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Synthesis of New Annelated Indole Systems : New Entry in the E-azaeburnane series.

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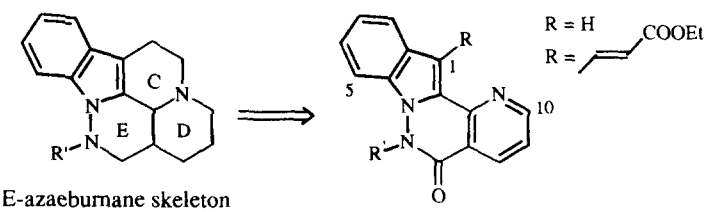
***Abstract**: Starting from a judiciously substituted N-aminoindole, the Heck reaction led to new classes of heterocyclic compounds: the pyrido[2',3'-d']pyridazino[2,3-a]indoles **7** and **8** and the pyrido[2',3'-d']diazepino[1,6,7-h,i]indole **15**. From compound **7** the pentacyclic E-azaeburnane **21** was prepared.*

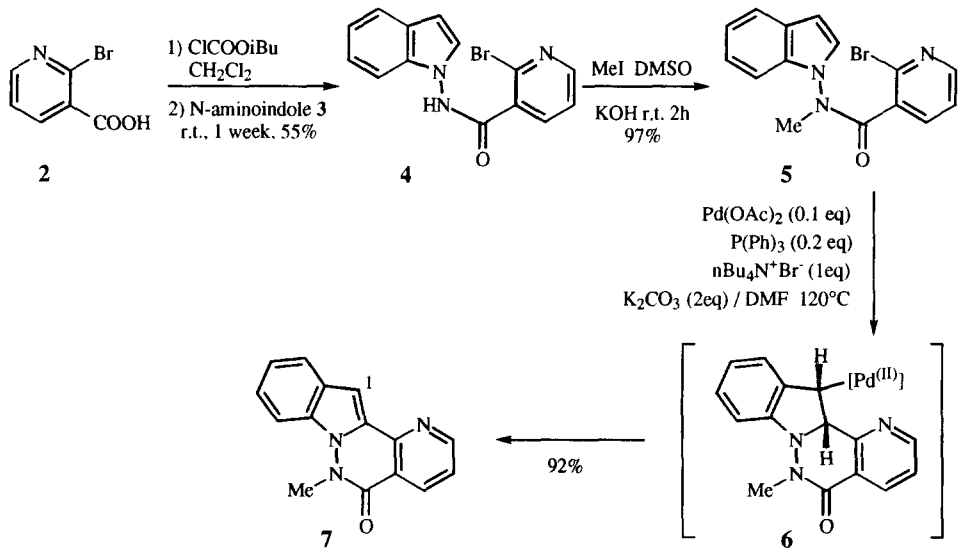
In the course of our study of E-azaeburnane[1], we were interested in the synthesis of a new heterocyclic system: the pyrido[2',3'-d']pyridazino[2,3-a]indole **1**,(substituted or not on the 1-position), which is precursor of the target pentacyclic skeleton.



E-azaeburnane skeleton
R' = H, Me

1

In a previous communication[2] we have described a convenient access to compound **7** based on the Heck reaction[3] (Scheme 1, Table 1 - entry 1).



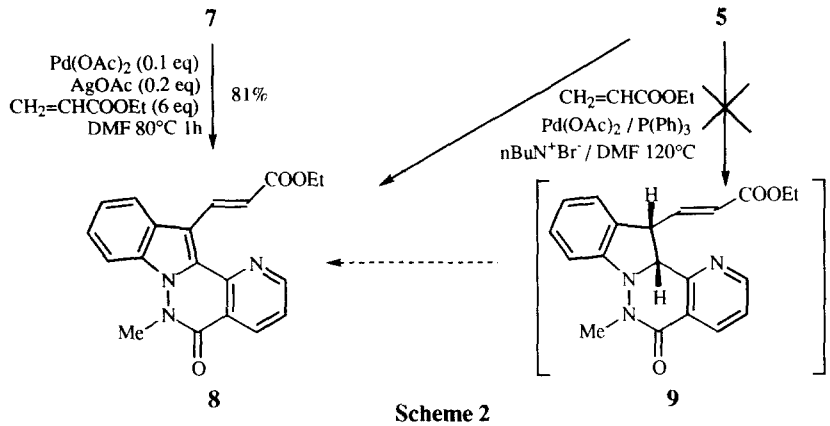
Scheme 1

In order to construct the ring C of the target molecule, two strategies were investigated. The first one consists in the use of an another Heck reaction step to functionalize the carbon of the indole (strategy A). The second starts with the pyridine ring hydrogenation prior to the construction of the ring C (strategy B).

STRATEGY A :

To prepare the C_1-alkylated compound type **1** (R = -CH=CH-COOEt), two possibilities were explored: (i) functionalization of the isolated product **7** or (ii) a tandem reaction from **5** creating the two C-C bonds in "one pot". This latter idea, based on the intermediate formation of the palladium-complex **6**, seemed to be all the more exciting in that the stereochemistry of **6** should possibly be favourable to the intermolecular insertion of ethyl acrylate rather than the β-elimination of palladium (II).

Indeed, palladium (II) catalysed coupling of **7** with ethyl acrylate in the presence of silver acetate provided the desired indole **8** in good yield (scheme 2). The *trans* stereochemistry of the acrylic double bond (typical for this type of reaction[4]) was supported by ^1H NMR data (^3J = 17 Hz).



Scheme 2

Direct synthesis of **8** by the tandem Heck reaction[5] was then investigated (**5** -> [**6**] -> **9** -> **8**). This study was also interesting since isolation of the indoline **9** would have provided an access to pentacyclic structures with a dihydroindole framework[6]. However the possible intermediate **9** could never be isolated.

A systematic study of experimental conditions of the above mentioned reaction showed that a stoichiometric amount of palladium (II) and a large excess of triphenylphosphine were necessary to obtain compound **8** (Scheme 2, Table 1- entry 5). Without this excess of triphenylphosphine, compound **8** could not be obtained (entry 3-4), whereas under catalytic conditions, the reaction only gave the tetracycle **7** (Table 1-entry 2).

entry		$Pd(OAc)_2$	PPh_3	nBu_4NBr	K_2CO_3	Time	Results
1	-	0.1 eq	0.2 eq	1 eq	2 eq	2h	**7**: 92%
2	2 eq	0.1 eq	0.2 eq	1 eq	2 eq	12h	**5**: 40% **7**: 40%
3	2 eq	1 eq	2 eq	1 eq	-	12h	**5**: 20% **7**: 20% *
4	15 eq	1 eq	2 eq	1 eq	-	48h	**5**: 10% **7**: 20% *
5	15 eq	1 eq	6 eq	1 eq	-	24h	**5**: 10% **8**: 63% **

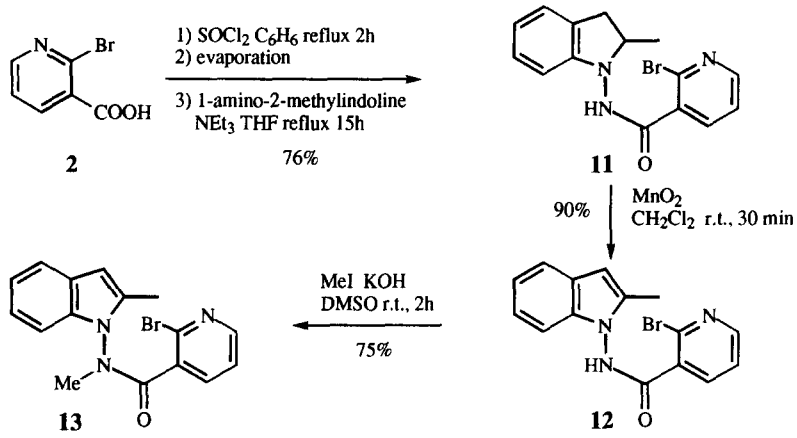
* additional tarry material was not analyzed

** cleaner reactions were also observed with a larger excess of triphenylphosphine.

Table 1

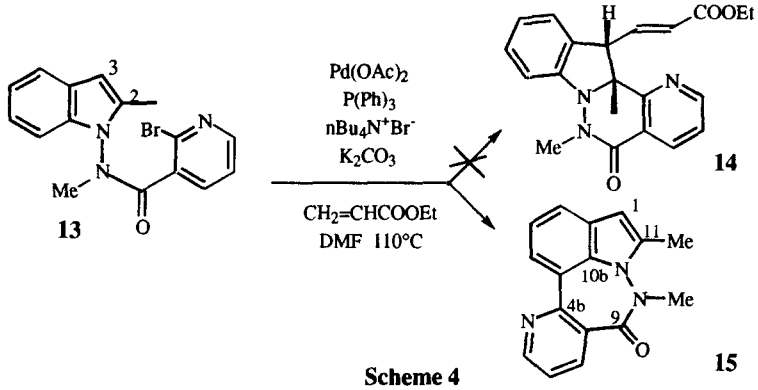
The absence of the intermediate indoline **9** in the reaction mixture can be explained by two mecanisms; (i) either an *in situ* dehydrogenation to give the tetracycle **8** takes place (path **5** -> [**6**] -> [**9**] -> **8**); or (ii) the reaction only follows the path **5** -> [**6**] -> **7** -> **8**. To test the possibility of obtaining a dihydroindole structure, we postulated that the presence of a substituent at indole C-2 would prevent dehydrogenation thereby favouring the tandem Heck reaction. With this in mind, we prepared the methylated derivative **13** (Scheme 3) and subjected it to the Heck reaction conditions.

In the course of the preparation of **13**, our experimental observation indicated that the oxidation of indoline **11** prior to *N*-methylation was preferable.



Scheme 3

Unfortunately, the tandem Heck reaction of compound **13** did not provide the desired indoline **14** but gave instead the novel tetracycle **15** (scheme 4 - table 2). We have also obtained **15** from a simple Heck reaction (entry 4). Additionally, it was observed that an excess of triphenylphosphine played an essential role for the formation of **15** (Table 2-entry 3 and 4).



Scheme 4

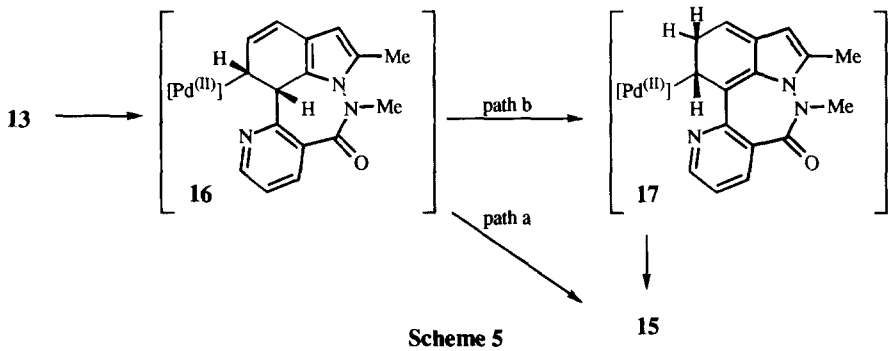
entry		$Pd(OAc)_2$	PPh_3	nBu_4NBr	K_2CO_3	Time	Results
1	15 eq	0.1 eq	0.6 eq	1 eq	2 eq	48h	**13**: 35% **15**: 15% *
2	15 eq	1 eq	6 eq	1 eq	-	24h	**13**: 20% **15**: 10% *
3	-	0.1 eq	0.2 eq	1 eq	2 eq	5h	traces of **13** and **15** *
4	-	0.1 eq	0.6 eq	1 eq	2eq	2h	**13**: 10% **15**: 41%

* additional tarry material was not analyzed

Table 2

The absence of compound **14** could be explained by the steric hindrance exerted by the C_2-methyl group.

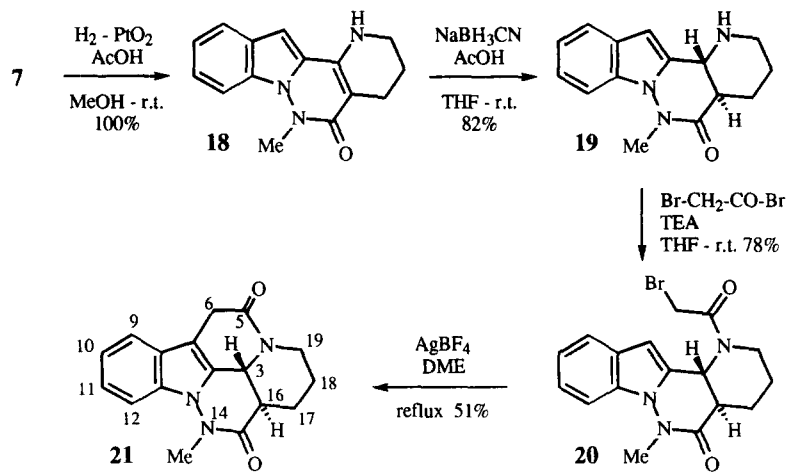
Also, HPdX elimination to give **15**, can probably occur after a facile [1,5] sigmatropic rearrangement followed by a classical β-elimination (path b) or through the base-assisted elimination (Br^- / DMF, AcO^-, K_2CO_3 when used) as postulated in the Scheme 1 for intermediate **6** (path a, Scheme 5). Indeed, when the reaction was carried out in the presence of ethyl acrylate, the trapping of palladium-complex intermediate was not observed.



Scheme 5

STRATEGY B :

From the compound **7** we were able to prepare the E-azaeburnane **21** according to the Scheme 6.



Scheme 6

Hydrogenation of **7** gave the unstable amine **18** which was further reduced with $NaBH_3CN$ in AcOH/THF to afford the single amine **19** in 82% yield. The expected *trans* stereochemistry of **19** was

properly established from a careful study of the ^{1}H-NMR 2D-COSYand NOESY spectra (see experimental part); especially the *trans* stereochemistry of D/E rings was confirmed by the appearence of a signal corresponding to H-6a at $\delta = 3.85$; dd; J = 10.6 Hz, 1 Hz (due to the N-H coupling which disappeared upon addition of D_2O).

Cyclization of α-bromoacetamide **20** (obtained in a 78% yield) was achieved with $AgBF_4$ in DME to give **21** in a 50 % yield. Attempts to prepare **21** under different other conditions were not successfull (e.g. K_2CO_3/DMF).

A detailed analysis of ^{1}H-NMR and 2D-COSY spectrum of **21** allowed the complete attribution of protons. The coupling constant between H_{2a} and H_{12b} (11Hz) confirmed the *trans* stereochemistry of D/E rings.

Conclusion

The use of the Heck reaction allowed the preparation of the tetracyclic compound **7** via a palladium-assisted ring closure of amide **5** and the functionalization of the 1-position of the indole **7**. Mechanistic study of this series of two reactions led to: (a) successfully perform a tandem HECK reaction to give directly compound **8** from the amide **5**; (b) synthesize compound **13** in an attempt to prepare E-azaeburnane derivatives containing a dihydroindole structure. In fact, palladium-catalysed cyclization of amide **13** gave a new heterocyclic system: the pyrido[2',3'-d']diazepino[1,6,7-h,i]indole **15**.

However, hydrogenation of the pyridine ring of **7** prior to the E-azaeburnane ring C construction, effectively allowed the formation of new E-azaeburnane derivatives which are of pharmacological interest. Further work in this area is in progress.

Acknowledgments

We wish to thank the Groupe de Recherches Servier for financial support and Prof. P. Potier for his interest during this work.

Experimental

Flash chromatography were performed using silica gel (Merck, 230-400 Mesh). Melting points were determined on a Tottoli apparatus. IR spectra were recorded on a Nicolet 250 FT-IR instrument. Mass spectral measurements were obtained with an AEI MS50 (EI) or a Kratos MS-80 (FAB, HRMS) spectrometer. UV spectra were recorded on a Perkin Elmer lamba 5 instrument. Proton NMR spectra were determined on Bruker AC 200-MHz, 250-MHz or 400-MHz instruments. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

N-(2'-bromonicotinoyl)aminoindole 4

A solution of 2-bromonicotinic acid[7] **2** (208 mg, 1.03 mmol) and triethylamine (160 µl, 1.13 mmol) in dry CH_2Cl_2 (15 ml) was stirred at r.t. for 10 minutes. Isobutyl chloroformate (150 µl, 1.13 mmol) was added, and after a further 2 hours stirring, N-aminoindole **3** (150 mg, 1.13 mmol) was added.

After an additionnal week of stirring, water (10 ml) was added to the mixture which was extracted with CH_2Cl_2 (3x10 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), evaporated and subjected to flash chromatography. Elution with ethyl acetate / heptane (50 / 50) gave two fractions. The first one was identified as N-aminoindole (60 mg, 40%). The second fraction was the desired compound **4** (178 mg, 55%) obtained as white crystals m.p. = 177-178°C. IR ($CHCl_3$): 3385; 3240; 1700; 1585. MS (EI): 317 - 315 ($M^{+\cdot}$); 236; 186 - 184; 158 - 156; 140; 131 (100%); 77. HRMS (EI): $C_{14}H_{10}BrN_3O$ calculated 315.0016 - 316.9995, found 315.0015 - 316.9985. UV (EtOH): 373.0 (3.661); 249.8 (4.01); 204.4 (4.29). Elemental analysis: calculated C 53.19 H 3.18 N 13.29 found C 52.92 H 3.27 N 13.4. ^1H n.m.r. (200 MHz, $CDCl_3$): 9.70 (br s, 1H exch D_2O, NH); 8.25 (dd, 1H, $H_{6'}$; $J_{6'-5'}$ = 5 Hz; $J_{6'-4'}$ = 1.5 Hz); 7.60 (dd, 1H, $H_{4'}$; $J_{4'-5'}$ = 7.5 Hz; $J_{4'-6'}$ = 1.5 Hz); 7.50 (d, 1H, H_4; J_{4-5} = 8 Hz); 7.30 (d, 1H, H_7; J_{7-6} = 8 Hz); 7.30 (d, 1H, H_2; J_{2-3} = 3 Hz); 7.20-7.00 (m, 3H, $H_{5'}$, H_5, H_6); 6.40 (d, 1H, H_3; J_{3-2} = 3 Hz). ^{13}C n.m.r.(62.9 MHz, $CDCl_3$): 166.3 (CO); 151.3 ($C_{6'}$); 138.5 ($C_{2'}$); 137.4 ($C_{3'}$); 135.4 ($C_{4'}$); 133.0 (C_{7a}); 126.8 (C_2); 126.6 (C_{3a}); 123.7 (C_4); 122.8 ($C_{5'}$); 122.2 (C_6); 121.3 (C_5); 108.7 (C_7); 104.5 (C_3).

N-(2'-bromonicotinoyl)-N-methylaminoindole 5

Hydrazide **4** (72 mg, 0.23 mmol) and iodomethane (29 µl, 0.46 mmol) were added to a suspension of potassium hydroxide (51 mg, 0.92 mmol) in dry DMSO (3 ml). After 30 minutes of stirring, water (10 ml) was added to the mixture which was extracted with CH_2Cl_2 (4x20 ml). The combined organic layers were washed with water (5x20 ml), dried ($MgSO_4$), evaporated and purified by flash chromatography. Elution with ethyl acetate / heptane (50 / 50) gave the desired compound **5** (73 mg, 97%) as a white powder. IR ($CHCl_3$): 1680; 1580. MS (EI): 331-329 ($M^{+\cdot}$); 250; 186 - 184; 158 - 156; 145 (100 %); 116. HRMS (EI) $C_{15}H_{12}BrN_3O$ calculated 329.0174 - 331.0153, found 329.0180 - 331.0130. UV (EtOH): 261.0 (4.02); 214.0 (4.51). ^1H n.m.r. (200 MHz, CD_3OD): 8.10 (dd, 1H, $H_{6'}$; $J_{6'-5'}$ = 5 Hz; $J_{6'-4'}$ = 1.5 Hz); 7.65 (dd, 1H, $H_{4'}$; $J_{4'-5'}$ = 8 Hz; $J_{4'-6'}$ = 1.5 Hz); 7.45 (t, 1H, H_6; J_{6-5} = J_{6-7} = 8 Hz); 7.40 (d, 1H, H_2; J_{2-3} = 3 Hz); 7.30 (t, 1H, H_5; J_{5-4} = J_{5-6} = 8 Hz); 7.20-7.00 (m, 3H, $H_{5'}$, H_4, H_7); 6.15 (d, 1H, H_3; J_{3-2} = 3 Hz); 3.55 (s, 3H, NMe). ^{13}C n.m.r.($CDCl_3$, 50.3 MHz): 169.0 (CO); 150.4 ($C_{6'}$); 138.2 ($C_{2'}$); 135.1 ($C_{3'}$); 134.3 ($C_{4'}$); 133.6 (C_{7a}); 127.3 (C_{3a}); 126.7 (C_2); 123.5 (C_4); 121.6-121.4 ($C_{5'}$-C_6-C_5); 108.6 (C_7); 103.4 (C_3); 35.9 (NMe).

6-methyl-7-oxopyrido[2',3'-d'] pyridazino[2,3-a]indole 7

A mixture of hydrazide **5** (100 mg; 0.30 mmol) , $Pd(OAc)_2$ (7 mg; 0.03 mmol), triphenylphosphine (16 mg; 0.06 mmol), tetrabutylammonium bromide (98 mg; 0.30 mmol) and potassium carbonate (84 mg; 0.60 mmol) in dry DMF (25 ml) was heated at 120°C under argon for 2h. After cooling, water (30 ml) was added and the mixture was extracted with CH_2Cl_2 (5x50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, evaporated and subjected to flash chromatography. Elution with ethyl acetate / heptane (50 / 50) and recrystallization provided tetracycle **7** (68 mg, 92%) as yellow crystals. m.p. = 172-173°C. IR ($CHCl_3$): 1650; 1590; 1555. MS (EI): 249 ($M^{+\cdot}$, 100%); 234. HRMS (EI) $C_{15}H_{11}N_3O$ calculated 249.0911, found 249.0907. UV (EtOH): 307.2 (4.34); 243.8 (4.27); 212.0 (4.48). Elemental analysis: calculated C 72.29 H 4.42 N 16.87 found C 72.02 H 4.62 N 16.79. ^1H n.m.r.

(200 MHz, $CDCl_3$): 8.90 (dd, 1H, H_{10}; J_{10-9} = 5 Hz; J_{10-8} = 2 Hz); 8.60 (dd, 1H, H_8; J_{8-9} = 8 Hz; J_{8-10} = 2 Hz); 7.90 (dd, 1H, H_2; J_{2-3} = 8 Hz; J_{2-4} = 1 Hz); 7.80 (dd, 1H, H_5; J_{5-4} = 8 Hz; J_{5-3} = 1 Hz); 7.50 (s, 1H, H_1); 7.43 (dd, 1H, H_9; J_{9-8} = 8 Hz; J_{9-10} = 5 Hz); 7.30 (td, 1H, H_4; J_{4-5} = J_{4-3} = 8 Hz; J_{4-1} = 1 Hz); 7.25 (td, 1H, H_3; J_{3-2} = J_{3-4} = 8 Hz; J_{3-5} = 1 Hz); 4.30 (s, 3H, NMe). ^{13}C n.m.r. (62.9 MHz, $CDCl_3$): 159.5 (CO); 154.6 (C_{10}); 146.8 (C_{11a}); 136.3 (C_8); 131.8 (C_{7a}); 129.0 (C_{5a}); 128.6 (C_{11b}); 126.0 (C_{1a}); 123.4 (C_2); 122.7 (C_9 - C_4); 120.9 (C_3); 111.4 (C_5); 97.5 (C_1); 36.7 (NMe).

1-(2'-*trans*-ethoxycarbonylvinyl)-6-methyl-7-oxopyrido[2',3'-d']pyridazino[2,3-a] indole 8

Palladium(II)coupling of 7 with ethyl acrylate

A mixture of tetracycle **7** (15 mg; 0.06 mmol) , $Pd(OAc)_2$ (1.3 mg; 0.006 mmol), silver acetate (20 mg; 0.12 mmol) and ethyl acrylate (20 µl; 0.18 mmol) in dry DMF (3 ml) was heated at 80°C under argon. After 30 minutes of stirring, ethyl acrylate (20 µl; 0.18 mmol) was added. After a further 30 minutes the mixture was allowed to come to r.t., filtered through a pad of celite and the celite washed with CH_2Cl_2. The filtrate was evaporated and purified by flash chromatography. Elution with ethyl acetate / heptane (50 / 50) provided the *trans* compound **8** (17 mg, 81%) as yellow crystals;(identical with the tandem HECK reaction product,*vide infra*).

Tamdem Heck reaction of hydrazide 5

A mixture of hydrazide **5** (30 mg; 0.09 mmol) , $Pd(OAc)_2$ (20 mg; 0.09 mmol), triphenylphosphine (95 mg; 0.54 mmol), tetrabutylammonium bromide (29 mg; 0.09 mmol) and ethyl acrylate (200 µl; 0.9 mmol) in dry DMF (8 ml) was heated at 110°C under argon for 5 days. After cooling, water (10 ml) was added and the mixture was extracted with CH_2Cl_2 (5x10 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, evaporated and subjected to flash chromatography. Elution with ethyl acetate / heptane (40 / 60) provided the trans compound **8** (20 mg, 63%) as yellow crystals.
m.p. = 172-173°C. IR($CHCl_3$): 1655; 1615; 1590; 1540. MS (EI): 347 ($M^{+\cdot}$); 302; 274 (100%); 248. ^1H n.m.r.(200 MHz, $CDCl_3$): 9.35 (d, 1H, $H_{1'}$; $J_{2'-1'}$ = 12 Hz); 8.95 (dd, 1H, H_{10}; J_{10-9} = 4 Hz; J_{10-8} = 1.5 Hz); 8.50 (dd, 1H, H_8; J_{8-9} = 6 Hz; J_{8-10} = 1.5 Hz); 8.05 (dd, 1H, H_2; J_{2-3} = 8 Hz; J_{2-4} = 1 Hz); 7.80 (dd, 1H, H_5, J_{5-4} = 6 Hz; J_{5-3} = 1 Hz); 7.20-7.40 (m, 3H, H_4, H_3, H_9); 6.55 (d, 1H, $H_{2'}$; $J_{1'-2'}$ = 17 Hz); 4.35 (q, 2H, CH_2; J_{CH2-Me} = 7 Hz); 4.20 (s, 3H, N-Me); 1.40 (t, 3H, Me; J_{Me-CH2} = 7 Hz).^{13}C (62.9 MHz, $CDCl_3$): 168.0 (COO); 160.7 (CON); 154.7 (C_{10}); 147.7 (C_{11a}); 138.7 ($C_{2'}$); 136.3 (C_8); 132.3 (C_{7a}); 131.0 (C_{5a}); 128.9 (C_{11b}); 127.3 (C_{1a}); 124.4 (C_2); 123.1 (C_9); 122.7 (C_4); 122.3 (C_3); 119.8 (C_1); 117.7 ($C_{1'}$); 111.8 (C_5); 60.3 (CH_2); 38.4 (NMe); 14.5 (CH_3).

1-(2'-bromonicotinoyl)amino-2-methylindoline 11

A suspension of 2-bromonicotinic acid **2**[7] (500 mg; 2.47 mmol) in dry benzene (25 ml) was brought to reflux and then thionylchloride (360 µl; 5.00 mmol) was added and the mixture refluxed for 2h. After cooling and evaporation to dryness, a solution of 1-amino-2-methylindoline **10**[8] (405 mg; 2.73 mmol) and triethylamine (380 µl; 2.72 mmol) in dry THF (25 ml) was added. The resulting solution was refluxed under argon overnight. After cooling, water (25 ml) was added to the mixture which was extracted with ethyl acetate (3x25 ml). The combined organic layers were washed with brine, dried ($MgSO_4$),

filtered, evaporated. The residue was triturated with heptane, filtered and dried to yield hydrazide **11** (622 mg, 76 %) as white crystals. m.p. = 169-170°C. IR ($CHCl_3$):1690; 1610; 1575; 1405. MS (EI): m / z = 333-331 ($M^{+\cdot}$); 332-330; 318-316; 317- 315; 186-184; 158-156; 147 (100%). HRMS (EI): $C_{15}H_{14}ON_3{}^{79}Br$ - $C_{15}H_{14}ON_3{}^{81}Br$ required 331.0318 - 333.0302, found 331.0318 - 333.0297. ^1H n.m.r. (200 MHz, CD_3OD): 8.50 (dd, 1H, $H_{6'}$; $J_{6'-5'}$ = 4.5 Hz; $J_{6'-4'}$ = 1.8 Hz); 8.05 (dd, 1H, $H_{4'}$; $J_{4'-5'}$ = 7.3 Hz; $J_{4'-6'}$ = 1.8 Hz); 7.50 (dd, 1H, $H_{5'}$; $J_{5'-4'}$ = 7.3 Hz; $J_{5'-4'}$ = 4.5 Hz); 7.10 (m, 2H, H_4, H_7); 6.85 (m, 2H, H_5, H_6); 3.80 (m, 1H, H_2); 3.15 (dd, 1H, $H_{3\alpha}$; $J_{3\alpha-3\beta}$ = 15 Hz; $J_{3\alpha-2}$ = 8 Hz); 2.70 (dd, 1H, $H_{3\beta}$; $J_{3\beta-3\alpha}$ = 15 Hz; $J_{3\beta-2}$ = 11.5 Hz); 1.49 (d, 3H, Me; J_{Me-2} = 6 Hz). ^{13}C n.m.r. (62.9 MHz, CD_3OD): 151.9 ($C_{6'}$); 139.7 ($C_{4'}$); 132.7 (C_{7a}); 129.2 (C_{3a}); 128.3 (C_4); 125.7 (C_6); 124.2 ($C_{5'}$); 122.4 (C_5); 110.9 (C_7); 66.3 (C_2); 36.8 (C_3); 18.6 (Me). (CO, $C_{2'}$ and $C_{3'}$ not observed).

1-(2'-bromonicotinoyl)amino-2-methylindole 12

MnO_2 (150 mg) was added to a solution of indoline **11** (100 mg; 0.30 mmol) in dry CH_2Cl_2 (10 ml),and the reaction stirred at r.t. for 30 minutes. The mixture was filtered through celite, washed with CH_2Cl_2 and evaporated to dryness to give the pure indole **12** (89 mg, 90%) as white crystals. MS (EI): 331-329 ($M^{+\cdot}$); 250; 186-184; 158-156; 145 (100%). HRMS (EI): $C_{15}H_{12}ON_3{}^{79}Br$ - $C_{15}H_{12}ON_3{}^{81}Br$ required 329.0156 - 331.0152, found 329.0162 - 331.0141. ^1H n.m.r. (200 MHz, CD_3OD): 8.55 (dd, 1H, $H_{6'}$; $J_{6'-5'}$ = 5 Hz; $J_{6'-4'}$ = 1.8 Hz); 8.20 (dd, 1H, $H_{4'}$; $J_{4'-5'}$ = 8 Hz; $J_{4'-6'}$ = 1.8 Hz); 7.60 (dd, 1H, $H_{5'}$; $J_{5'-4'}$ = 8 Hz; $J_{5'-6'}$ = 5 Hz); 7.45 (dd, 1H, H_4; J_{4-5} = 8 Hz; J_{4-6} = 1.2 Hz); 7.35 (dd, 1H, H_7; J_{7-6} = 8 Hz; J_{7-5} = 1 Hz); 7.15 (dt, 1H, H_6; J_{6-5} = J_{6-7} = 8 Hz; J_{6-4} = 1.2 Hz); 7.05 (dt, 1H, H_5; J_{5-6} = J_{5-4} = 8 Hz; J_{5-7} = 1 Hz); 6.30 (s, 1H, H_3); 2.45 (s, 3H, Me). ^{13}C n.m.r. (62.9 MHz, CD_3OD): 152.5 ($C_{6'}$); 148.7 ($C_{2'}$); 140.0 ($C_{4'}$); 137.6 ($C_{3'}$); 128.0 (C_{7a}); 124.3 (C_4); 122.6 (C_6); 121.4 ($C_{5'}$); 120.9 (C_5); 109.3 (C_7); 100.3 (C_3); 11.7 (Me). (CO, C_{3a}, C_2 not observed).

1-(2'-bromonicotinoyl)methylamino-2-methylindole 13

Hydrazide **12** (300 mg, 0.90 mmol) and iodomethane (112 µl, 1.80 mmol) were added to a suspension of potassium hydroxide (200 mg, 3.60 mmol) in dry DMSO (8 ml). After 1 hour of stirring, water (150 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (8x200 ml). The combined organic layers were concentrated to 50 ml, washed with water (4x20 ml), dried ($MgSO_4$), evaporated and subjected to flash chromatography. Elution with CH_2Cl_2 / ethyl acetate (96 / 4) yielded the desired compound **13** (232 mg, 75%) as a colorless oil. IR($CHCl_3$): 1675; 1580; 1460; 1400. MS (EI): 345-343 ($M^{+\cdot}$); 186-184; 159; 130 (100%). HRMS (EI): $C_{16}H_{14}ON_3{}^{79}Br$ - $C_{16}H_{14}ON_3{}^{81}Br$ required 343.0327 - 345.0288, found 343.0318 - 345.0297. ^1H n.m.r.(200 MHz, CD_3OD): 8.10 (dd, 1H, $H_{6'}$; $J_{6'-5'}$ = 5 Hz; $J_{6'-4'}$ = 1.8 Hz); 7.60 (dd, 1H, $H_{4'}$; $J_{4'-5'}$ = 8 Hz; $J_{4'-6'}$ = 1.8 Hz); 7.50-7.00 (m, 4H, H_4, H_5, H_6, H_7); 6.90 (dd, 1H, $H_{5'}$; $J_{5'-6'}$ = 5 Hz; $J_{5'-4'}$ = 8 Hz); 6.10 (s, 1H, H_3); 3.40 (s, 3H, N-Me); 2.35 (s, 3H, Me).^{13}C n.m.r. (62.9 MHz, CD_3OD): 169.2 (CO); 148.7 ($C_{6'}$); 145.5 ($C_{2'}$); 136.5 ($C_{3'}$); 134.3 ($C_{4'}$); 128.6 (C_{7a}); 125.4 (C_{3a}); 120.7 (C_4); 120.1 (C_6); 120.0 ($C_{5'}$); 118.6 (C_5); 107.3 (C_7); 99.7 (C_3); 33.2 (N-Me); 8.9 (Me).(C_2 not observed).

11,12-dimethyl-10-oxopyrido[2',3'-d'] diazepino[1,6,7-h,i] indole 15

Hydrazide **13** (30 mg; 87 µmol), tetrabutylammonium bromide (28 mg; 0.09 mmol) and K_2CO_3 (24 mg; 0.17 mmol) were added to a mixture of $Pd(OAc)_2$ (2 mg; 9 µmol) and triphenylphosphine (15 mg; 0.06 mmol) in dry DMF (8 ml) at 110°C. The mixture was stirred at 110°C for 2h. After cooling, water (20 ml) was added and the mixture was extracted with CH_2Cl_2 (6x50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered, evaporated and purified by flash chromatography. Elution with ethyl acetate / heptane (50 / 50) provided tetracycle **15** (9.6 mg, 41%) as white crystals. m.p.=157-158°C. IR ($CHCl_3$): 1630; 1590. MS (FAB): 264 (MH^+); 232; 165.Elemental analysis: calculated C 72.99 H 4.98 N 15.96 found C 73.25 H 4.76 N 15.66. ^1H n.m.r. (200 MHz, CD_3OD): 8.75 (dd, 1H, H_6; J_{6-7} = 5 Hz; J_{6-8} = 1.8 Hz); 8.30 (dd, 1H, H_8; J_{8-7} = 8 Hz; J_{8-6} = 1.8 Hz); 8.15 (d, 1H, H_2; J_{2-3} = 7.8 Hz); 7.50 (d, 1H, H_4; J_{4-3} = 7.8 Hz); 7.40 (dd, 1H, H_7; J_{7-8} = 8 Hz; J_{7-6} = 5 Hz); 7.35 (t, 1H, H_3; J_{3-2} = J_{3-4} = 7.8 Hz); 6.50 (d, 1H, H_1; J_{1-Me} = 1 Hz); 3.10 (s, 3H, N-Me); 2.45 (d, 3H, Me; J_{Me-1} = 1 Hz). ^{13}C (62.9 MHz, CD_3OD): 152.9 (C_6); 147.0 (C_{4b}); 141.5 (C_8); 137.3 (C_{8a}); 132.3 (C_{10b}); 131.7 (C_{11}); 127.7 (C_{1a}); 126.0 (C_2); 123.4 (C_7); 122.8 (C_4); 122.7 (C_3); 121.3 (C_{4a}); 109. 7 (C_1); 38.5 (NMe); 13.7 (Me).

6-methyl-7-oxo[8,9,10,11] tetrahydro-pyrido[2',3'-d'] pyridazino[2,3-a]indole 18

8 drops of glacial acetic acid and a small amount of PtO_2 were added to a solution of indole derivative **7** (110 mg, 442 µmol) in dry methanol (30ml).The suspension was stirred for 2 hours under a positive pressure of hydrogen, then filtered over celite and washed with methanol. The solution was evaporated *in vacuo* to give the desired,but unstable, enamine **18** (107 mg, 100%). MS (EI): 253 ($M^{+\cdot}$, 100%). ^1H n.m.r. (200 MHz, $CDCl_3$): 7.85 (b, 2H, H_2; J_{2-3} = 8.0 Hz); 7.65 (d, 1H, H_5; J_{4-5} = 8.0 Hz); 7.30-7.10 (m, 2H, H_3, H_4); 6.50 (s, 1H, H_1); 4.85 (bs, 1H, H_{11}); 4.20 (s, 3H, N-Me); 3.45 (t, 2H, H_{10}; J_{9-10} = 4.8 Hz); 2.70 (t, 2H, H_8; J_{8-9} = 6.5 Hz); 2.00 (m, 2H, H_9).

6-methyl-7-oxo[7,8,9,10,11,11a] hexahydro-pyrido[2',3'-d'] pyridazino[2,3-a]indole 19

A solution of enamine **18** (270 mg, 1.07 mmol) and acetic acid (6 ml) in dry THF (3 ml) was stirred under argon. After 5 minutes, $NaBH_3CN$ (675 mg, 10 mmol) was added portionwise. After stirring for a further 4 hours, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in EtOAc (50 ml), washed with a saturated aqueous solution of K_2CO_3 (3x50 ml) and then with water until neutral pH was obtained. The combined organic layers were dried (Na_2SO_4), evaporated *in vacuo* and the resultant oil was subjected to flash chromatography on alumina II-III. Elution with EtOAc/heptane (1:1) provided amine derivative **19** (225 mg, 82%) as yellow crystals. m.p.= 148-152°C. IR ($CHCl_3$) 3028; 2400; 1680; 1525; 1420; 1216; 929. MS (EI): 255 ($M^{+\cdot}$, 100%); 212; 197. MS (CI): 256 ($[M+H]^+$, 100%). HRMS: (EI) $C_{15}H_{17}N_3O$ calculated 255.13715 found 255.1378. ^1H n.m.r. (400 MHz, $CDCl_3$): 7.60 (d, 2H, H_2; J_{2-3} = 8.7 Hz); 7.35 (d, 1H, H_5; J_{4-5} = 8.7 Hz); 7.25 (t, 1H, H_4); 7.15 (t, 1H, H_3); 6.40 (s, 1H, H_1); 3.85 (dd, 1H, H_{11a}; J_{11a-7a} = 10.6 Hz; J_{11a-1} = 1 Hz); 3.60 (s, 3H, N-Me); 3.25 (m, 1H, H_{10eq}); 2.75 (ddd, 1H, H_{10ax}; $J_{10ax-10eq}$ = 13 Hz; $J_{10ax-9ax}$ = 13 Hz; $J_{10ax-9eq}$ = 2.6 Hz); 2.35-2.10 (m, 2H, H_{8eq}, H_{7a}); 1.95-1.55 (m, 2H, H_{8ax}, H_{9eq}); 1.50 (tt, 1H, H_{9ax}).

6-methyl-7-oxo[7,8,9,10,11,11a]-N-11-(2'-*bromoacetyl*)-hexahydro-pyrido[2',3'-d'] pyridazino[2,3-a]indole 20

Triethylamine (200 µl, 1,44 mmol) was added to solution of amine **19** (200 mg, 784 µmol) in dry THF, under argon. After stirring for 5 minutes, bromo-2-acetyl bromide (280 µl, 3.2 mmol) was added. Stirring was maintained for a further 30 minutes, after which the reaction mixture was diluted in EtOAc (50 ml), washed with a 1% TEA aqueous solution (3x50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The resultant oil was subjected to flash chromatography on alumina II-III. Elution with EtOAc/heptane (1:1) and crystallization in acetone/ethanol provided compound **20** (229 mg, 78%) as yellow crystals. m.p.= 148-152°C. MS (EI): 377 ([M+1]$^{+\cdot}$); 375 ([M-1]$^{+\cdot}$); 296 (-Br); 254 (-CH_2COBr). HRMS: (EI) $C_{17}H_{18}N_3O_2Br$ calculated 375.0583 and 377.0563 found 375.0578 and 377.0572. ^1H n.m.r. (250 MHz, $CDCl_3$): 7.60 (d, 1H, H_2); 7.50-7.05 (m, 3H, H_3, H_4, H_5); 6.15 (s 1H, H_1); 5.15 (d, 1H, H_{11a}; $J_{11a\text{-}7a}$ = 12.9 Hz); 4.00 (s, 2H, $H_{2'}$); 3.90 (m, 1H, H_{10}); 3.60 (s, 3H, N-Me); 3.45-3.20 (m, 1H, H_{10}); 2.90-2.60 (m, 1H, H_{7a}); 2.40-2.00 (m, 2H, H_9); 2.00-1,50 (m, 2H, H_8).

Trans-(3RS, 16RS)-14-methyl-14,15-dihydro-14-aza-20,21-dinoreburnanemin-5,15-dione 21

A solution of **20** (70 mg, 187 mmol) in dry DME was added to dry silver tetrafluoroborate (90 mg, 462 mmol) and the reaction mixture was stirred at reflux for 4 hours under argon. After evaporation of DME *in vacuo*, the resultant residue was dissolved in EtOAc (50ml), washed with a 1% TEA aqueous solution (3x50 ml) then with water (3x50 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The resulting oil was subjected to flash chromatography on silica gel. Elution with ethyl acetate/heptane (1:1) provided pentacycle **21** (28 mg, 51%). IR($CHCl_3$) 3023; 1680; 1635; 1448; 1316; 1260; 1235. MS (EI): 295 (M$^{+\cdot}$, 100%); 266; 211. HRMS: (EI) $C_{17}H_{17}N_3O$ calculated 295.1321 found 295.1330. ^1H n.m.r. (400 MHz, $CDCl_3$): 7.55 (d, 1H, H_9); 7.45 (d, 1H, H_{12}); 7.25 (m, 2H, H_{10}, H_{11}); 4.70 (bd, 1H, H_{19eq}; $J_{19ax\text{-}19eq}$ = 13 Hz); 4.35 (dt, 1H, H_3; $J_{3\text{-}16}$ = 11 Hz; $J_{3\text{-}6}$ = 3 Hz); 3.65 (bs, 5H, H_6, N-Me); 2.60 (dt, 1H, H_{19ax}; $J_{19ax\text{-}19eq}$ = 15 Hz; $J_{19ax\text{-}18ax}$ = 15 Hz; $J_{19ax\text{-}18eq}$ = 3 Hz); 2.30-2.15 (m, 2H, H_{17eq}, H_{16}); 1.75-1.60 (m, 1H, H_{17ax}); 1.40 (m, 1H, H_{18ax}). ^{13}C n.m.r. (62,9 MHz, $CDCl_3$): 169.9 (CO); 166.6 (CO); 135.1; 126.1; 124.8; 123,4; 121.0; 119.6; 109.4; 103.0; 53.19; 45.96; 41.90; 36.74; 29.68; 24.30; 14.31.

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6 Some dihydroindolic compounds are more interesting than indolic compounds, espacially in the field of tyrosine hydroxylase inductors, cf 1c.

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