.0, MeOH) ; IR (cm^{-1}) : 3422, 3012, 1699, 1507. MS (EI) : 303 (M-31, 25), 248 (20), 204

(100). ^{1}H NMR ($CDCl_3$) δ : 1.50 (s, 9H, t-Boc), 1.3-1.7 (m, 6H), 1.85 (td, J = 11.4, 2.6 Hz, H-6 ax), 2.53 (m, H-2), 2.95 (dt, J = 11.4, 3.4 Hz, H-6 eq), 3.43 (dd, J = 7.1, 2.6 Hz, H-7), 3.50 (dd, J = 7.1, 2.6 Hz, H-7), 3.67 (dd, J = 10.4, 5.1 Hz, H-9), 4.07 (t, J = 10.4 Hz, H-10), 4.28 (dd, J = 10.4, 5.1 Hz, H-10), 5.08 (br s, NH), 7.40-7.70 (m, 5H ar.). ^{13}C NMR : δ 18.4, 23.8, 27.4 , 28.5, 30.2, 42.4 and 45.3 (C-6 and C-7), 56.8 (C-2), 60.0 (C-10), 61.4 (C-9), 79.4 (Cq), 127.8, 128.3, 129.0, 135.2 (Cq ar.), 156.4 (C=0). Anal. Calcd for $C_{19}H_{30}N_2O_3$: C : 68.24, H : 9.04, N : 8.38 . Found C : 67.97, H : 9.07 , N : 8.41.

***N*-Boc-aminomethylpiperidine (9)** : Compound (**8**) (1.0 g, 2.99 mmol) in MeOH (10 mL) was hydrogenolyzed in the presence of 10% Pd/C (0.15 g) (4 h). After filtration over celite and evaporation of the solvent, compound (**9**) was obtained pure by crystallization from MeOH (0.54 g, 84 %). mp : 156-157°C (MeOH/Et_2O). $[\alpha]^{20}_D$: + 9° (c = 1.0, $CHCl_3$) ; *IR* (cm^{-1}) : 3329, 1702, 1455. MS (CI) : 215 (MH^+). ^{1}H NMR ($CDCl_3$) δ : 1.3-1.9 (m, 6H), 1.42 (s, 9H, t-Boc), 2.52 (m, H-2), 2.62 (td, J = 11.8, 2.8 Hz, H-6ax), 2.92 (m, 2xH-7), 3.09 (br d, J = 13.6 Hz, NH), 3.19 (dt, J = 11.8, 2.5 Hz, H-6 eq). ^{13}C NMR ($CDCl_3$) : 24.8, 26.3, 28.5 (3 x CH_3), 30.1, 46.4 and 46.6 (C-6 and C-7), 56.3 (C-2), 79.3 (Cq), 156.3 (C=O). Anal. Calcd for $C_{11}H_{22}N_2O_2$: C : 61.65, H : 10.35, N : 13.07 . Found C : 61.63, H : 10.41 , N : 13.00.

Acylation of compound (9) ; amide (10) : To a solution of secondary amine (**9**) (1.18 g, 5.51 mmol) in CH_2Cl_2 (20 mL) were added a 15 % aqueous solution (15 mL) of NaOH and chloroacetyl chloride (683 μL, 8.55 mmol). After stirring at rt for 3 h, water (20 mL) was added. Organic layer was separated, then aqueous layer was extracted twice with CH_2Cl_2. The extracts were washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified on a silica gel column chromatography (CH_2Cl_2/MeOH : 98/2) providing chloroamide (**10**) (1.4 g, 87 %) as a colourless oil. IR (cm^{-1}) : 3334, 1707, 1642. MS (EI) : 292, 290 (25), 162, 160 (75), 84 (100). ^{1}H NMR ($CDCl_3$)(2 rotamers) : δ : 1.42 and 1.44 (2s, t-Boc), 1.5-1.9 (m, 12H), 2.69 (td, J = 13.0, 2.1 Hz, 1H, H-6ax), 3.07 (dt, J = 13.0, 4.6 Hz, H-6 eq), 3.38 (m, 4H, 2xH-9a, 2xH-6), 4.09 and 4.11 (2 AB systems, J = 14.2 Hz, 2xH-10), 4.48, 4.66, 4.88, 5.12 (4m, 4xH-7). ^{13}C NMR ($CDCl_3$) δ : 19.2, 25.1, 25.7, 26.1, 26.7, 28.4 (CH_3), 37.5, 40.2, 41.4, 41.6, 42.3, 48.8 and 53.1 (2 x C-9a), 79.3 (Cq, t-Boc), 156.3 (C=0, t-Boc), 167.8 and 168.5 (2xC=0).

(*S*)-2-*tert*-Butoxycarbonyl-4-oxooctahydro-2*H*-pyrido[1,2-*a*]pyrazine (11) : To a solution of **10** (321 mg, 1.10 mmol) in THF (5 mL) was added NaH (50% in oil, 66 mg, 1.43 mmol) at 0 °C. The resulting mixture was stirred at rt for 3 h, then quenched with water. Classical work-up furnished a residue from which **11** was obtained pure in 68 % yield (191 mg) by crystallization from Et_2O. Colourless crystals, mp : 76-78°C (MeOH/Et_2O) ; $[\alpha]^{20}_D$ = + 22° (c = 1.0, $CHCl_3$) ; IR (cm^{-1}) : 3016, 1685, 1636, 1420. MS (EI) : 254 (20), 239 (8), 198 (27), 153 (48), 83 (100). ^{1}H NMR (CD_3OD) δ : 1.2-2.1 (m, 15H), 2.65 (td, J = 13.1, 2.7 Hz, H-6ax), 3.50 (m, 2H, H-1ax and H-9a), 3.91 (dd, J = 13.6, 4.4 Hz, H-1eq), 4.11 (m, 2 x H-3), 4.68 (dd, J = 13.1, 2.1 Hz, H-6 eq). ^{13}C NMR (CD_3OD) δ : 23.7, 25.1, 30.4, (3 CH_2), 28.4 (3 x Me), 42.3 (C-1), 45.7 and 48.3 (C-4

and C-6), 55.4 (C-9a), 80.8 (Cq t-Boc), 157.3 (C=0, t-Boc), 165.2 (C-4). Anal. Calcd for $C_{13}H_{22}N_2O_3$: C : 61.39, H : 8.72, N : 11.01 . Found C : 61.01, H : 8.88 , N : 11.30.

(*S*)-2-*tert*-Butoxycarbonyl-1,6,7,8,9,9a-hexahydro-2*H*-pyrido[1,2-*a*]pyrazine (12) : To a suspension of $LiAlH_4$ (50 mg, 1.31 mmol) in Et_2O (5 mL) at -10 °C, was added a solution of lactame (**11**) (35 mg, 0.14 mmol) in Et_2O (5 mL). After stirring at rt for 2 h, the solution was treated with water (0.1 mL), then 15 % aq. solution of NaOH (0.1 mL) and then water (0.3 mL). After filtration the organic layer was evaporated *in vacuo*. Crude material which was rapidly purified by flash chromatography on silica gel furnishing **12** as a colourless oil (31 mg, 94 %). $[\alpha]^{20}_D$: + 194° (c = 1.0, $CHCl_3$) ; IR (cm^{-1}) : 3086, 1654, 1588, 1404 ; MS (EI) : 238 (8), 182 (70), 84 (100) ; ^1H NMR ($CDCl_3$) δ : 1.1-1.7 (m, 15H), 2.48 (m, 4H, 2xH-1, H-6ax, H-9a), 3.95 (dd, J = 12.7, 1.7 Hz, H-6eq), 5.05 (d, J = 6.5 Hz, H-4), 5.82 (dd, J = 6.5, 1.1 Hz, H-3) ; ^{13}C NMR ($CDCl_3$) δ : 23.9, 25.6, 28.8 ($3xCH_2$), 28.5 ($3xCH_3$), 46.9 and 52.6 (C-1 and C-6), 54.9 (C-9a), 80.4 (Cq t-Boc), 104.1 (C-4), 120.8 (C-3), 151.8 (C=0). Anal. Calcd for $C_{13}H_{22}N_2O_2$: C : 65.52, H : 9.30, N : 11.75 . Found C : 65.83, H : 9.27 , N : 11.60.

(*S*)-4-Oxooctahydro-2*H*-pyrido[1,2-*a*]pyrazine (13) : A solution of N-Boc derivative (**11**) (97 mg, 0.38 mmol) in MeOH/HCl (2.2 N) (5 mL) was stirred at rt for 30 min, then evaporated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL), then washed twice with an aq. saturated solution of $NaHCO_3$. Organic layer was dried over $MgSO_4$ then evaporated. The residue was purified on a silica gel column chromatography (CH_2Cl_2/MeOH : 98/2 then 90/10) furnishing lactame (**13**) (57 mg, 98 %) as a colourless oil. $[\alpha]^{20}_D$ + 30° (c = 2.5, $CHCl_3$) ; IR (cm^{-1}) : 3425, 1628, 1448 ; MS (EI) : 154 (50), 125 (74), 97 (100) ; ^1H NMR ($CDCl_3$) δ : 1.1-1.8 (m, 6H), 2.32 (td, J = 12.6, 2.8 Hz, H-6ax), 2.61 (dd, J = 13.0, 7.9 Hz, H-1), 3.08 (dd, J = 13.0, 4.9 Hz, H-1), 3.17 (m, H-9a), 3.37 (AB system, J = 15.2 Hz, 2xH-3), 4.62 (ddt, J = 12.6, 3.9, 2.0 Hz, H-6 eq). ^{13}C NMR ($CDCl_3$) δ : 23.9, 25.2, 30.9, 41.7 (C-6), 49.6 and 50.7 (C-1 and C-3), 56.5 (C-9a), 167.4 (C-4). Anal. Calcd for $C_8H_{14}N_2O$: C : 62.31, H : 9.15, N : 18.17 . Found C : 62.54, H : 9.31 , N : 18.01.

(*S*)-Octahydro-2*H*-pyrido[1,2-*a*]pyrazine (14) : Compound (**14**) (30 mg, 95 %) was prepared by reduction of **13** (35 mg) as described for **12**. Colourless oil $[\alpha]^{20}_D$: + 4° (c = 1.4, MeOH) ; IR (cm^{-1}) : 3420, 1558, 1123 ; MS (CI) : 141 (MH^+), ^1H NMR ($CDCl_3$) δ : 1.1-2.9 (m, 15H). ^{13}C NMR ($CDCl_3$) δ : 24.2, 25.7, 29.8 (3 x CH_2), 46.1 (C-6), 52.3 (C-1), 56.2 and 56.3 (C-3 and C-4), 63.0 (C-9a). Anal. Calcd for $C_8H_{16}N_2$: C : 68.52, H : 11.50, N : 19.98 . Found C : 68.39, H : 11.76 , N : 19.85.

(4*R*,9a*S*)-1,1,4-Triphenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazine (16) : A solution of amino alcohol (**15c**)[9] (110 mg, 0.28 mmol), mesyl chloride (22 μL, 0.28 mmol) and Et_3N (79 μL, 0.57 mmol) in CH_2Cl_2 (15 mL) was stirred at rt for 1 h. The resulting mixture was then washed with a saturated solution of NH_4Cl, then dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by silica gel flash chromatography (CH_2Cl_2/MeOH : 95/5)furnishing **16** as a colourless oil (92 mg,

90 %). $[\alpha]^{20}_D$: + 46° (c = 1.0, $CHCl_3$) ; IR (cm^{-1}) : 3394, 2945, 1654, 1405 ; MS (CI) : 369 (MH^+), 167, 98 ; ^1H NMR (C_6D_6) δ : 1.0-1.8 (m, 6H), 1.88 (td, J = 10.7, 2.2 Hz, H-6ax), 2.25 (t, J = 10.8 Hz, H-3ax), 2.30 (dd, J = 11.9, 2.8 Hz, H-9a), 2.65 (br d, J = 10.7 Hz, H-6 eq), 2.78 (dd, J = 10.8, 2.7 Hz, H-3eq), 3.87 (dd, J = 10.8, 2.7 Hz, H-4) ; 7.1-7.2 (m, 15 H) ; ^{13}C NMR ($CDCl_3$) δ : 25.2, 25.4, 25.7 (3 x CH_2), 54.5 (C-4), 57.6 (C-6), 65.4 (C-3), 66.7 (C-1), 71.3 (C-9a), 126.0-131.1 (CH ar.), 143.6, 145.3, 147.6 (Cq ar.). Anal. Calcd for $C_{26}H_{28}N_2$: C : 84.74, H : 7.66, N : 7.60 . Found C : 84.83, H : 7.77 , N : 7.40.

***N*-Carbamate (17)** : To a solution of amino alcohol (**15c**)[9] (0.85 g, 2.2 mmol) and methyl chloroformate (170 μL, 2.2 mmol) in $CHCl_3$ (25 mL) was added a 15 % aqueous solution of NaOH (1 mL). The resulting mixture was stirred at rt for 3 h. After usual work-up, the residue was purified by silica gel chromatography (CH_2Cl_2/MeOH : 95/5) furnishing carbamate (**17**) as a colourless oil (0.78 g, 80 %). IR (cm^{-1}) : 3180, 2941, 1624 ; MS (EI) : 413 (M-31, 1), 392 (10), 262 (15), 204 (100) ; ^1H NMR ($CDCl_3$) δ 0.6-1.7 (m, 7H), 2.48 (br d, J = 12.7 Hz, H-6 eq) , 3.49 (s, OMe), 3.80-4.20 (m, 3H, 2 x H-10, H-9), 4.47 (t, J = 4.7 Hz, H-2) ; ^{13}C NMR ($CDCl_3$) δ : 19.4, 20.5, 22.9 (3 x CH_2), 40.8 (C-6), 51.9 (OMe), 63.0 and 63.1 (C-2, C-9), 68.4 (C-7), 70.1 (C-10), 127.0-129.7 (CH, Ar.), 140.7, 140.9, 142.9 (Cq ar.), 166.7 (C=O). Anal. Calcd for $C_{28}H_{32}N_2O_3$: C : 75.65, H : 7.25, N : 6.30 . Found C : 75.61, H : 6.98 , N : 6.41.

(8a*S*)-Diphenyl-3-oxooctahydroimidazo[1,5-*a*]pyridine (18) : A solution of carbamate (**17**) (0.56 g, 1.26 mmol) in methanol (10 mL) was hydrogenolyzed for 12 h in the presence of 10 % Pd/C (75 mg). After filtration over celite and evaporation of the solvent, compound (**18**) was obtained by crystallization from ether (0.34 g, 91 %). mp : 120-122°C (MeOH/H_2O), $[\alpha]^{20}_D$: -288° (c = 1.0, MeOH), IR (cm^{-1}) : 2892, 1802, 1295 ; MS (EI) : 292 (50), 180 (7), 165 (7), 84 (100) ; ^1H NMR ($CDCl_3$) δ : 0.7-1.9 (m, 6H), 2.75 (td, J = 12.3, 3.3 Hz, H-5ax), 3.95 (dt, J = 12.3, 3.7 Hz, H-5eq), 4.11 (dd, J = 11.6, 3.1 Hz, H-8a), 5.68 (br s, NH), 7.0-7.5 (m, 10 H ar.), ^{13}C NMR ($CDCl_3$) δ : 23.8, 24.3, 28.3 (3 x CH_2), 41.4 (C-5), 63.9 (C-8a), 66.8 (C-1), 126.3-128.5 (CH, ar.), 141.8 and 145.3 (Cq ar.), 160.1 (C-3). Anal. Calcd for $C_{19}H_{20}N_2O$: C : 78.05, H : 6.89, N : 9.58 . Found C : 77.65, H : 6.61 , N : 9.11.

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