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Synthesis of (-)-Chanoclavine I

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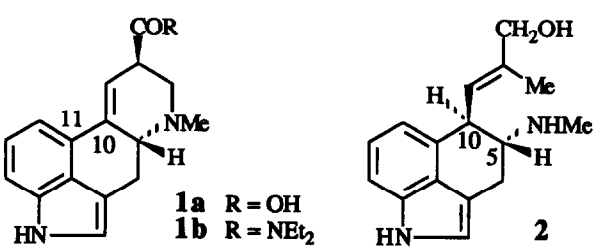
Abstract : The total enantioselective synthesis of (-)-chanoclavine I **2** in twelve steps from indole-4-carboxaldehyde **4** is described The key-step **3** → **6** which involves the formation of the C ring by creation of the C5-C10 bond is catalyzed by a chiral palladium (0) complexes. The chiral ergoline synthon **6** is produced with an excellent diastereo-and enantioselectivity (up to 95% ee).

The chemistry, pharmacology and biosynthesis of ergot alkaloids have been extensively highlighted in several reviews and books [1] . The structural characteristic of ergot alkaloids such as lysergic acid **1** is the presence of the tetracyclic ergoline ring system In addition to tetracyclic derivatives a number of tricyclic analogues in which the D ring is not closed are found in nature The first compound of this class of 6,7-secoagroclavine was chanoclavine I **2** (isolated from *Claviceps purpurea*) [2] which is of particular interest regarding its role as biosynthetic precursor of lysergic acid **1a** and its well known amide derivative **1b** [3] (scheme 1). The total synthesis of ergot alkaloids has received increasing attention during the past decade. Two main strategies were developed. The first involved the creation of the C ring by the formation of the C10-C11 bond [4-8] . The second one, related to the biomimetic pathway, by creation of the C5-C10 bond [9-15] .

However few enantioselective syntheses have been reported so far and they required a stoichiometric amount of chiral auxiliary [16] or a separation of enantiomers on a chiral column [17] . We present here the first enantioselective synthesis of (-)-chanoclavine I **2**, obtained in twelve steps with 1.6% overall yield from the indole-4-carboxaldehyde **4**. Our strategy is based on the formation of the C5-C10 bond, catalyzed by a chiral palladium (0) complex.

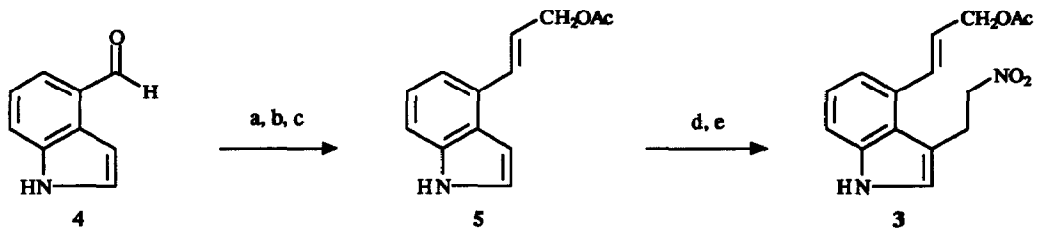
Scheme 1



We have previously reported an intramolecular palladium catalyzed allylation [18] of the nitroacetate **3** which is obtained in five steps from indole-4-carboxaldehyde **4**, as bifunctional starting material [19] . The Horner-Emmons reaction of **4** with trimethylphosphonoacetate, in the presence of potassium carbonate, in

refluxing THF gave the unsaturated ester [13b, 20] in 95% yield. Reduction of this ester with Dibal, in THF / CH_2Cl_2 afforded the allylic alcohol [13a] which was converted into allylic acetate 5 with Ac_2O, NEt_3 (scheme 2). The C-3 functionalisation of 5 was achieved in two steps. Treatment with 1-dimethylamino 2-nitroethylene, in the presence of TFA afforded the unsaturated nitroacetate [21]. Reduction of the double bond with $NaBH_4$ in THF / MeOH furnished the desired nitroacetate 3 [(22)] in 50% overall yield from the aldehyde 4.

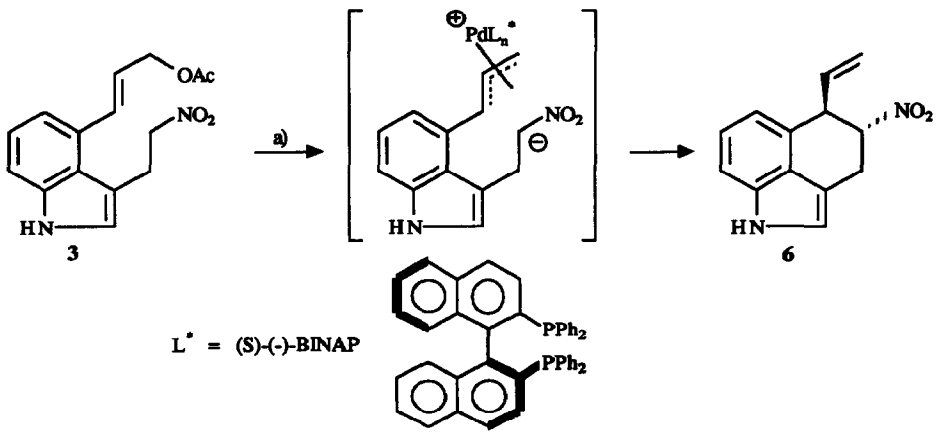
Scheme 2



a) $(MeO)_2P(O)CH_2CO_2Me$, K_2CO_3, THF reflux, 95% ; b) Dibal, THF-CH_2Cl_2, -78°C, 95% ; c) Ac_2O, NEt_3, CH_2Cl_2, 95% ; d) $Me_2NCH{=}CHNO_2$, TFA, CH_2Cl_2, 0°C, 70% ; e) $NaBH_4$, MeOH, THF, -20°C, 80%.

We then focused our attention on the asymmetric formation of the C5-C10 bond of the nitro acetate 3 using palladium zero complexes [23]. The best results of this key cyclisation were obtained by using $Pd(dba)_2$ and (S,S)-CHIRAPHOS as the chiral diphosphine, in THF at reflux [18]. We optimised these results by employing $Pd(OAc)_2$ and (S)-(-)-BINAP in THF at room temperature. The desired enantiomer (5R) is obtained under these mild conditions with 60% yield, and diastereo- and enantiostereoselectivity of up to 95% [23] (scheme 3). This increase of diastereo-and enantioselectivity can be rationalised by the ligand pocket effect [24]. With BINAP, the electrophilic allyl-palladium complex is a seven membered ring. The steric effects cause an increase of the asymmetric induction. This reaction was carried out without any protection of the indolic nucleus. It represents a convenient method for creating such tricyclic nitro compound, which is a good precursor of tricyclic ergot alkaloids.

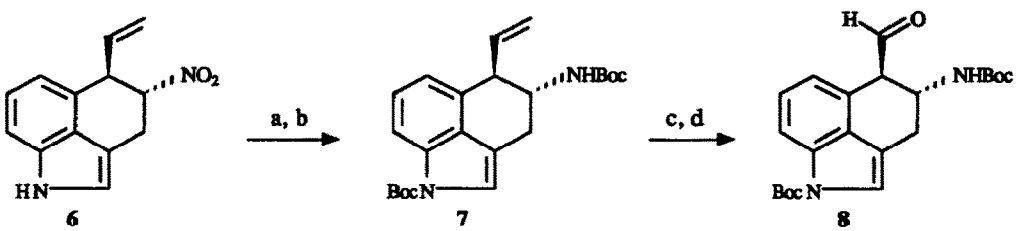
Scheme 3



a) $Pd(OAc)_2$ 3%, (S)-(-)-BINAP 6%, K_2CO_3, THF, r. t, 60%.

For the synthesis of (-)-chanoclavine I, we chose essentially the same technology, using the trans aldehyde, devised by Kozikovski and Oppolzer in its racemic form. The nitro groupment was then reduced to primary amine with Zn amalgam [11d], and the two nitrogens were converted to the corresponding carbamates **7** with Boc_2O in CH_3CN, at room temperature [25]. The dicarbamate **7** was then treated with a catalytic amount of OsO_4, in the presence of NMO, in a mixture of acetone / H_2O to furnish the crude diol [26]. This compound was cleaved with $NaIO_4$, in methanol / H_2O to yield the key unstable aldehyde **8** [13b,27] (scheme 4).

Scheme 4

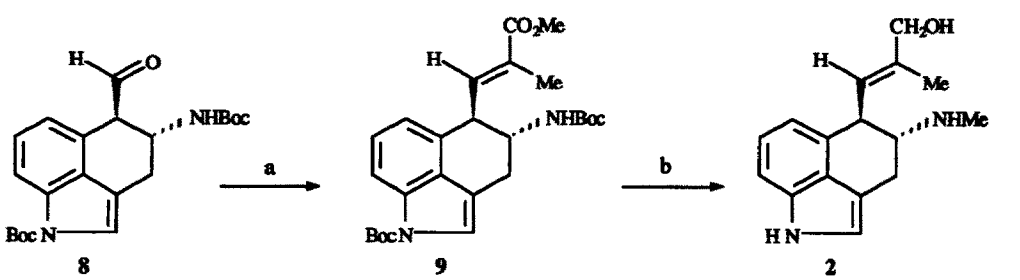


6 **7** **8**

a) Zn(Hg), HCl, MeOH, reflux, 95% ; b) Boc_2O, CH_3CN, DMAP 10%, r. t., 92% ; c) OsO_4 10%, NMO, acetone / H_2O, r. t., 80% ; d) $NaIO_4$, MeOH / H_2O, 0°C, 87%.

Wittig reaction on the aldehyde **8** with (α-carbomethoxyethylidene)triphenylphosphorane in THF afforded the unsaturated ester **9** [9b]. Reduction of the ester and the primary carbamate and deprotection of the indole was achieved by treatment with LAH, in THF / Et_2O, under reflux. The (-)-chanoclavine I **2** was then obtained after chromatography with 13% yield [9b,28] (scheme 5). This result can be explained by the three steps occurring in one pot and by the poor solubility of chanoclavine I in organic solvents.(Pyridine is the only suitable solvent).

Scheme 5



8 **9** **2**

a) $Ph_3P{=}C(Me)CO_2Me$, THF, 50°C, 73% ; b) $LiAlH_4$ excess, Et_2O / THF, reflux, 13%.

In summary, we performed the first total asymmetric synthesis of (-)-chanoclavine I from optically active nitro compound **6**. This method can be applied to other 6,7-secoagroclavines, like (+)-paliclavine or rugulovasine. The optically active aldehyde **8** represents a versatile intermediate in the synthesis of such ergot alkaloids. This work illustrates the potential of chiral palladium (0) complexes in organic synthesis.

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EXPERIMENTAL SECTION

General methods : Et_2O and THF were distilled from sodium/benzophenone under argon atmosphere. CH_2Cl_2, CH_3CN, NEt_3, pyridine were distilled from calcium hydride. TLC were performed on commercial aluminium backed silica gel 60 F_{254} (Merck). Flash column chromatography were carried out on 230-400 mesh silica gel (Merck). Melting points (m.p.) were determined in a slow melting apparatus, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 and a Brücker IR-FT 45. Optical rotations were determined in a Perkin-Elmer 241. ^1H and ^{13}C-NMR spectra were recorded on a Brücker AM-250 and a Brücker AM-200 FT spectrometers, standard TMS δ (ppm) = 0, s = singlet, d = doublet, t = triplet, m = multiplet, J = spin-spin coupling constant (Hz).

methyl-(E)-3-(4-indolyl)propenoate : To a stirred refluxing solution of trimethylphosphonoacetate (22.0 g, 120 mmol) and indole-4-carboxaldehyde 4 (14.5 g, 100 mmol) in dry THF (200 ml), under argon, was added K_2CO_3 (34.5 g, 250 mmol). Stirring was continued for 16 hrs, until TLC showed no starting material. The solvent was removed, and the residue was dissolved and partitioned between water and ether. The aqueous layer was extracted with ether. The organic phases were washed with water, then with brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash chromatography (Et_2O/cyclohexane : 4/6) to yield the crystalline pale yellow methyl-(E)-3-(4-indolyl)propenoate (19.1g, 95%), m. p. 127°C (lit. 125-126°C). TLC (Et_2O/hexane : 1/1) : R_f = 0.55; Anal. for $C_{12}H_{11}NO_2$ calc. C 71.64, H 5.47, N 6.97 found C 71.51, H 5.49, N 7.11; IR : (KBr) : 3353, 2970, 1691, 1623, 1280, 1437, 1326, 1119, 870 cm^{-1}, MS (EI, 70 eV) : 201 (M^+, base), 170, 141, 115, 89, 70, 63, 57; ^1H-NMR : (200 MHz, $CDCl_3$) : 8.69 (1H, broad s), 8.18 (1H, d, J = 16 Hz), 7.40-7.20 (4H, m), 6.85 (1H, m), 6.15 (1H, d, J = 16 Hz), 3.89 (3H, s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 168.1, 144.0, 136.2, 126.8, 126.3, 125.6, 121.8, 120.5, 117.5, 113.3, 101.0, 51.6.

4-[(E)-3-hydroxypropenyl]indole : To a solution of methyl-(E)-3-(4-indolyl)propenoate (19.1 g, 95 mmol) in dry THF (250 ml), at -78°C, under argon, was added dropwise 1 N diisobutylaluminium hydride in CH_2Cl_2 (400 ml, 400 mmol). The mixture was stirred 1 hr at r. t., then cooled to -78°C and water was carefully added dropwise (100 ml). The stirred mixture was allowed to warm to r. t. for 45 minutes and precipitated. Addition of brine (200 ml) was followed by filtration over silica gel and washing with AcOEt. The aqueous layer was extracted with AcOEt. The organic layers were washed with brine, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (Et_2O/cyclohexane : 6/4) yielded 4-[(E)-3-hydroxypropenyl]indole (15.6 g, 95%), m. p. 74-75°C (white solid). TLC (Et_2O/cyclohexane : 1/1) : R_f = 0.20; IR : (neat) : 3420, 2940, 2880, 1500, 1410 , 1345, 1100, 1000, 970, 900 cm^{-1}; MS (EI, 70 eV) ($C_9H_{11}NO$) : 173 ($M^{+\cdot}$), 144, 130 (base), 89, 70, 63, 55; ^1H-NMR : (200 MHz, $CDCl_3$) : 8.56 (1H, broad s), 7.15-6.97 (4H, m), 6.93 (1H, d, J = 15 Hz), 6.58 (1H, m), 6.38 (1H, d t, J = 15, 5.8 Hz), 4.22 (2H, d t, J = 5.8, 1.3 Hz), 2.38 (1H, broad s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 136.1, 129.8, 129.0, 128.8, 126.0, 124.5, 121.9, 117.6, 110.6, 100.8, 64.1.

(E)-3-(4-indolyl)propenyl acetate 5 : To a solution of 4-[(E)-3-hydroxypropenyl]indole (15.6 g, 90 mmol) in dry CH_2Cl_2 (100 ml), at 0°C, under argon, was added acetic anhydride (9 ml, 96 mmol), followed by careful addition of triethylamine (16.6 ml, 125 mmol). The mixture was stirred 1 hr at 4-5°C, and 3 hrs at r. t. The mixture was washed with water, with HCl (0.6 N), then with water. The aqueous layer was extracted with

CH_2Cl_2. The organic phases were washed with brine, dried ($MgSO_4$), filtered and evaporated. Flash chromatography (Et_2O/cyclohexane : 6/4) yielded (E)-3-(4-indolyl)propenyl acetate **5** (18.4 g, 95%) as a white solid, m. p. 82-84°C. TLC (Et_2O/cyclohexane : 1/1) : R_f = 0.46; Anal. for $C_{13}H_{13}NO_2$ calc. C 72.56, H 6.05, N 6.51 found C 72.45, H 6.07, N 6.39; IR : (KBr): 3400, 3060, 2960, 1730, 1500, 1420, 1370, 970, 900 cm^{-1}; MS (DCI, NH_3) : 215 (M^+), 233 ($M+NH_4^+$), 173, 156 (base); ^{1}H-NMR : (200 MHz, $CDCl_3$) : 8.40 (1H, broad s), 7.36-7.17 (4H, m), 7.11 (1H, d, J = 16 Hz), 6.77 (1H, m), 6.51 (1H, d t, J = 16, 6.5 Hz), 4.86 (2H, d, J = 6.5 Hz), 2.17 (3H, s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 171.1, 136.1, 133.0, 128.3, 126.0, 124.6, 123.5, 121.9, 117.9, 110.9, 100.8, 65.6, 21.0.

(E)-3-[3-[(E)-2-nitroethenyl]-4-indolyl]propenyl acetate : To a stirred solution of 1-dimethylamino-2-nitroethylene (6.33 g, 54.6 mmol) in dry CH_2Cl_2 (40 ml), at 0°C, under argon, was added dropwise trifluoroacetic acid (9.6 ml, 124 mmol) dissolved in dry CH_2Cl_2 (25 ml), followed ten minutes after, by the careful addition of (E)-3-(4-indolyl)propenyl acetate **5** (10.66 g, 49.6 mmol) dissolved in dry CH_2Cl_2 (75 ml). The mixture was stirred 3 hrs at 0°C, then 3 hrs at r. t. The reaction mixture was poured onto ice. The organic layer was washed with water. The aqueous layer was extracted with CH_2Cl_2. The organic phases were washed with saturated Na_2CO_3, with brine, then dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (AcOEt/cyclohexane : 1/4) yielded (E)-3-[3-[(E)-2-nitroethenyl]-4-indolyl]propenyl acetate (9.93 g, 70%) as an orange solid, m. p. 150°C. TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.40; Anal. for $C_{15}H_{14}N_2O_4$ calc. C 62.94, H 4.90, N 9.79 found C 62.83, H 4.97, N 9.68; IR : (neat) : 3400, 3100, 2950, 1720, 1630, 1610, 1260, 800 cm^{-1}; MS (EI, 70 eV) : 286 ($M^{+\cdot}$), 196, 180, 154, 127, 115, 85 (base), 43; ^{1}H-NMR : (250 MHz, $CDCl_3$) : 8.83 (1H, broad s), 8.58 (1H, d, J = 13.4 Hz), 7.70 (1H, d, J = 3 Hz), 7.54 (1H, d, J = 13.4 Hz), 7.40-7.23 (4H, m), 6.28 (1H, dt, J = 16, 6 Hz), 4.85 (2H, d, J = 6 Hz), 2.18 (3H, s); ^{13}C-NMR : (50 MHz, $(CD_3)_2CO$) : 170.7, 137.4, 134.4, 132.5, 130.8, 130.7, 128.4, 126.5, 123.5, 123.3, 120.6, 111.8, 108.7, 64.2, 20.6.

(E)-3-[(2-nitroethyl)-4-indolyl]propenyl acetate **3** : To a stirred solution of (E)-3-[3-[(E)-2-nitroethenyl]-4-indolyl]propenyl acetate (9.93g, 34.7 mmol) in dry THF (350 ml), at -15°C, under argon, was added portionwise sodium borohydride (5.27g, 139 mmol) during 1 hr. MeOH (17 ml, 417 mmol) was added dropwise during this time. Stirring was continued for 20 minutes, and the reaction mixture was quenched, at 0°C, with 10% of acetic acid solution, to pH = 7. The mixture was concentrated, then poured onto water, and extracted with Et_2O. The organic layers were washed with water, with brine, then dried ($MgSO_4$), filtered, and evaporated. Flash chromatography (AcOEt/cyclohexane : 1/4) yielded (E)-3-[(2-nitroethyl)-4-indolyl]propenyl acetate **3** (8 g, 80%) as a white solid, m. p. 89-90°C. TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.53; Anal. for $C_{15}H_{16}N_2O_4$ calc. C 62.50, H 5.59, N 9.72 found C 62.33, H 5.60, N 9.63; IR : (KBr) : 3310, 3060, 2995, 2920, 1710, 1605, 1535, 1420, 1375, 960, 900 cm^{-1}; MS (EI, 70 eV) : 288 ($M^{+\cdot}$), 198, 181, 167, 127, 115, 85, 43 (base); ^{1}H-NMR : (200 MHz, $CDCl_3$) : 8.22 (1H, broad s), 7.37-7.05 (5H, m), 6.25 (1H, d t, J = 16, 6 Hz), 4.81 (2H, d, J = 6 Hz), 4.65 (2H, t, J = 7 Hz), 3.60 (2H, t, J = 7 Hz), 2.13 (3H, s); ^{13}C-NMR : (50MHz, $CDCl_3$) : 171.0, 137.0, 132.0, 130.0, 126.0, 124.0, 122.0, 118.0, 111.0, 110.0, 76.0, 65.0, 26.0, 21.0.

(4R, 5R)-4-nitro-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **6** : A mixture of K_2CO_3 (9.58 g, 69.4 mmol), $Pd(OAc)_2$ (0.187 g, 0.83 mmol) and (S)-(-)-BINAP (1.048 g, 1.66 mmol) in dry THF (30 ml) was stirred at r. t., under argon. The mixture turned from light orange to dark red. A solution of (E)-3-[(2-nitroethyl)-4-indolyl]propenyl acetate **3** (8 g, 27.7 mmol) in dry THF (60 ml) was added dropwise, then stirred for 6 hrs.

The reaction mixture was filtered through silica gel, and the crude residue was washed with THF. The solvent was removed under reduced pressure. Flash chromatography (AcOEt/cyclohexane : 1/9) yielded (4R, 5R)-4-nitro-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **6** (3.6 g, 57%) as a white solid, m. p. 210°C (MeOH). TLC (AcOEt/cyclohexane : 3/7): R_f = 0.58; $[\alpha]_D^{20}$ = - 77 (c = 1, CH_2Cl_2); IR : (KBr) : 3380, 2960, 1525, 1450, 1290 cm^{-1}; MS (EI, 70 eV) ($C_{13}H_{12}N_2O_2$) : 228 (M^+), 181 (base), 154, 127, 115, 77, 63; ^{1}H-NMR : (250 MHz, $(CD_3)_2CO$) : 10.0 (1H, broad s), 7.25 (1H, d, J = 8 Hz), 7.12 (1H, m), 7.10 (1H, m), 6.76 (1H, d, J = 8 Hz), 5.91 (1H, d d d, J = 17, 10, 9 Hz), 5.30 (1H, d, J = 10 Hz), 5.22 (1H, d, J = 17 Hz), 4.94 (1H, m), 4.27 (1H, t, J = 9 Hz), 3.50 (2H, d, J = 7.5 Hz); ^{13}C-NMR : (50 MHz, $(CD_3)_2CO$) : δ (ppm) : 136.5, 134.9, 128.7, 126.0, 123.5, 120.2, 116.5, 110.6, 108.0, 88.5, 48.3, 27.5.

(4R, 5R)-4-amino-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole : Zn(Hg) was prepared as followed : to a solution of $HgCl_2$ (2 g) in water (20 ml) and concentrated HCl (1 ml) was added zinc powder (10 g). After 10 minutes of vigourous stirring, at r. t., the amalgam was washed with HCl (0.1 N), with EtOH, then with Et_2O. The amalgam was filtered and dried under reduced pressure to furnish Zn(Hg) (9 g).

To a stirred refluxing solution of (4R, 5R)-4-nitro-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **6** (0.228 g, 1 mmol) in MeOH (4 ml) and HCl 2N (1 ml) was added Zn(Hg) (0.250 g) portionwise, under argon. Stirring was continued for 3 hrs, then the reaction mixture was cooled to r. t. and basified with NaOH 20% up to pH = 9. The mixture was filtered and the amalgam was washed with water and Et_2O. The filtrate was extracted with Et_2O. The organic phases were dried (Na_2SO_4), filtered, and evaporated. (4R, 5R)-4-amino-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole (0.180 g, 95%) was obtained as a white solid, m. p. 178-180°C (dec.). TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.10; $[\alpha]_D^{20}$ = - 83.5 (c = 1, CH_2Cl_2); IR : (neat) : 3400, 3200, 2960, 1600, 1440, 1340, 900, 740 cm^{-1}; ^{1}H-NMR : (200 MHz, $(CD_3)_2CO$) : 7.95 (1H, broad s), 7.25-7.14 (2H, m), 6.92-6.86 (2H, m), 5.90 (1H, d d d, J = 17, 10, 9 Hz), 5.38 (1H, d, J = 10 Hz), 5.23 (1H, d, J = 17 Hz), 3.84 (1H, t, J = 9 Hz), 3.40 (1H, d d d, J = 9, 7.6, 4 Hz), 3.27 (1H, d d, J = 16 , 4 Hz), 3.00 (1H, d d, J = 16, 7.6 Hz), 2.50 (2H, m); ^{13}C-NMR : (50 MHz, $(CD_3)_2CO$) : 138.8, 133.7, 131.4, 126.0, 122.8, 118.8, 118.2, 116.3, 110.9, 108.9, 67.9, 55.5, 25.5.

(4R, 5R)-1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **7** : To a solution of (4R, 5R)-4-amino-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole (0.093 g, 0.47 mmol) and Boc_2O (0.225 g, 1.03 mmol) in dry CH_3CN (5 ml), under argon, was added DMAP (0.006 g, 0.05 mmol) at r. t. The mixture was stirred for 2 hrs, and the solvent was removed under reduced pressure. A flash chromatography (eluant : CH_2Cl_2/hexane : 2/8) yielded (4R, 5R)-1-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamino)-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **7** (0.172 g, 92%) as a white solid, m. p. 110-112°C. TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.75; $[\alpha]_D^{20}$ = - 71 (c = 1, CH_2Cl_2); IR : (neat) : 3446, 2980, 1731, 1441, 1393, 1370, 1283, 1152, 923, 844, 767 cm^{-1}; MS (EI, 70 eV) ($C_{23}H_{30}N_2O_4$): 398 (M^+), 343, 281, 225, 41 (base); ^{1}H-NMR : (200 MHz, $CDCl_3$) : 7.85 (1H, d, J = 7.5 Hz), 7.32 (1H, m), 7.27 (1H, t, J = 7.5 Hz), 7.00 (1H, d, J = 7.5 Hz), 5.88 (1H, d d d, J = 15, 10, 9 Hz), 5.41 (1H, d, J = 10 Hz), 5.27 (1H, d, J = 15 Hz), 3.77 (1H, t, J = 9 Hz), 3.45 (1H, d t, J = 9, 5 Hz), 3.25 (1H, d d, J = 15, 5 Hz), 2.95 (1H, d d, J = 15, 9 Hz), 1.68 (9H, s), 1.50 (9H, s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 154.1, 149.9, 137.1, 133.2, 129.9, 128.0, 125.1, 119.9, 119.2, 115.7, 114.5, 113.5, 83.6, 83.1, 60.5, 44.9, 27.6, 27.4.

(4R, 5R)-1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-(1',2'-dihydroxyethyl)-1,3,4,5-tetrahydro benz[c,d]indole : To a stirred solution of (4R, 5R)-1-ter-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-vinyl-1,3,4,5-tetrahydrobenz[c,d]indole **7** (0.170 g, 0.43 mmol) in acetone (0.10 ml), under argon, was added water (0.25 ml) at 0°C, followed by dropwise addition of OsO_4 1% in t-BuOH (0.5 ml). NMO (0.062 g, 0.47 mmol) was then added and the mixture was warmed up to r. t. Stirring was continued for 48 hrs, then the mixture was quenched with a saturated solution of $Na_2S_2O_5$ for 3 hrs. The aqueous layer was extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and evaporated to give (4R, 5R)-1-tert-butoxycarbonyl-4-(N-tertbutoxycarbonylamino)-5-(1',2'-dihydroxyethyl)-1,3,4,5-tetrahydrobenz[c,d]indole (0.150 g, 80%). TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.10; IR : (neat) : 3600-3100, 3020, 2980, 2940, 1710, 1500, 1440, 1380, 1160, 760 cm^{-1}; MS (EI, 70 eV) ($C_{23}H_{32}N_2O_6$): 432 ($M^{+\cdot}$), 392, 315, 297, 259, 241, 198 (base), 169, 154, 57; ^{1}H-NMR : (200 MHz, $CDCl_3$) : 7.81 (1H, d, J = 7.5 Hz), 7.34 (1H, m), 7.24 (1H, t, J = 7.5 Hz), 7.11 (1H, d, J = 7.5 Hz), 4.00 (1H, m), 3.70 (3H, m), 3.45 (1H, m), 3.20 (1H, d m, J = 15 Hz), 3.00 (2H, broad s), 2.90 (1H, d m, J = 15 Hz), 1.70 (9H, s), 1.50 (9H, s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 155.7, 149.9, 128.3, 125.2, 123.3, 121.5, 113.6, 113.3, 84.5, 79.8, 73.2, 62.5, 59.0, 47.0, 28.2, 23.9.

(4R, 5R)-1-ter-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-formyl-1,3,4,5-tetrahydrobenz[c,d]indole **8**

To a solution of (4R, 5R)-1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-(1',2'-dihydroxyethyl)-1,3,4,5-tetrahydrobenz[c,d]indole (0.144 g, 0.33 mmol) in MeOH (6 ml) and water (3 ml), at 0°C, under argon, was added $NaIO_4$ (0.071 g, 0.36 mmol). The mixture was stirred 15 minutes at this temperature, and then filtered through silica gel. The aqueous layer was extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4), filtered, and evaporated. The crude (4R, 5R)-1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-5-formyl-1,3,4,5-tetrahydrobenz[c,d]indole **8** was obtained (0.116 g, 87%) as an oil. TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.50; $[\alpha]_D^{20}$ = - 59 (c = 1, CH_2Cl_2); IR : (neat) : 3300, 3010, 2960, 1730, 1710, 1500, 1440, 1380, 850, 760 cm^{-1}; MS (EI, 70 eV) ($C_{22}H_{28}N_2O_5$) : 400 (M^+), 372, 322, 283, 199, 154, 57 (base); ^{1}H-NMR : (200 MHz, $CDCl_3$) : 9.65 (1H, d, J = 3 Hz), 7.90 (1H, d, J = 8 Hz), 7.35-7.10 (2H, m), 7.07 (1H, d, J = 8 Hz), 4.20 (1H, d d, J = 9, 3 Hz), 3.25-2.80 (3H, m), 1.67 (9H, s), 1.50 (9H, s).

methyl-(E)-3-[(4R, 5R)-1-ter-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-1,3,4,5-tetrahydrobenz[c,d] indol-5-yl]-2-methylpropenoate **9** : A solution of the crude (4R, 5R)-1-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamino)-5-formyl-1,3,4,5-tetrahydrobenz[c,d]indole **8** (0.066 g, 0.164 mmol) and crystalline (α-carbomethoxyethylidene)triphenylphosphorane [13b](0.120 g, 0.34 mmol) in dry THF (2 ml) was stirred and warmed up to 50°C for 2 hrs, under argon. The solvent was removed under reduced pressure. The crude (E)-methyl-3-[1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-1,3,4,5-tetrahydrobenz[c,d]indol-5-yl]-2-methylpropenoate **9** was purified by flash chromatography (AcOEt/cyclohexane : 1/9). methyl-(E)-3-[(4R, 5R)-1-tert-butoxycarbonyl-4-(N-ter-butoxycarbonylamino)-1,3,4,5-tetrahydrobenz[c,d]indol-5-yl]-2-methyl propenoate **9** (0.056 g, 73%) was isolated as an oil. TLC (AcOEt/cyclohexane : 3/7) : R_f = 0.50; $[\alpha]_D^{20}$ = - 98 (c = 1, CH_2Cl_2); IR : (film) : 2960, 1720, 1680, 1440, 1380, 910 cm^{-1}; MS (EI, 70 eV) ($C_{26}H_{34}N_2O_6$) : 470 (M^+), 415, 397, 353, 265, 221, 57 (base); ^{1}H-NMR : (200 MHz, $CDCl_3$) : 7.90 (1H, d, J = 8 Hz), 7.40 (1H, m), 7.30 (1H, t, J = 8 Hz), 6.95 (1H, d, J = 8 Hz), 6.75 (1H, d, J = 10 Hz), 4.15 (1H, m), 3.77 (4H, s + m), 3.15 (1H, d d, J = 16, 4 Hz), 2.90 (1H, d d, J = 16, 9 Hz), 2.10 (3H, s), 1.70 (9H, s), 1.40 (9H, s); ^{13}C-NMR : (50 MHz, $CDCl_3$) : 168.1, 154.9, 149.8, 140.5, 138.6, 133.4, 130.2, 129.6, 127.6, 125.3, 120.7, 114.0, 113.8, 83.5, 79.5, 52.0, 51.7, 41.3, 28.2, 28.1, 15.5.

(-)-chanoclavine I 2 : To a suspension of $LiAlH_4$ (0.027 g, 0.72 mmol) in dry Et_2O (0.5 ml), a solution of methyl-(E)-3-[(4R, 5R)-1-tert-butoxycarbonyl-4-(N-tert-butoxycarbonylamino)-1,3,4,5-tetrahydrobenz[c,d] indol-5-yl]-2-methylpropenoate **9** (0.056 g, 0.12 mmol) in dry THF (0.5 ml) was added carefully at r. t., under argon. The mixture was stirred, under reflux, for 2 hrs, then cooled to 0°C and quenched with a solution of saturated Na_2SO_4. The aqueous layer was extracted with CH_2Cl_2. The organic phases were dried (Na_2SO_4), filtered and evaporated. Chromatography (TLC : $CHCl_3$/n-BuOH/NH_4OH aq. 25% : 2/1/0.020) gave (-)-chanoclavine I **2** (0.004 g, 13%) as a pale yellow solid, m. p. 192°C. TLC ($CHCl_3$/n-BuOH/NH_4OH aq. 25% : 2/1/0.02) : R_f = 0.43; $[\alpha]_D^{20}$ = - 213 (c = 0.4, pyridine) [litt. $[\alpha]_D^{20}$ = - 240 (c = 1, pyridine)]; IR : (neat) : 3250, 3050, 2870, 2810, 1620, 1605, 1450, 1380, 1260, 1220, 920 cm^{-1}; MS (EI, 70 eV) ($C_{16}H_{20}N_2O_1$) : 256 (M^+, base), 237, 223, 196, 168, 155; ^1H-NMR : (200 MHz, C_5D_5N) : 11.65 (1H, broad s), 7.60-6.95 (4H, m), 5.85 (1H, d d, J = 10, 1.5 Hz), 4.45 (2H, s), 4.25 (1H, t, J = 9 Hz), 3.40 (1H, d d, J = 15, 5 Hz), 3.20 (1H, m), 3.00 (1H, d d, J = 15, 9 Hz), 2.44 (3H, s), 2.20 (2H, broad s), 2.05 (3H, d, J = 1.5 Hz).

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