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Synthesis of 4-Arylpyridines and Substituted β-Carbolines via 1,4-Grignard-Addition to Pyridinecarboxamides.

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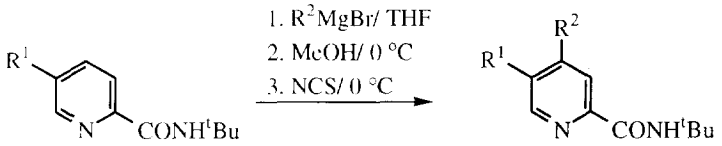
Abstract: 2,5-Pyridinedicarboxamides **1** and **2**, 5-bromo-3-pyridinecarboxamide **7** and 3-hydroxy-2,5-pyridinedicarboxamide **9** undergo 1,4-addition with Grignard reagents to give the 2,4,5- or 3,4,5- and 2,3,4,5-substituted pyridines **3-6**, **8** and **10** after oxidation with NCS or oxygen. After selective transformation of amides **5** and **8** to carbamates **17** and **19**, a modified intramolecular Goldberg amide arylation furnishes the β-carbolines **22** and **24** in good yields.

Highly substituted 4-arylpyridine structures are present in a large number of naturally and unnaturally occurring substances with interesting pharmacological activities. For instance some β-carboline-3-carboxylates[1] show anticonvulsive and anxiolytic properties. Also noteworthy is the antitumor and antiviral activity of lavendamycin[2, 3] and streptonigrin alkaloids.[4] Consequently these molecules have been subject to numerous synthetic efforts. Most approaches are based on de novo construction of the pyridine ring either by thermolysis of 3-(2-alkylindol-3-yl)-2-azidoacrylates,[5] aza Wittig reaction of 3-(indol-3-yl)-2-iminophosphoranoacrylates with aldehydes,[6] Bischler-Napieralski-, Pictet-Spengler-, Knoevenagel-Stobbe reaction[7-10] or by [4+2] cycloaddition of electron deficient 1,2,4-triazines with enamines[11] followed, if necessary, by oxidation of di- and tetrahydro-β-carbolines, nitrene insertion or palladium(0)-promoted closure of the pyrrole ring. Recently a convergent route to β-carbolines and streptonigrin analogues via cross-coupling of 3-fluoro-4-iodopyridines and 2-pivaloylaminophenylboronic acid derivates and acid mediated ring closure under relatively harsh conditions has been reported,[12, 13] but to the best of our knowledge there is no example for the synthesis of a β-carboline via 1,4-dihydropyridine chemistry. We now report the rapid construction of 2,4,5-, 3,4,5- and 2,3,4,5-substituted pyridines by 1,4-addition reaction of pyridinecarboxamides and the regioselective transformation to aminopyridines and β-carbolines.

Results and Discussion

1,4-Addition of Grignard reagents to pyridinecarboxamides

Pyridines with electron withdrawing substituents (e.g. COR, CO_2R, CN, NO_2, $CONR^1R^2$) in 3- or better in 3- and 5-position are known to form dihydropyridines on treatment with complex metal hydrides and carbanions.[14, 15] Among the reactions which proceed without prior quaternization of the pyridine nitrogen are the addition of Grignard or lithium reagents to 3-(4,4-dimethyloxazolin-2-yl)pyridine[16] and the addition of lithium reagents to N-phenyl-3-pyridinecarboxamide.[17] Previously we have described the synthesis of symmetrical and unsymmetrical 2,5-pyridinedicarboxamides by addition of excess dimethylaluminumamide or controlled addition of two different dimethyl- or methylchloroaluminumamides with or without intermediate workup (e. g. amide **1** in 98% yield and amide **2** in 92% yield, both in a one pot procedure).[18] As we found now, the addition of ethyl- and phenylmagnesium bromide to amide **1** resulted in the clean formation of a single product along with unchanged material. Attempts to oxidize the dihydropyridines after aqueous workup with air or MnO_2 in CH_2Cl_2 failed, but quenching of the mixture with a slight excess of MeOH and oxidation with NCS smoothly furnishes the pyridines **3** and **4**. For synthetic purposes amide **2** was used which gave the dihydropyridines **5** and **6** in a quantitative exothermic reaction, even with an ortho substituted arylmagnesium bromide. As confirmed by ^1H NMR analysis of the pyridines **3-6**, 4-addition has occurred exclusively in all cases (Scheme 1, Table 1).



1, 2 **3-6**

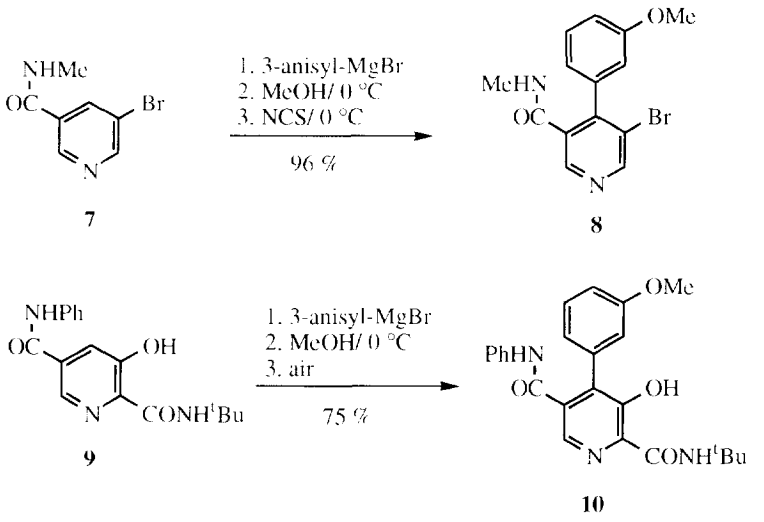
Scheme 1

Table 1. 1,4-Addition of Grignard Reagents to 2,5-Pyridinedicarboxamides **1** and **2**

compd	R^1	R^2 (eq. R^2MgBr)	conditions	product	yield%
1	$CONH^tBu$	Et (5.0)	8 h/ r.t.	**3**	70
1	$CONH^tBu$	Ph (5.3)	2 h/ reflux	**4**	84
2	CONHMe	3-anisyl (5.5)	2 h/ r.t.	**5**	97
2	CONHMe	2-anisyl (6.2)	4 h/ r.t.	**6**	95

As a test case for a substrate sterically hindered by two ortho substituents, amide **7**, prepared from commercially available 5-bromo-3-pyridinecarboxylic acid, was treated with 3-methoxyphenylmagnesium bromide. Oxidation of the dihydropyridine with NCS gave pyridine **8** in almost quantitative yield. Reaction of the 3-hydroxy derivative **9**, readily available from N^2-(1,1-dimethylethyl)-N^5-phenyl-2,5-pyridinedicarboxamide,[18] with 3-methoxyphenylmagnesium bromide resulted in the precipitation of a insoluble polyanionic

species which formed a green solution on heating. Aqueous workup and air oxidation gave the desired 4-substituted pyridine **10** along with unchanged material.



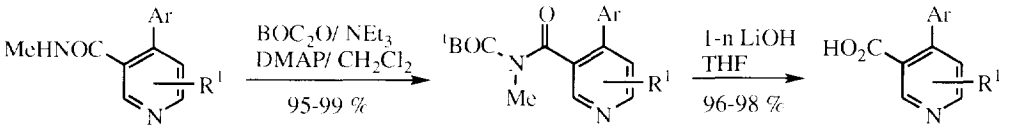
7 **8**

9 **10**

Scheme 2

Selective transformation of 2,5-pyridinedicarboxamides to aminopyridines and ß-carbolines

The diamides **5**, **6** and **8** were chosen as model compounds. The desired differentiation of the amide groups was achieved with di-*tert*-butyl dicarbonate/ DMAP,[19-21] wich left the *tert*-butylamide group untouched and gave **5a**, **6a** and **8a**. Hydrolysis with 1 M LiOH in THF led to the 3-pyridinecarboxylic acids **5b**, **6b** and **8b** in almost quantitative yield (Scheme 3).



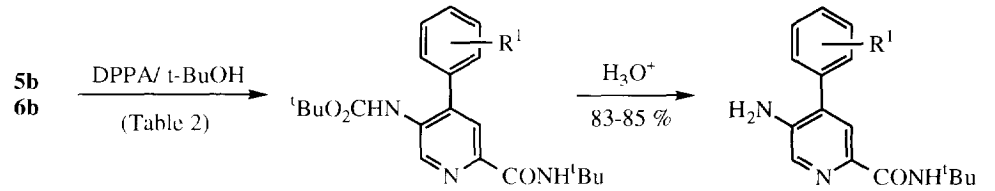
compd	R^1	Ar
5	2-CONH^{t}Bu	3-anisyl
6	2-CONH^{t}Bu	2-anisyl
8	5-Br	3-anisyl

5a, **6a**, **8a** **5b**, **6b**, **8b**

Scheme 3

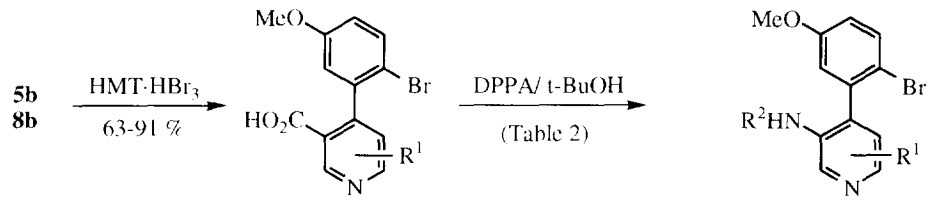
Curtius rearrangement[22] of the purified pyridinecarboxylic acids **5b** and **6b** furnished carbamates **11** and **13** (together with a small amount of the aminopyridine **14**). Acidic hydrolysis of **11** and **13** generated the amino-

pyridines **12** and **14**, which were diazotized and treated with sodium azide to give the azides. Thermolysis of the azides in xylene or 1,2-dichlorobenzene afforded β-carbolines in discouragingly low yields (≤ 15%).



11: R^1 = 3-OMe
13: R^1 = 2-OMe

12: R^1 = 3-OMe
14: R^1 = 2-OMe



15: R^1 = 2-$CONH^tBu$
16: R^1 = 5-Br

compd	R^1	R^2
17	2-$CONH^tBu$	$CO_2{}^tBu$
18	2-$CONH^tBu$	H
19	5-Br	$CO_2{}^tBu$
20	5-Br	H

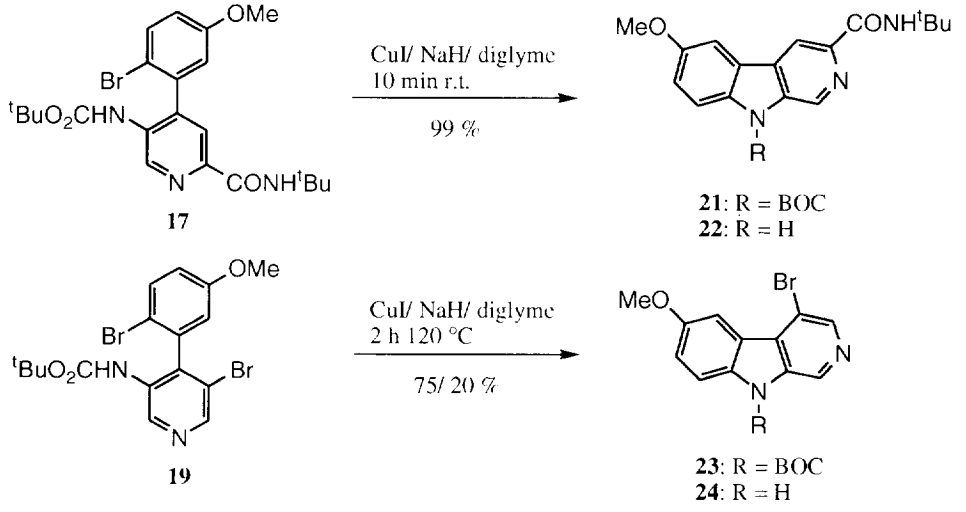
Scheme 4

Table 2. Curtius Rearrangement of 4-Aryl-3-pyridinecarboxylic Acids **5b**, **6b**, **15**, **16**

compd	R^1	R^2	R^3	conditions	product	yield%
5b	2-$CONH^tBu$	H	3-OMe	16 h	**11**/ **12**	81/ 0
6b	2-$CONH^tBu$	H	2-OMe	16 h	**13**/ **14**	68/ 11
15	2-$CONH^tBu$	Br	3-OMe	20 h	**17**/ **18**	47/ 18
16	5-Br	Br	3-OMe	30 h	**19**/ **20**	68/ 6

So we turned to a copper(I)-promoted ring closure in form of a modified intramolecular Goldberg amide arylation[23-25] of 4-(2'-bromophenyl)-3-aminopyridine derivates. Acids **5b** and **8b** were brominated with hexamethylenetetramine·HBr_3[26] and the 4-(6-bromo-3-methoxyphenyl)-3-pyridinecarboxylic acids **15** and **16** were obtained regioselectively as proved by NOE experiments (Scheme 4). Curtius rearrangement gave the N-BOC protected aminopyridines **17** and **19** (together with small amounts of the aminopyridines **18** and **20**), which were cyclized with NaH/ CuI in diglyme to the N-BOC protected or partially deprotected β-carbolines

21, **23** and **24** in almost quantitative yields (Scheme 5). Hydrolysis of the protected β-carbolines **21** and **23** with HCl/ AcOH led to the β-carbolines **22** and **24**. Extension of this promising approach to more complex carboline derivatives is under current investigation in our laboratory.



Scheme 5

Experimental

General Methods. Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 300 spectrometer (300 MHz) with tetramethylsilane as internal standard. IR spectra were determined on a Bruker ISS 25 spectrometer. Mass spectra (MS) were recorded on a Fisons VG Trio 2, VG Autospec Q or VG ZAB-E (Cs-gun) and a Finnegan TSQ 700 at 70 eV (EI) unless stated otherwise. Elemental analyses were performed on an Elemental Vario EL apparatus. Analytical thin-layer chromatography was performed on Merck silica plates with F-254 indicator. Preparative flash chromatography (FC) was performed with Merck silica gel 60 (230-400 mesh). Diglyme and CH_2Cl_2 were dried over activated molecular sieves (4 Å). THF was distilled from sodium/ benzophenone under argon. 5-Bromo-3-pyridinecarboxylic acid was purchased from Aldrich. All reactions involving air-sensitive reagents were performed in oven-dried glassware under argon.

1,4-Addition of Grignard reagents to pyridinecarboxamides. Standard procedure. N^2,N^5-Bis(1,1-dimethylethyl)-4-ethyl-2,5-pyridinedicar ,oxamide (3). To a solution of EtMgBr (prepared from EtBr, 50.00 mmol, 5.45 g, 3.73 ml and Mg, 55.00 mmol, 1.34 g) in THF (100 ml) at 0 °C was slowly added amide **1** (10.00 mmol, 2.77 g) in THF (40 ml) and the resulting red mixture was stirred at r.t. for 8 h. After recooling to 0 °C, the mixture was quenched with MeOH (≈ 70 mmol, 2.8 ml) and solid NCS (13.00 mmol, 1.74 g) was added in portions. After the mixture was stirred for 2 h at 0 °C, aqueous NH_3/ NH_4Cl was added. Extraction with CH_2Cl_2 (5 × 40 ml), drying with Na_2SO_4, filtration, concentration in vacuo, FC (EtOAc/ cyclohexane 1:1) and recrystallization from diethyl ether/ pentane gave **3** (2.14 g, 70%) as colorless needles, mp 181-182 °C:

^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7.0 Hz, CH_2CH_3), 1.49 (s, 18 H, $C(CH_3)_3$), (q, 3 H, J = 7.0 Hz, CH_2CH_3), 5.75 (s, 1 H, CONH), 7.93 (s, 1H, CONH), 8.02 (s, 1 H, Ar), 8.37 (s, 1 H, Ar); IR ($CHCl_3$) 3427, 3370, 1669 cm^{-1}; MS m/z (rel intensity) 305 (13, M^+), 290 (100), 262 (9), 233 (14), 220 (32), 205 (21). Anal. Calcd for $C_{17}H_{27}N_3O_2$: C, 66.85; H, 8.91; N, 13.76. Found: C, 66.87; H, 8.94; N, 13.52.

N^2,N^5-Bis(1,1-dimethylethyl)-4-phenyl-2,5-pyridinedicarboxamide (4). To a solution of PhMgBr (prepared from PhBr, 53.00 mmol, 8.32 g, 5.55 ml and Mg, 60.00 mmol, 1.46 g) in THF (100 ml) at 0 °C was slowly added amide **1** (10.00 mmol, 2.77 g) in THF (40 ml) and the resulting mixture was refluxed for 2 h. Workup as described above, followed by FC (EtOAc/ cyclohexane 1:1) and recrystallization from diethyl ether/ cyclohexane gave **4** (2.97 g, 84%) as colorless needles, mp 176-178 °C: ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9 H, $C(CH_3)_3$), 1.51 (s, 9 H, $C(CH_3)_3$), 5.17 (s, 1 H, CONH), 7.46 (m, 5 H, Ar), 8.01 (s, 1H, CONH), 8.13 (s, 1 H, Ar), 8.77 (s, 1 H, Ar); IR ($CHCl_3$) 3428, 1662 cm^{-1}; MS m/z (rel intensity) 353 (21, M^+), 338 (100), 310 (13), 281 (21), 268 (44), 253 (19); HRMS (EI) calcd for $C_{21}H_{27}N_3O_2$ 353.2103, found 353.2091.

N^2-(1,1-Dimethylethyl)-4-(3-methoxyphenyl)-N^5-methyl-2,5-pyridinedicarboxamide (5). To a solution of 3-methoxyphenylmagnesium bromide (prepared from 3-methoxybromobenzene, 110.0 mmol, 20.57 g, 13.81 ml and Mg, 120.0 mmol, 2.92 g) in THF (150 ml) at 0 °C was slowly added amide **2** (20.00 mmol, 4.70 g) in THF (80 ml) and the resulting mixture was stirred for 2 h at r.t. Workup as described above, followed by FC (CH_2Cl_2/ acetone 4:1) gave **5** (6.62 g, 97%) as a glassy yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 2.78 (d, 3 H, J = 5.0 Hz, $CONHCH_3$), 3.82 (s, 3 H, OCH_3), 5.64 (br. d, 1 H, $CONHCH_3$), 6.79 (m, 3 H, Ar), 7.34 (m, 1 H, Ar), 8.00 (s, 1H, CONH), 8.12 (s, 1 H, Ar), 8.73 (s, 1 H, Ar); IR ($CHCl_3$) 3448, 3371, 1665 cm^{-1}; MS m/z (rel intensity) 341 (25, M^+), 326 (100), 256 (37), 241 (46), 184 (38). Anal. Calcd for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.36. Found: C, 66.37; H, 6.75; N, 12.29.

N^2-(1,1-Dimethylethyl)-4-(2-methoxyphenyl)-N^5-methyl-2,5-pyridinedicarboxamide (6). To a solution of 2-methoxyphenylmagnesium bromide (prepared from 2-methoxybromobenzene, 124.0 mmol, 23.19 g, 15.26 ml and Mg, 135.0 mol, 3.28 g) in THF (150 ml) at 0 °C was slowly added amide **2** (20.00 mmol, 4.70 g) in THF (80 ml) and the resulting mixture was stirred for 4 h at r.t. Workup as described above, followed by FC (CH_2Cl_2/ EtOH 12:1) gave **6** (6.48 g, 95%) as a glassy slightly yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 9 H, $C(CH_3)_3$), 2.74 (d, 3 H, J = 5.0 Hz, $CONHCH_3$), 3.71 (s, 3 H, OCH_3), 5.74 (d, 1 H, J = 5.0 Hz, $CONHCH_3$), 6.86 - 7.47 (m, 4 H, Ar), 8.03 (s, 1H, CONH), 8.04 (d, 1 H, J = 0.8 Hz, Ar), 8.80 (d, 1 H, J = 0.8 Hz, Ar); IR ($CHCl_3$) 3448, 3370, 1664 cm^{-1}; MS m/z (rel intensity) 341 (23, M^+), 326 (100), 256 (38), 241 (50); HRMS (EI) calcd for $C_{19}H_{23}N_3O_3$ 341.1739, found 341.1736.

5-Bromo-N-methyl-3-pyridinecarboxamide (7). 5-Bromo-3-pyridinecarboxylic acid (10.0 mmol, 2.02 g) in thionyl chloride (30 ml) was refluxed for 2 h. After removal of thionyl chloride in vacuo the residue was dissolved in dry CH_2Cl_2 and a slow stream of gaseous methylamine was passed through the solution at 0 °C for 15 min. After stirring the mixture at r.t. overnight, it was washed with aqueous citric acid and saturated $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated. The residue was recrystallized from EtOAc/ hexane to give **7**[27] (1.87 g, 87%) as colorless crystals, mp 148-149 °C: ^{1}H NMR ($CDCl_3$) δ 3.04 (d, 3 H, J = 5.0 Hz, $CONHCH_3$), 6.43 (br. s, 1 H, $CONHCH_3$), 8.26 (t, 1 H, J = 2.0 Hz, Ar), 8.78 (d, 1 H, J = 2.0 Hz, Ar), 8.87 (d, 1 H, J = 2.0 Hz, Ar); IR ($CHCl_3$) 3362, 3340, 1670; MS m/ z (rel intensity) 216 (48), 215 (78), 214 (52, M^+), 213 (74), 186 (86), 184 (88), 158 (98), 156 (100), 135 (59).

5-Bromo-4-(3-methoxyphenyl)-N-methyl-3-pyridinecarboxamide (8). To a solution of 3-methoxyphenylmagnesium bromide (prepared from 3-methoxybromobenzene, 84.00 mmol, 15.71 g, 10.54 ml and Mg,

90.00 mmol, 2.19 g) in THF (150 ml) at 0 °C was slowly added amide **7** (20.00 mmol, 4.30 g) in THF (80 ml) and the resulting mixture was stirred for 2 h at r.t. Workup as described above, followed by FC (hexane/ acetone 1:1) gave **8** (6.16 g, 96%) as a glassy yellow solid: ^{1}H NMR ($CDCl_3$) δ 2.66 (d, 3 H, J = 5.0 Hz, $CONHCH_3$), 3.84 (s, 3 H, OCH_3), 5.36 (br. s, 1 H, $CONHCH_3$), 6.78 - 7.06 (m, 3 H, Ar), 7.42 (t, 1 H, J = 8.0 Hz, Ar), 8.83 (s, 1 H, Ar), 8.86 (s, 1 H, Ar); IR ($CHCl_3$) 3447, 1664 cm^{-1}; MS *m/z* (rel intensity) 322 (97, M^+), 320 (100, M^+), 292 (74), 290 (76), 249 (13), 247 (13). Anal. Calcd for $C_{14}H_{13}BrN_2O_2$: C, 52.36; H, 4.08; N, 8.72. Found: C, 52.39; H, 4.17; N, 8.54.

N^2-(1,1-Dimethylethyl)-3-hydroxy-4-(3-methoxyphenyl)-N^5-phenyl-2,5-pyridinedicarboxamide (10). To a solution of 3-methoxyphenylmagnesium bromide (prepared from 3-methoxybromobenzene, 37.50 mmol, 7.01 g, 4.71 ml and Mg, 40.00 mmol, 0.97 g) in THF (70 ml) at 0 °C was slowly added amide **9**[18] (5.00 mmol, 1.57 g) in THF (20 ml) and the resulting suspension was heated to 60 °C. After 4 h the suspension was almost dissolved and the mixture was recooled to 0 °C and quenched with aqueous NH_3/ NH_4Cl. The mixture was stirred in an open flask overnight, extracted with CH_2Cl_2 (5 × 40 ml), dried with Na_2SO_4, filtered and concentrated in vacuo. FC (hexane/ acetone 2:1) and recrystallization from diethyl ether/ petroleum ether gave **10** (1.58 g, 75%) as colorless crystals, mp 132-133 °C: ^{1}H NMR (DMSO-d_6) δ 1.49 (s, 9 H, $C(CH_3)_3$), 3.71 (s, 3 H, OCH_3), 6.90 -7.54 (m, 9 H, Ar), 8.30 (s, 1 H, Ar), 8.38 (s, 1 H, CONH), 10.25 (s, 1 H, $CONHPh$), 13.10 (s, 1 H, OH); IR ($CHCl_3$) 3366, 1674, 1638 cm^{-1}; MS *m/z* (rel intensity) 419 (57, M^+), 404 (21), 327 (21), 271 (57), 254 (45), 226 (100), 170 (44); HRMS (EI) calcd for $C_{24}H_{25}N_3O_4$ 419.1845, found 419.1900.

N-[3-[6-[(1,1-Dimethylethylamino)carbonyl]-4-(3-methoxyphenyl)]pyridinecarbonyl]]-N-methyl carbamic acid (1,1-dimethylethyl) ester (5a). A mixture of amide **5** (19.59 mmol, 6.68 g), di-*tert*-butyl dicarbonate (28.41 mmol, 6.20 g), DMAP (2.05 mmol, 0.25 g) and NEt_3 (10 ml) in dry CH_2Cl_2 (250 ml) was stirred for 20 h at r.t. After addition of a second portion of di-*tert*-butyl dicarbonate (20.62 mmol, 4.50 g), the mixture was stirred for additional 20 h and extracted with cold 10% aqueous citric acid (3 × 80 ml). The organic layer was washed with saturated $NaHCO_3$, dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by FC (cyclohexane/ EtOAc 6:4) to give **5a** (8.47 g, 98%) as a glassy yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 9 H, $C(CH_3)_3$), 1.51 (s, 9 H, $C(CH_3)_3$), 3.12 (s, 3 H, $CONCH_3$), 3.81 (s, 3 H, OCH_3), 6.94 (m, 3 H, Ar), 7.32 (m, 1 H, Ar), 8.00 (s, 1H, CONH), 8.22 (s, 1 H, Ar), 8.47 (s, 1 H, Ar); IR ($CHCl_3$) 3375, 1734, 1670 cm^{-1}; MS *m/z* (rel intensity) 441 (10, M^+), 326 (100), 426 (10), 398 (8), 356 (21), 340 (31), 326 (100), 311 (13), 284 (29), 256 (21), 241 (28); HRMS (EI) calcd for $C_{24}H_{31}N_3O_5$ 441.2264, found 441.2227.

N-[3-[6-[(1,1-Dimethylethylamino)carbonyl]-4-(2-methoxyphenyl)pyridinecarbonyl]]-N-methyl carbamic acid (1,1-dimethylethyl) ester (6a). A mixture of amide **6** (10.00 mmol, 3.41 g), di-*tert*-butyl dicarbonate (15.0 mmol, 3.27 g), DMAP (0.82 mmol, 0.10 g) and NEt_3 (5 ml) in dry CH_2Cl_2 (150 ml) was stirred for 20 h at r.t. After addition of a second portion of di-*tert*-butyl dicarbonate (11.45 mmol, 2.50 g), the mixture was stirred for additional 20 h. Workup as described above followed by FC (cyclohexane/ EtOAc 6:4) gave **6a** (4.19 g, 95%) as a glassy yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 9 H, $C(CH_3)_3$),1.50 (s, 9 H, $C(CH_3)_3$), 3.04 (s, 3 H, $CONCH_3$), 3.71 (s, 3 H, OCH_3), 6.86 - 7.43 (m, 4 H, Ar), 7.98 (s, 1H, CONH), 8.17 (s, 1 H, Ar), 8.54 (d, 1H, J = 0.8 Hz, Ar); IR ($CHCl_3$) 3371, 1732, 1672 cm^{-1}; MS *m/z* (rel intensity) 441 (10, M^+), 426 (12), 398 (10), 365 (25), 326 (100), 310 (31); HRMS (EI) calcd for $C_{24}H_{31}N_3O_5$ 441.2264, found 441.2281.

N-[3-[5-Bromo-4-(3-methoxyphenyl)pyridinecarbonyl]]-N-methyl carbamic acid (1,1-dimethylethyl) ester (8a). A mixture of amide **8** (15.89 mmol, 5.10 g), di-*tert*-butyl dicarbonate (23.05 mmol, 5.03 g), DMAP (0.82 mmol, 0.10 g) and NEt_3 (5 ml) in dry CH_2Cl_2 (150 ml) was stirred for 30 h at r.t. Workup as described above followed by FC (hexane/ acetone 1:1) gave **8a** (6.64 g, 99%) as a viscous yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 9 H, $C(CH_3)_3$), 2.94 (s, 3 H, $CONCH_3$), 3.80 (s, 3 H, OCH_3), 6.78 - 7.00 (m, 3 H, Ar), 7.34 (t, 1 H, J = 8.0 Hz, Ar), 8.48 (s, 1 H, Ar), 8.83 (s, 1 H, Ar); IR ($CHCl_3$) 1734, 1671 cm^{-1}; MS *m/ z* (rel intensity) 422 (11, M^+), 420 (11, M^+), 321 (100, M^+), 319 (92), 292 (50), 290 (52). Anal. Calcd for $C_{19}H_{21}BrN_2O_4$: C, 54.17; H, 5.02; N, 6.65. Found: C, 54.24; H, 4.92; N, 7.02.

6-[(1,1-Dimethylethylamino)carbonyl]-4-(3-methoxyphenyl)-3-pyridinecarboxylic acid (5b). To a solution of carbamate **5a** (9.16 mmol, 4.04 g) in THF (100 ml) was added aqueous 1 M LiOH (12 ml) and the mixture was stirred for 24 h at r.t. Diethyl ether was added, the aqueous layer was separated and the organic layer was extracted with 0.5 M NaOH (3 × 40 ml). The combined aqueous extracts were acidified with solid citric acid, extracted with THF/ EtOAc (1:2; 7 × 30 ml), dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by FC (CH_2Cl_2/ EtOH 7:3) to give **5b** (2.94 g, 98%) as a glassy slightly yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.45 (s, 9 H, $C(CH_3)_3$), 3.80 (s, 3 H, OCH_3), 6.96 (m, 1 H, Ar), 7.18 (m, 2 H, Ar), 7.33 (t, 1 H, J = 8.0 Hz, Ar), 7.88 (m, 1 H, Ar), 8.00 (s, 1H, CONH), 8.56 (s, 1 H, Ar); IR (KBr) 3367, 1685, 1600 cm^{-1}; MS *m/ z* (rel intensity) 327 (64, $[M-H]^+$), 313 (7), 284 (21), 269 (99), 257 (21), 242 (48), 199 (43), 184 (100); HRMS (EI) calcd for $C_{18}H_{19}N_2O_4$ 327.1345, found 327.1344.

6-[(1,1-Dimethylethylamino)carbonyl]-4-(2-methoxyphenyl)-3-pyridinecarboxylic acid (6b). To a solution of carbamate **6a** (7.14 mmol, 3.15 g) in THF (80 ml) was added aqueous 1 M LiOH (20 ml) and the mixture was stirred for 2 d at r.t. In view of incomplete conversion (DC control) the mixture was treated with additional LiOH (20 ml) and stirred at 50 °C for 3 h. Workup as described above followed by FC (CH_2Cl_2/ EtOH 7:3) gave **6b** (2.29 g, 98%) as a glassy slightly yellow solid: ^{1}H NMR (DMSO-d_6) δ 1.42 (s, 9 H, $C(CH_3)_3$), 3.69 (s, 3 H, OCH_3), 6.88-7.36 (m, 4 H, Ar), 7.77 (s, 1 H, Ar), 8.01 (s, 1H, CONH), 8.77 (s, 1 H, Ar); IR (KBr) 1685, 1609 cm^{-1}; MS *m/ z* (rel intensity) 327 (100, $[M-H]^+$), 296 (23), 281 (95), 257 (37), 242 (74), 196 (82); HRMS FAB (+ve) calcd for $C_{18}H_{21}N_2O_4$ 329.1489, found 329.1501.

5-Bromo-4-(3-methoxyphenyl)-3-pyridinecarboxylic acid (8b). To a solution of carbamate **8a** (15.44 mmol, 6.50 g) in THF (120 ml) was added aqueous 1 M LiOH (50 ml) and the mixture was stirred for 1 d at r.t. Workup as described above followed by FC (CH_2Cl_2/ EtOH 7:3) gave **8b** (4.57 g, 96%) as a glassy slightly yellow solid: ^{1}H NMR (DMSO-d_6) δ 3.76 (s, 3 H, OCH_3), 6.76-7.34 (m, 4 H, Ar), 8.59 (s, 1 H, Ar), 8.65 (s, 1 H, Ar), 12.80 (br. s, 1H, COOH); IR (KBr) 3373, 1654, 1590 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{10}BrNO_3$ 306.9844, found 306.9861.

6-[N-(1,1-Dimethylethyl)aminocarbonyl]-4-(6-bromo-3-methoxyphenyl)-3-pyridinecarboxylic acid (15). A solution of acid **5b** (3.35 mmol, 1.10 g) in CH_2Cl_2/ MeOH (17 ml, 10:7) was treated with HMT·HBr_3[26] (3.81 mmol, 1.45 g) and the mixture was stirred at r.t. overnight. A second portion of HMT·HBr_3 (5.20 mmol, 1.98 g) was added and the mixture was stirred overnight. Saturated aqueous Na_2SO_3 was added and the mixture was acidified with solid citric acid, extracted with THF/ EtOAc (1:1; 8 × 30 ml), dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by FC (CH_2Cl_2/ EtOH 4:1) to give **15** (1.25 g, 91%) as a glassy slightly yellow solid: ^{1}H NMR (MeOD-d4) δ 1.50 (s, 9 H, $C(CH_3)_3$), 3.80 (s, 3 H, OCH_3), 6.87 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 6.90 (d, 1 H, J = 3.0 Hz, Ar), 7.50 (d, 1 H, J = 9.0 Hz, Ar), 7.87 (s, 1 H, Ar),

8.94 (s, 1 H, Ar); IR ($CHCl_3$) 3368, 1685, 1612 cm^{-1}; HRMS FAB (+ve) calcd for $C_{18}H_{20}BrN_2O_4$ 407.0606, found 407.0570.

5-Bromo-4-(6-bromo-3-methoxyphenyl)-3-pyridinecarboxylic acid (16). A solution of acid **8b** (12.66 mmol, 3.90 g) in CH_2Cl_2/ MeOH (80 ml, 10:7) was treated with HMT·HBr_3 (36.23 mmol, 13.80 g) over 4 d and the mixture was stirred for an additional day. Workup as described above followed by FC (CH_2Cl_2/ EtOH 4:1) gave **16** (3.10 g, 63%) as a glassy slightly yellow solid: ^1H NMR (DMSO-d_6) δ 3.75 (s, 3 H, OCH_3), 6.70 (d, 1 H, J = 3.0 Hz, Ar), 6.86 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.50 (d, 1 H, J = 9.0 Hz, Ar), 8.73 (s, 1 H, Ar), 8.89 (s, 1 H, Ar); IR (KBr) 1593 cm^{-1}; HRMS FAB (+ve) calcd for $C_{13}H_{10}Br_2NO_3$ 385.9027, found 385.9020.

Curtius rearrangement of pyridinecarboxylates. Standard procedure. To a suspension of the dry acid (15.00 mmol), NEt_3 (16.50 mmol, 1.67 g, 2.29 ml) in *tert*-BuOH (150 ml) under argon DPPA (16.50 mmol, 4.54 g, 3.56 ml) was slowly added. After stirring for 1 h at r.t. the resulting mixture was refluxed for 16-30 h. Removal of the volatile components in vacuo, dilution with CH_2Cl_2, washing with saturated NaCl, drying with Na_2SO_4, filtration and concentration in vacuo, followed by FC and recrystallization gave the pure products

3-[6-[(1,1-Dimethylethylamino)carbonyl]-4-(3-methoxy-phenyl)pyridinyl]carbamic acid (1,1-dimethylethyl) ester (11). Reaction of acid **5b** (4.92 g) for 16 h, standard workup, FC (cyclohexane/ EtOAc 1:1) and recrystallization from diethyl ether/ hexane gave **11** (4.85 g, 81%) as long colorless needles, mp 171-172 °C: ^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 1.51 (s, 9 H, $C(CH_3)_3$), 3.85 (s, 3 H, OCH_3), 6.66 (s, 1 H, N*H*COOC$(CH_3)_3$), 6.86-7.06 (m, 3 H, Ar), 7.42 (t, 1 H, J = 8.0 Hz, Ar), 7.95 (s, 1H, CONH), 8.03 (s, 1 H, Ar), 9.30 (s, 1 H, Ar); IR ($CHCl_3$) 3414, 1730, 1664 cm^{-1}; MS *m/ z* (rel intensity) 399 (7, M^+), 384 (5), 356 (5), 328 (36), 314 (13), 258 (22), 57 (100). Anal. Calcd for $C_{22}H_{29}N_3O_4$: C, 66.14; H, 7.32; N, 10.52. Found: C, 66.05; H, 7.30; N, 10.55.

5-Amino-N-(1,1-dimethylethyl)-4-(3-methoxyphenyl)-2-pyridinecarboxamide (12). Carbamate **11** (4.01 mmol, 1.60 g) was stirred with 37% HCl/ AcOH (1:10; 15 ml) at r.t. for 2 d. Dilution with H_2O, neutralization with solid Na_2CO_3, extraction with CH_2Cl_2 (6 × 30 ml), drying with Na_2SO_4, filtration, concentration in vacuo and FC (toluene/ EtOAc 1:1) gave starting material (176 mg, 11%) and **17**, which was recrystallized from diethyl ether/ hexane to give 1.00 g (83%) of pure material as colorless crystals, mp 208-209 °C: ^1H NMR ($CDCl_3$) δ 1.49 (s, 9 H, $C(CH_3)_3$), 3.84 (s, 3 H, OCH_3), 4.14 (s, 2 H, $ArNH_2$), 6.90-7.08 (m, 4 H, Ar), 7.77 (s, 1H, CONH), 7.96 (s, 1 H, Ar), 7.99 (s, 1 H, Ar); IR ($CHCl_3$) 3399, 1655, 1615 cm^{-1}; MS *m/ z* (rel intensity) 299 (28, M^+), 284 (29), 243 (17), 227 (100), 214 (52), 199 (61). Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.01; H, 6.93; N, 14.03.

3-[6-[(1,1-Dimethylethylamino)carbonyl]-4-(2-methoxyphenyl)pyridinyl]carbamic acid (1,1-dimethylethyl) ester (13) and 5-amino-N-(1,1-dimethylethyl)-4-(2-methoxyphenyl)-2-pyridinecarboxamide (14). Reaction of acid **6b** (4.92 g) for 20 h, standard workup and FC (toluene/ EtOAc 1:1) gave two fractions. The first fraction gave **13** (4.07 g, 68%) as a glassy colorless solid:^1H NMR ($CDCl_3$) δ 1.48 (s, 9 H, $C(CH_3)_3$),1.50 (s, 9 H, $C(CH_3)_3$), 3.81 (s, 3 H, OCH_3), 6.59 (s, 1 H, N*H*COOC$(CH_3)_3$), 7.00 - 7.50 (m, 4 H, Ar), 7.96 (s, 1H, CONH), 8.00 (s, 1 H, Ar), 9.13 (s, 1 H, Ar); IR ($CHCl_3$) 3417, 3368, 1728, 1663 cm^{-1}; MS *m/ z* (rel intensity) ; HRMS (EI) calcd for $C_{22}H_{29}N_3O_4$ 399.2158, found 399.2168. Recrystallization of the second fraction from EtOAc/ hexane gave **14** (0.49 g, 11%) as colorless crystals, mp 207-208 °C:^1H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 3.80 (s, 3 H, OCH_3), 4.04 (s, 2 H, $ArNH_2$), 6.97 - 7.46 (m, 4 H, Ar), 7.79 (s, 1H, CONH), 7.93 (s, 1 H, Ar), 7.99 (s, 1 H, Ar); IR ($CHCl_3$) 3399, 1657, 1615 cm^{-1}; MS *m/ z* (rel intensity)

299 (21, M^+), 284 (24), 227 (100), 214 (60), 199 (73), 184 (33). Anal. Calcd for $C_{17}H_{21}N_3O_2$: C, 68.20; H, 7.07; N, 14.04. Found: C, 68.28; H, 7.11; N, 13.73.

5-Amino-N-(1,1-dimethylethyl)-4-(2-methoxyphenyl)-2-pyridinecarboxamide (14). Treatment of carbamate **13** (5.61 mmol, 2.24 g) as described above followed by FC (toluene/ EtOAc 1:1) gave starting material (134 mg, 6%) and **14** (1.43 g, 85%).

3-[4-(6-Bromo-3-methoxyphenyl)-6-[(1,1-dimethylethylamino)carbonyl]pyridinyl]carbamic acid (1,1-dimethylethyl) ester (17) and 5-amino-4-(6-bromo-3-methoxyphenyl)-N-(1,1-dimethylethyl)-2-pyridinecarboxamide (18). Reaction of acid **15** (6.11 g) for 20 h, standard workup and FC (toluene/ EtOAc 1:1) gave two fractions. Recrystallization of the first fraction from diethyl ether/ hexane gave **17** (3.37 g, 47%) as colorless crystals, mp 205-206 °C: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 1.51 (s, 9 H, $C(CH_3)_3$), 3.82 (s, 3 H, OCH_3), 6.17 (s, 1 H, $NHCOOC(CH_3)_3$), 6.76 (d, 1 H, J = 3.0 Hz, Ar), 6.91 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.60 (d, 1 H, J = 9.0 Hz, Ar), 7.94 (s, 1 H, Ar), 7.95 (s, 1H, CONH), 9.27 (s, 1 H, Ar); IR ($CHCl_3$) 3419, 1731, 1666 cm^{-1}; MS *m/ z* (rel intensity) 479 (12, M^+), 477 (12, M^+), 409 (39), 407 (44), 338 (26), 336 (28), 57 (100). Anal. Calcd for $C_{22}H_{28}BrN_3O_4$: C, 55.24; H, 5.90; N, 8.78. Found: C, 55.15; H, 5.83; N, 8.82. Recrystallization of the second fraction from EtOAc/ pentane gave **18** (1.02 g, 18%) as colorless crystals, mp 195-197 °C: ^{1}H NMR ($CDCl_3$) δ 1.50 (s, 9 H, $C(CH_3)_3$), 3.80 (s, 3 H, OCH_3), 3.94 (s, 2 H, $ArNH_2$), 6.78 (d, 1 H, J = 3.0 Hz, Ar), 6.87 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.57 (d, 1 H, J = 9.0 Hz, Ar), 7.78 (s, 1H, CONH), 7.87 (s, 1 H, Ar), 8.02 (s, 1 H, Ar); IR ($CHCl_3$) 3402, 1658, 1616 cm^{-1}; MS *m/ z* (rel intensity) 379 (25, M^+), 377 (26, M^+), 364 (30), 307 (98), 305 (100), 294 (63), 292 (67), 279 (45), 277 (47), 242 (62), 198 (90); HRMS (EI) calcd for $C_{17}H_{20}N_3O_2$ 377.0739, found 377.0744.

3-[5-Bromo-4-(6-bromo-3-methoxyphenyl)pyridinyl]carbamic acid (1,1-dimethylethyl) ester (19) and 3-amino-5-bromo-4-(6-bromo-3-methoxyphenyl)pyridine (20). Reaction of acid **16** (5.81 g) for 30 h, standard workup and FC (toluene/ EtOAc 1:1) gave two fractions. Recrystallization of the first fraction from diethyl ether/ petroleum ether gave **19** (4.68 g, 68%) as colorless crystals, mp 113-114 °C: ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9 H, $C(CH_3)_3$), 3.84 (s, 3 H, OCH_3), 5.90 (s, 1 H, $NHCOOC(CH_3)_3$), 6.72 (d, 1 H, J = 3.0 Hz, Ar), 6.96 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.65 (d, 1 H, J = 9.0 Hz, Ar), 8.55 (s, 1 H, Ar), 9.32 (s, 1 H, Ar); IR ($CHCl_3$) 3420, 1732 cm^{-1}; MS *m/ z* (rel intensity) 460 (3, M^+), 458 (6, M^+), 456 (3, M^+), 404 (7), 402 (14), 400 (7), 323 (5), 321 (5), 279 (58), 277 (76), 57 (100); HRMS (EI) calcd for $C_{17}H_{18}Br_2N_2O_3$ 455.9684, found 455.9704. Recrystallization of the second fraction from EtOAc/ pentane gave **20** (0.32 g, 6%) as pale yellow crystals, mp 144-147 °C: ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 2 H, $ArNH_2$), 3.83 (s, 3 H, OCH_3), 6.75 (d, 1 H, J = 3.0 Hz, Ar), 6.90 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.63 (d, 1 H, J = 9.0 Hz, Ar), 8.09 (s, 1 H, Ar), 8.22 (s, 1 H, Ar); IR ($CHCl_3$) 3447, 1617 cm^{-1}; MS *m/ z* (rel intensity) 360 (11, M^+), 358 (21, M^+), 356 (11, M^+), 279 (93), 277 (100). Anal. Calcd for $C_{12}H_{10}Br_2N_2O$: C, 40.26; H, 2.82; N, 7.82. Found: C, 40.59; H, 3.11; N, 7.59.

9-*tert*-Butyloxycarbonyl-N-(1,1-dimethylethyl)-6-methoxy-β-carboline-3-carboxamide (21). A mixture of carbamate **17** (1.09 mmol, 0.52 g), CuI (2.63 mmol, 0.50 g) and powdered 95% NaH (3.00 mmol, 76 mg) in dry diglyme (40 ml) under argon was stirred at r.t. for 15 min. The mixture was poured into aqueous 5% NH_3, extracted with CH_2Cl_2 (6 × 30 ml), dried with Na_2SO_4, filtered and concentrated in vacuo to give the crude product (> 95% by ^{1}H NMR). FC (CH_2Cl_2/ EtOH 10:1) and recrystallization from diethyl ether/ hexane furnished **21** (0.43 g, 99%) as colorless crystals, mp 169-170 °C: ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9 H, $C(CH_3)_3$), 1.79 (s, 9 H, $C(CH_3)_3$), 3.94 (s, 3 H, OCH_3), 7.22 (dd, 1 H, J = 9.0 Hz, J = 2.5 Hz, Ar), 7.54 (d, 1 H, J = 2.5

Hz, Ar), 8.10 (s, 1 H, CONH), 8.27 (d, 1 H, J = 9.0 Hz, Ar), 8.76 (s, 1 H, Ar), 9.40 (s, 1 H, Ar); IR (KBr) 3377, 1728, 1674 cm^{-1}; MS m/z (rel intensity) 397 (21, M^+), 341 (25), 326 (74), 297 (23), 282 (29), 256 (32), 241 (55), 225 (43), 212 (35), 196 (55), 57 (100); HRMS (EI) calcd for $C_{22}H_{27}N_3O_4$ 397.2002, found 397.2002.

N^3-(1,1-Dimethylethyl)-6-methoxy-9*H*-β-carboline-3-carboxamide (22). Carbamate **21** (1.28 mmol, 0.51 g) was stirred with 37% HCl/ AcOH (1:10; 10 ml) at r.t. for 2 d. Dilution with H_2O, neutralization with solid Na_2CO_3, extraction with CH_2Cl_2 (6 × 30 ml), drying with Na_2SO_4, filtration, concentration in vacuo and FC (CH_2Cl_2/ EtOH 10:1) gave starting material (36 mg, 7%) and **22** which was recrystallized from EtOAc/ hexane to give 0.32 g (83%) of pure material as slightly yellow crystals, mp 259-261 °C: ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 9 H, $C(CH_3)_3$), 3.90 (s, 3 H, OCH_3), 7.22 (dd, 1 H, J = 9.0 Hz, J = 2.5 Hz, Ar), 7.47 (d, 1 H, J = 9.0 Hz, Ar), 7.56 (d, 1 H, J = 2.5 Hz, Ar), 8.15 (s, 1 H, CONH), 8.77 (s, 1 H, Ar), 8.87 (s, 1 H, Ar), 8.98 (s, 1 H, NH); IR ($CHCl_3$) 3467, 1656 cm^{-1}; MS m/z (rel intensity) 297 (50, M^+), 282 (48), 241 (21), 225 (94), 212 (37), 197 (100). Anal. Calcd for $C_{17}H_{19}N_3O_2$: C, 68.67; H, 6.44; N, 14.13. Found: C, 68.55; H, 6.46; N, 14.00.

4-Bromo-9-*tert*-butyloxycarbonyl-6-methoxy-β-carboline (23) and 4-bromo-6-methoxy-9*H*-β-carboline (24). A mixture of carbamate **19** (3.10 mmol, 1.42 g), CuI (3.78 mmol, 0.72 g) and powdered NaH 95% (3.20 mmol, 77 mg) in dry diglyme (100 ml) under argon was stirred at 120 °C for 2 h. The mixture was poured into aqueous 5% NH_3. The hot solution was extracted with hot toluene (10 × 30 ml) and the extract was concentrated in vacuo. FC (toluene/ EtOAc 1:1) gave two fractions. Recrystallization of the first fraction from EtOAc/ hexane gave **23** (0.88 g, 75%) as colorless needles (decomposition to 4-bromo-6-methoxy-β-carboline on heating): ^{1}H NMR (pyridine-d_5) δ 1.68 (s, 9 H, $C(CH_3)_3$), 3.88 (s, 3 H, OCH_3), 7.45 (dd, 1 H, J = 10.5 Hz, J = 3.0 Hz, Ar), 8.32 (d, 1 H, J = 3.0 Hz, Ar), 8.46 (d, 1 H, J = 10.5 Hz, Ar), 8.84 (s, 1 H, Ar), 9.72 (s, 1 H, Ar); IR (KBr) 1736 cm^{-1}; MS m/z (rel intensity) 378 (4, M^+), 376 (4, M^+), 322 (24), 320 (24), 278 (32), 276 (33), 263 (22), 261 (21), 57 (100). Anal. Calcd for $C_{17}H_{17}BrN_2O_3$: C, 54.13; H, 4.54; N, 7.43. Found: C, 54.17; H, 4.58; N, 7.19. Recrystallization of the second fraction from EtOAc/ hexane gave **24** (0.17 g, 20%) as slightly yellow needles, mp 255-257 °C: ^{1}H NMR (DMSO-d_6) δ 3.88 (s, 3 H, OCH_3), 7.32 (dd, 1 H, J = 9.0 Hz, J = 3.0 Hz, Ar), 7.60 (d, 1 H, J = 9.0 Hz, Ar), 8.05 (d, 1 H, J = 3.0 Hz, Ar), 8.38 (s, 1 H, Ar), 8.87 (s, 1 H, Ar), 11.77 (s, 1 H, NH); IR (KBr) 3121, 3054, 2758, 2658, 1504 cm^{-1}; MS m/z (rel intensity) 278 (97, M^+), 276 (100, M^+), 263 (84), 261 (85), 235 (26), 233 (26). Anal. Calcd for $C_{12}H_9BrN_2O$: C, 52.01; H, 3.27; N, 10.11. Found: C, 51.82; H, 3.22; N, 9.95.

4-Bromo-6-methoxy-9*H*-β-carboline (24). Carbamate **23** (1.06 mmol, 0.40 g) was stirred with 37% HCl/ AcOH 1/ 10 (10 ml) at r.t. for 2 d. Workup as decribed for **22** (extraction with hot toluene/ THF 1:1) and FC (CH_2Cl_2/ EtOH 10:1) gave starting material (20 mg, 5%) and **24** (0.26 g, 86%), after recrystallization from EtOAc/ hexane.

References and Notes

1. Dorey, G.; Poissonnet, G.; Potier, M.-C.; Prado de Carvalho, L.; Venault, P.; Chapouthier, G.; Rossier, J.; Potier, P.; Dodd, R. H. *J. Med. Chem.* **1989**, *32*, 1799-1804.
2. Balitz, D. M.; Bush, J. A.; Bradner, W. T.; Doyle, T. W.; O'Herron, F. A.; Nettleton, D. E. *J. Antibiotic.* **1982**, *35*, 259-265.
3. Erickson, W. R.; Gould, S. J. *J. Am. Chem. Soc.* **1985**, *107*, 5831-5832.

4. Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, D. D.; Kitos, P. A. *J. Med. Chem.* **1987**, *30*, 1918-1928.
5. Moody, C. J.; Ward, J. G. *J.Chem. Soc. Perkin Trans. 1* **1984**, 2895-2901.
6. Molina, P.; Murcia, F.; Fresneda, P. M. *Tetrahedron Lett.* **1994**, *35*, 1453-1456.
7. Rao, A. V. R.; Chavan, S. P.; Sivadasan, L. *Tetrahedron* **1986**, *42*, 5065-5071.
8. Neef, G.; Eder, U.; Huth, A.; Rahtz, D.; Schmiechen, R.; Seidelmann, D. *Heterocycles* **1983**, *20*, 1295-1313.
9. Hibino, S.; Okazaki, M.; Ichikawa, M.; Sato, K.; Ishizu, T. *Heterocycles* **1985**, *23*, 261-264.
10. Ciufolini, M. A.; Bishop, M. J. *J. Chem. Soc. Chem. Commun.* **1993**, 1463-1464.
11. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790-5795.
12. Godard, A.; Rovera, J.-C.; Marsais, F.; Ple, N.; Queguiner, G. *Tetrahedron* **1992**, *48*, 4123-4134.
13. Rocca, P.; Godard, A.; Marsais, F. *Tetrahedron* **1993**, *49*, 3325-3342.
14. Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1-42.
15. Stout, D. M.; Meyers, A. I. *Chem. Rev.* **1982**, *82*, 223-243.
16. Gabel, R. A.; Meyers, A. I. *Heterocycles* **1978**, *11*, 133-138.
17. Epsztajn, J.; Bieniek, A.; Brzezinski, J. Z.; Jozwiak, A. *Tetrahedron Lett.* **1983**, *24*, 4735-4738.
18. Schlecker, W.; Mulzer, J. Huth, A.; Ottow, E.; *Liebigs Ann. Chem.*, in print.
19. Grehn, L. G.; Gunnarsson, K.; Ragnarsson, U. *J. Chem. Soc. Chem. Commun.* **1985**, 1317-1318.
20. Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424-2426.
21. Solvolysis of N-benzoyl-N-phenyl carbamic acid (1,1-dimethylethyl) ester was performed with 2-diethylaminoethylamine but not with LiOH. We tested the method with N-phenyl-2-pyridinecarboxamide as a model compound for pyridoylanilides which gave after *tert*-butyloxycarbonylation and hydrolysis of the crude product 2-pyridinecarboxylate in 95% yield.
22. Yamada, S.; Ninomiya, K.; Shioiri, T. *J. Am. Chem. Soc.* **1972**, *94*, 6203-6205.
23. Greiner, A. *Synthesis* **1989**, 312-313.
24. Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691-1696.
25. Hall, R. J.; Marchant, J.; Oliveira-Campos, A. M. F.; Queiroz, M.-J. R. P.; Shannon, P. V. R. *J. Chem. Soc. Perkin Trans 1* **1992**, 3439-3450.
26. Bisarya, S. C.; Rao, R. *Synth. Commun.* **1993**, *23*, 779-788.
27. Brown, A. D.; Dickinson, R. P.; Wythes, M. J., WO 93 21,178, 1993; *Chem. Abstr.* **1994**, *120*, 217271v.

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