Synthesis of spirocyclic carbazole- and acridine-lactams†

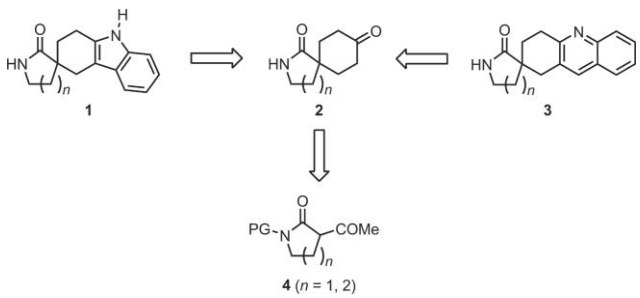
Martina Würdemann and Jens Christoffers*

Received 2nd November 2009, Accepted 9th February 2010
First published as an Advance Article on the web 25th February 2010
DOI: 10.1039/b922827f

Spirocyclic carbazole- and acridine-lactams were prepared by Fischer-indole or Friedländer-quinoline synthesis starting from spirocyclic ketones with a lactam ring. All annulation products were obtained as mixtures of separable regioisomers, which differ only in the position of one methyl group. The starting materials were prepared from 2-pyrrolidone and 2-piperidone by a sequence of protection (by *N*-allylation), α-acylation, iron-catalyzed Michael reaction followed by Robinson-annulation, palladium-catalyzed *N*-deprotection and catalytic hydrogenation. The overall yields of this six-step sequence are 13 and 17%, respectively, and the racemic ketones are obtained as single diastereoisomers.

Introduction

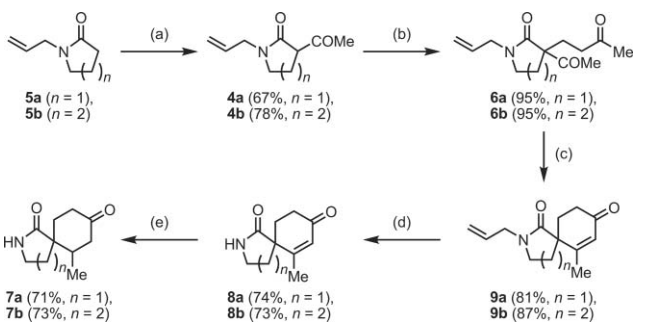
Spirocyclic compounds are challenging synthetic targets in organic chemistry.[1] Because of their conformational rigidity they are often used as scaffolds in medicinal chemistry.[2] Whereas spirocyclic structures with an indole moiety are often reported in the literature,[3] respective quinoline derivatives are less frequently precedented.[4] Most prominent examples of such spirocyclic indoles with an additional lactam moiety are probably the spirotryprostatins, which exhibit very potent antitumor activity.[5] In this work, we wish to report on the synthesis of spirocyclic carbazole-lactams **1** and acridine-lactams **3** from ketones **2** by Fischer-indole[6] and Friedländer-quinoline synthesis (Scheme 1).[7] Spirocyclic ketones **2** would be accessible by Robinson annulation of *N*-protected α-acetyl lactams[8] **4** followed by hydrogenation. They are useful scaffolds for combinatorial chemistry with a high degree of novelty.



Scheme 1 Synthetic plan for spiro-indole-lactams **1** and spiro-quinoline-lactams **3** from α-acetyl lactams **4** *via* spirocyclic keto-lactams **2**.

Results and discussion

Based on our previous work with α-acetyl lactams **4**[9] we had initially chosen the benzyl group as a protective group PG in the synthesis of spirocyclic ketones **2**. However, we had to recognize that this group is very difficult to remove from *N*-benzyl lactams and therefore made the decision to use the *N*-allyl group for the protection of our lactams. *N*-Allylation of butyrolactam and valerolactam with allyl bromide proceeded in DMF in the presence of KOH. Both compounds **5a**[10] and **5b**[11] were isolated in 49% yield after distillation. The spirocyclic ketones **7a** and **7b** were then prepared in five steps starting with deprotonation (LDA) and α-acetylation with MeOAc (Scheme 2). The use of EtOAc, Ac_2O, AcCl or AcCN as acetylating reagents gave lower yields. The Michael reaction of β-oxolactams **4** was performed with an excess of methyl vinyl ketone (MVK) according to an iron-catalyzed protocol developed in our group.[12] Experiments with acrolein as a Michael acceptor were unfortunately not successful. For this reason, an additional methyl group is retained as a structural difference to the lactams of our initial plan. The next step was the intramolecular Robinson-type aldol reaction of 1,5-diketones **6** mediated by pyrrolidinium acetate giving spirocyclic enones **9** with correct regiochemistry.[13] The cleavage of the



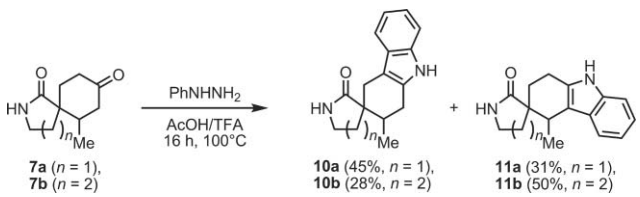
Scheme 2 Synthesis of spirocyclic keto-lactams **7** from *N*-allyl lactams **5**. Reagents and conditions: (a) 1. 1.2 eq. LDA soln., THF, –78 °C, 0.5 h, 2. 3 eq. MeOAc, 23 °C, 0.5 h; (b) 0.1 eq. $FeCl_3 \cdot 6\,H_2O$, 2 eq. MVK, CH_2Cl_2, 23 °C, 16 h; (c) 1 eq. pyrrolidine, 1 eq. HOAc, CH_2Cl_2, 23 °C, 16 h; (d) 0.05 eq. $Pd(OAc)_2$, H_2O, TFA, 80 °C, 16 h; (e) Pd/C, 1 atm H_2, *i*-PrOH, 50 °C, 16 h.

Institut für Reine und Angewandte Chemie, Carl von Ossietzky-Universität Oldenburg, D-26111, Oldenburg, Germany. E-mail: jens.christoffers@uni-oldenburg.de; Fax: +49 441 798 3873; Tel: +49 441 798 4744

† Electronic supplementary information (ESI) available: Synthetic procedures for and characterization data of compounds **4b**, **5b**, **6b**,**7b**, **8b**, **9b**, **10b**, **11b**, **12b**, and **13b**. CCDC reference number 748342. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b922827f

N-allyl group was then first attempted by isomerization-hydrolysis with $Pd(tfa)_2$–DPPP according to a recent literature report.[14] We were, however, only able to achieve double bond isomerization under the reported conditions. After tedious optimization of reaction parameters, it turned out that allyl-cleavage can be achieved with 5 mol% $Pd(OAc)_2$ in TFA–water without any phosphane ligand. Yields up to 75% were achieved for products **8a** and **8b** on a 5 g-scale. On larger scales, lower conversions limit the yields and results sometimes become irreproducible. Finally, catalytic hydrogenation proceeded smoothly and should be performed in isopropanol as solvent in order to prevent acetal formation (if EtOH or MeOH are used).[15] The racemic products **7a** and **7b** now have an additional stereocenter, but they are obtained as single diastereoisomers as evidenced by NMR. Attempts to elucidate the relative configuration by ROESY experiments were not successful, but the relative configuration was established at a later stage by X-ray crystallography (*vide infra*) to be *cis* (methyl and lactam-carbonyl group).

The Fischer indolization of racemic spiroketones **7** was performed under standard conditions[16] (Scheme 3) and yielded a mixture of regioisomeric products **10** and **11** with overall yields of 76% (five-membered lactam, ratio **10a** : **11a** *ca.* 2 : 1) and 78% (six-membered lactam, ratio **10b** : **11b** *ca.* 1 : 2). In each case, both isomers actually differ only in the position of the methyl group on the carbazole part (either at C-2 or C-4). They were separable by column chromatography and are obtained in about the same amounts. All four compounds are crystalline materials, which are hardly soluble in $CDCl_3$, so NMR spectra were obtained in a mixture of $CDCl_3$–CD_3OD. All the proton and carbon resonances of all four products, **10a**, **10b**, **11a** and **11b**, were unequivocally assigned by 2D-NMR techniques (H,H-COSY, HMBC and HMQC experiments).



Scheme 3 Synthesis of regioisomeric indole-lactams.

From compound **10b**, single crystals were obtained for an X-ray structure determination.[17] An ORTEP-representation is given in Fig. 1. First of all, the constitution of compound **10b** (methyl group at position 2) was confirmed. Secondly, the relative configuration of all compounds was established to be *cis* (methyl and lactam-carbonyl group). Therefore, the *syn*-hydrogenation of enones **8a** and **8b** had proceeded *anti* with respect to the lactam-carbonyl groups. This relative configuration is given in the formula of compounds **7a** and **7b** in Scheme 4, but omitted in all other structures for simplicity.

The synthesis of spiro-acridine-lactams was accomplished in glacial acetic acid at 100 °C. 2-Aminobenzaldehyde always had to be freshly prepared by reduction of 2-nitrobenzaldehyde with iron-powder.[18] As observed for indole formation, again a mixture of regioisomeric products **12** and **13** with overall yields of 77% (five-membered lactam) and 71% (six-membered lactam) was obtained. The ratio of 3-methyl- (**12**) and 1-methyl-isomers (**13**) was *ca.* 2 : 1.

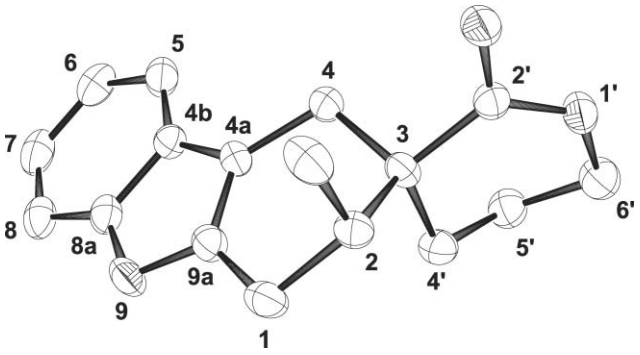
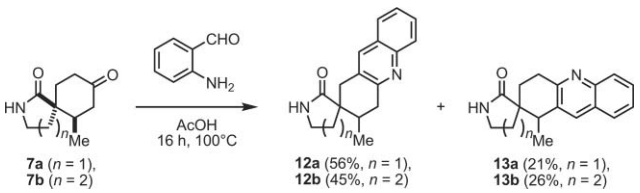


Fig. 1 ORTEP representation of the structure of racemic compound **10b** in the solid state.



Scheme 4 Synthesis of regioisomeric quinoline-lactams.

Their separation by column chromatography was challenging due to their low solubility in common solvents, but finally succeeded with toluene–acetone–NEt_3 as the mobile phase. NMR spectra were obtained in a mixture of $CDCl_3$–CD_3OD. All the proton and carbon resonances of all four products, **12a**, **12b**, **13a** and **13b**, were unequivocally assigned by 2D-NMR techniques (H,H-COSY, HMBC, HMQC experiments).

Experimental

General methods

Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with ethyl acetate (EA), *tert*-butyl methyl ether (MTBE), toluene or methanol (MeOH) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 500 and Avance DPX 300 at 23 °C. Multiplicities in ^{13}C-NMR were determined with DEPT experiments. EI-MS, CI-MS and HR-MS spectra were obtained with a Finnigan MAT 95 spectrometer, GC-MS (EI) spectra with a Focus GC and a DSQ MS-detector (Thermo-Fisher). IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. *ortho*-Aminobenzaldehyde was always freshly prepared by reduction of nitrobenzaldehyde with iron-powder as reported previously.[18] All other starting materials were commercially available.

1-Allyl-2-pyrrolidone (5a)

Allyl bromide (30.6 ml, 42.6 g, 352 mmol) was added dropwise to a stirred suspension of 2-pyrrolidone (30.0 g, 352 mmol) and KOH powder (19.8 g, 352 mmol) in DMF (110 ml). The mixture was further stirred at 60 °C for 16 h, then diluted with water (150 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic extracts were dried ($MgSO_4$). After filtration

and evaporation of the solvent the residue was submitted to vacuum distillation through a 10 cm Vigreux column. The product **5a** was obtained as the main fraction (bp. 80 °C at 5 mbar) and as a colorless liquid (21.8 g, 174 mmol, 49%). ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 2.03$ (pentet, $J = 7.6$ Hz, 2H), 2.42 (t, $J = 8.1$ Hz, 2H), 3.36 (t, $J = 7.0$ Hz, 2H), 3.89 (d, $J = 6$ Hz, 2H), 5.18 (d, br, $J = 16$ Hz, 1H), 5.19 (d, br, $J = 11$ Hz, 1H), 5.73 (ddt, br, $J = 16$ Hz, $J = 11$ Hz, $J = 6$ Hz, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): $\delta = 17.52$ (CH_2), 30.72 (CH_2), 44.90 (CH_2), 46.46 (CH_2), 117.46 (CH_2), 132.21 (CH), 174.44 (C) ppm. MS (EI, 70 eV): m/z (%) = 125 (79) [M$^+$], 70 (100), 41 (56). IR (ATR): $\nu =$ 3082 (w), 2978 (m), 2948 (m), 2994 (m), 1676 (vs), 1494 (m), 1462 (m), 1438 (m), 1416 (s), 1281 (m), 1264 (s), 1199 (m), 993 (m), 923 (s) cm^{-1}. HRMS: calcd. 125.0841 (for $C_7H_{11}NO$), found 125.0839 [M$^+$]. $C_7H_{11}NO$ (125.17).

3-Acetyl-1-allyl-2-pyrrolidone (4a)

LDA (198 mmol, 110 ml of a 1.8 mol dm^{-3} solution in THF–heptane–ethylbenzene) was added dropwise over a period of 30 min to a stirred and cooled (dry ice–acetone bath) solution of lactam **5a** (21.1 g, 169 mmol) in abs. THF (170 ml). Subsequently, MeOAc (40.3 ml, 37.6 g, 507 mmol) was added in one portion, and the mixture was stirred and warmed to ambient temperature (30 min). Half concentrated hydrochloric acid (100 ml) was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 ml). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue submitted to chromatography (SiO_2, MTBE, R_f 0.38) to give the title compound **4a** as a colorless oil (19.0 g, 114 mmol, 67%). Alternatively, the product can be purified by vacuum distillation (bp. 92 °C at 1.3 mbar). ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 2.05$ (ddt, $J = 13.4$ Hz, $J = 5.4$ Hz, $J = 9.0$ Hz, 1H), 2.44 (s, 3H), 2.55 (ddt, $J = 13.4$ Hz, $J = 8.4$ Hz, $J = 5.6$ Hz, 1H), 3.29 (dt, $J = 5.3$ Hz, $J = 9.4$ Hz, 1H), 3.39 (dt, $J = 3.6$ Hz, $J = 9.2$ Hz, 1H), 3.61 (dd, $J = 9.2$ Hz, $J = 6.0$ Hz, 1H), 3.84–3.91 (m, 2H), 5.17 (d, br, $J = 16$ Hz, 1H), 5.19 (d, $J = 10$ Hz, 1H), 5.70 (ddt, $J =$ 16 Hz, $J = 10$ Hz, $J = 6$ Hz, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): $\delta = 19.30$ (CH_2), 29.74 (CH_3), 44.84 (CH_2), 45.27 (CH_2), 55.47 (CH), 117.84 (CH_2), 131.61 (CH), 169.29 (C), 203.52 (C) ppm. MS (EI, 70 eV): m/z (%) = 167 (54) [M$^+$], 124 (100), 96 (47). IR (ATR): 3083 (w), 2985 (m), 2893 (m), 1714 (s), 1675 (vs), 1644 (m), 1493 (m), 1418 (s), 1357 (m), 1263 (s), 1164 (m), 993 (m), 928 (s) cm^{-1}. HRMS: calcd. 167.0946 (for $C_9H_{13}NO_2$), found 167.0950 [M$^+$]. $C_9H_{13}NO_2$ (167.21).

3-Acetyl-1-allyl-3-(3-oxobutyl)-2-pyrrolidone (6a)

$FeCl_3$·6 H_2O (1.10 g, 4.07 mmol) and MVK (6.6 ml, 5.71 g, 81.4 mmol) were subsequently added to a stirred solution of lactam **4a** (6.80 g, 40.7 mmol) in CH_2Cl_2 (40 ml). After stirring the mixture for 16 h at 23 °C, all volatile materials were removed *in vacuo* and the residue chromatographed on SiO_2 (MTBE, R_f 0.23) to yield the title compound **6a** (9.16 g, 38.6 mmol, 95%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 1.75$ (ddd, $J = 13.1$ Hz, $J =$ 8.5 Hz, $J = 7.1$ Hz, 1H), 2.08–2.16 (m, 1H), 2.14 (s, 3H), 2.20–2.26 (m, 1H), 2.29 (s, 3H), 2.41–2.45 (m, 2H), 2.58 (ddd, $J = 13.2$ Hz, $J = 7.8$ H, $J = 4.2$ Hz, 1H), 3.22–3.32 (m, 2H), 3.87–3.89 (m, 2H), 5.17 (d, br, $J = 17$ Hz, 1H), 5.20 (d, br, $J = 10$ Hz, 1H), 5.71 (ddt, $J = 17$ Hz, $J = 10$ Hz, $J = 6$ Hz, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): $\delta = 26.15$ (CH_3), 26.45 (CH_2), 27.57 (CH_2), 29.89 (CH_3), 38.56 (CH_2), 43.81 (CH_2), 45.55 (CH_2), 61.56 (C), 118.20 (CH_2), 131.72 (CH), 171.86 (C), 205.60 (C), 207.16 (C) ppm. MS (EI, 70 eV): m/z (%) = 237 (5) [M$^+$], 195 (28), 167 (17), 138 (100). IR (ATR): 3080 (w), 2925 (m), 1708 (m), 1677 (vs), 1494 (s), 1417 (s), 1356 (s), 1270 (s), 1164 (s), 931 (s) cm^{-1}. HRMS: calcd. 237.1365 (for $C_{13}H_{19}NO_3$), found 237.1361 [M$^+$]. $C_{13}H_{19}NO_3$ (237.30).

2-Allyl-6-methyl-2-azaspiro[4.5]dec-6-ene-1,8-dione (9a)

Pyrrolidine (8.4 ml, 7.2 g, 101 mmol) was added to a cooled (ice water bath) and stirred solution of lactam **6a** (24.0 g, 101 mmol) in CH_2Cl_2 (50 ml). Subsequently, glacial acetic acid (5.8 ml, 6.1 g, 101 mmol) was added, the cooling bath was removed and the mixture stirred for 16 h at ambient temperature. After concentrating the reaction mixture to half of its volume, it was transferred directly on top of a SiO_2 column and chromatographed (MTBE, R_f 0.11) to give the title compound **9a** (17.9 g, 81.6 mmol, 81%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 1.93$ (s, 3H), 1.93–1.96 (m, 1H), 2.13–2.23 (m, 2H), 2.33–2.44 (m, 2H), 2.56–2.62 (m, 1H), 3.37–3.45 (m, 2H), 3.88 (dd, $J = 15.1$ Hz, $J =$ 6.3 Hz, 1H), 4.01 (dd, $J = 15.1$ Hz, $J = 6.0$ Hz, 1H), 5.23 (d, br, $J = 17$ Hz, 1H), 5.24 (d, br, $J = 10$ Hz, 1H), 5.75 (ddt, br, $J =$ 17 Hz, $J = 10$ Hz, $J = 6$ Hz, 1H), 5.96 (s, br, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): $\delta = 20.58$ (CH_3), 28.30 (CH_2), 31.07 (CH_2), 33.79 (CH_2), 44.39 (CH_2), 46.07 (CH_2), 50.43 (C), 118.96 (CH_2), 129.37 (CH), 132.28 (CH), 161.46 (C), 175.19 (C), 198.34 (C) ppm. MS (EI, 70 eV): m/z (%) = 219 (19) [M$^+$], 218 (18), 204 (19), 191 (100), 176 (8), 163 (56), 150 (5), 135 (33), 122 (17). IR (ATR): 3081 (w), 2949 (m), 1669 (vs), 1439 (s), 1417 (s), 1377 (m), 1343 (m), 1326 (m), 1268 (s), 1232 (m), 1187 (m), 1167 (m), 993 (m), 954 (m), 929 (m), 858 (m) cm^{-1}. HRMS: calcd. 219.1259 (for $C_{13}H_{17}NO_2$), found 219.1257 [M$^+$]. $C_{13}H_{17}NO_2$ (219.28).

6-Methyl-2-azaspiro[4.5]dec-6-en-1,8-dione (8a)

$Pd(OAc)_2$ (344 mg, 1.5 mmol, 0.05 eq) was added to a solution of lactam **9a** (6.72 g, 30.6 mmol) in H_2O (15 ml) and TFA (15 ml). The resulting mixture was stirred for 16 h at 80 °C. All volatile materials were removed *in vacuo* and the residue dissolved in MeOH (5 ml) and chromatographed on SiO_2 (MTBE–MeOH 5 : 1, R_f 0.24) to give the title compound **8a** (4.04 g, 22.5 mmol, 74%) as a colorless oil. ^{1}H-NMR ($CDCl_3$, 500 MHz): $\delta = 1.98$ (d, $J = 1.3$ Hz, 3H), 2.00–2.03 (m, 1H), 2.28–2.44 (m, 4H), 2.58–2.63 (m, 1H), 3.47 (t, $J = 7.0$ Hz, 2H), 5.98 (q, $J = 1.1$ Hz, 1H), 6.59 (s, br, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): $\delta = 20.14$ (CH_3), 30.38 (CH_2), 30.50 (CH_2), 33.42 (CH_2), 39.60 (CH_2), 49.10 (C), 129.15 (CH), 160.46 (C), 179.06 (C), 197.73 (C) ppm. MS (EI, 70 eV): m/z (%) = 179 (16) [M$^+$], 178 (18), 164 (36), 151 (100), 123 (87). IR (ATR): 3335 (m), 3086 (w), 2927 (m), 2900 (m), 1693 (vs), 1651 (vs), 1445 (m), 1430 (s), 1372 (s), 1267 (s), 1190 (s), 1064 (m), 884 (m), 711 (s), 687 (s), 666 (s), 619 (s) cm^{-1}. HRMS: calcd. 179.0946 (for $C_{10}H_{13}NO_2$), found 179.0950 [M$^+$]. $C_{10}H_{13}NO_2$ (179.22).

cis-6-Methyl-2-azaspiro[4.5]decane-1,8-dione (7a)

A mixture of lactam **8a** (7.62 g, 42.5 mmol), Pd/C (425 mg, 10% w/w Pd), and *i*PrOH (65 ml) was degassed (three cycles of freeze,

pump, thaw) and stirred at 50 °C for 2 d under an atmosphere of H_2 (balloon). The solvent was removed *in vacuo* and the residue chromatographed on SiO_2 (MTBE–MeOH 5 : 1, R_f 0.40) to give the title compound **7a** (5.49 g, 30.3 mmol, 71%) as a colorless solid, m.p 142–143 °C. ^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 1.08 (d, J = 6.7 Hz, 3H), 1.75–1.81 (m, 1H), 1.92–2.01 (m, 2H), 2.23–2.28 (m, 4H), 2.97 (t, J = 13.4 Hz, 1H), 3.01–3.08 (m, 1H), 3.33–3.42 (m, 2H), 6.31 (s, 1H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$, 125 MHz): δ = 16.75 (CH_3), 33.30 (CH_2), 34.61 (CH_2), 37.80 (CH_2), 39.11 (CH), 39.16 (CH_2), 44.61 (C), 45.80 (CH_2), 180.09 (C), 211.61 (C) ppm. MS (EI, 70 eV): m/z (%) = 181 (60) [M$^+$], 139 (23), 138 (28), 112 (34), 98 (100). IR (ATR): 3184 (m), 3081 (w), 2876 (m), 1711 (vs), 1674 (vs), 1457 (m), 1416 (m), 1347 (m), 1285 (s), 1130 (m), 803 (s), 771 (s), 707 (s), 670 (s), 620 (s) cm^{-1}. HRMS calcd. 181.1103 (for $C_{10}H_{15}NO_2$), found 181.1099 [M$^+$]. $C_{10}H_{15}NO_2$ (181.23).

Fischer-indolization of lactam 7a

A mixture of ketone **7a** (207 mg, 1.14 mmol), glacial AcOH (2.8 ml), TFA (1.0 ml) and $PhNHNH_2$ (136 mg, 1.26 mmol) was stirred for 16 h at 100 °C in a tightly closed reaction vial. The mixture was poured onto ice water (*ca.* 20 g) and the resulting emulsion extracted with CH_2Cl_2 (3 × 10 ml). The combined organic layers were dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was chromatographed on SiO_2 (EtOAc) to yield carbazole **10a** (130 mg, 0.51 mmol, 45%) in the first fraction (R_f 0.30) and carbazole **11a** (91 mg, 0.36 mmol, 31%) in the second fraction (R_f 0.17).

cis-1,2,3,4-Tetrahydro-2-methylspiro[carbazole-3,3′-pyrrolidine]-2′-one (10a)

Colorless solid, mp. 235–236 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD 1 : 1, 500 MHz): δ = 1.22 (d, J = 6.9 Hz, 3H; 2-Me), 1.96–2.05 (m, 1H; 4′-H), 2.14–2.22 (m, 2H; 2-H, 4′-H), 2.55–2.63 (m, 2H; 1-H, 4-H), 3.02 (dd, J = 16.7 Hz, J = 5.3 Hz, 1H; 1-H), 3.10 (d, J = 15.7 Hz, 1H; 4-H), 3.28–3.36 (m, 2H; 2 × 5′-H), 7.01–7.04 (m, 1H; 6-H), 7.06–7.10 (m, 1H; 7-H), 7.30 (d, J = 7.9 Hz, 1H; 8-H), 7.42 (d, J = 7.7 Hz, 1H; 5-H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$–CD_3OD 1 : 1, 125 MHz): δ = 15.85 (CH_3; 2-Me), 26.73 (CH_2; C-4), 29.14 (CH_2; C-1), 33.43 (CH; C-2), 34.50 (CH_2; C-4′), 39.00 (CH_2; C-5′), 46.23 (C; C-3), 106.33 (C; C-4a), 110.94 (CH; C-8), 117.62 (CH; C-5), 118.92 (CH; C-6), 120.96 (CH; C-7), 127.94 (C; C-4b), 132.22 (C; C-9a), 136.79 (C; C-8a), 182.63 (C; C-2′) ppm. MS (EI, 70 eV): m/z (%) = 254 (85) [M$^+$], 180 (8), 167 (10), 157 (96), 143 (100), 130 (20). IR (ATR): 3364 (m), 3187 (m), 3075 (w), 2971 (w), 2870 (m), 1677 (vs), 1463 (s), 1433 (m), 1285 (s), 1257 (m), 1234 (m), 796 (m), 734 (vs), 625 (s) cm^{-1}. HRMS calcd. 254.1419 (for $C_{16}H_{18}N_2O$), found 254.1412 [M$^+$]. $C_{16}H_{18}N_2O$ (254.33).

cis-1,2,3,4-Tetrahydro-4-methylspiro[carbazole-3,3′-pyrrolidine]-2′-one (11a)

Colorless solid, mp. 206–208 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD 1 : 1, 500 MHz): δ = 1.34 (d, J = 6.9 Hz, 3H; 4-Me), 1.57–1.62 (m, 1H; 2-H), 1.96–2.04 (m, 2H; 2 × 4′-H), 2.38 (ddd, J = 13.3 Hz, J = 11.9 Hz, J = 6.2 Hz, 1H; 2-H), 2.67–2.75 (m, 1H; 1-H), 2.83 (ddd, J = 16.7 Hz, J = 6.2 Hz, J = 1.8 Hz, 1H; 1-H), 3.16 (q, J = 6.9 Hz, 1H; 4-H), 3.26 (ddd, J = 10.2 Hz, J = 7.7 Hz, J = 2.6 Hz, 1H; 5′-H), 3.40–3.46 (m, 1H; 5′-H), 7.00–7.03 (m, 1H; 6-H), 7.05–7.08 (m, 1H; 7-H), 7.28–7.30 (m, 1H; 8-H), 7.43–7.45 (m, 1H; 5-H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$–CD_3OD 1 : 1, 125 MHz): δ = 18.64 (CH_3; 4-Me), 20.23 (CH_2; C-1), 26.06 (CH_2; C-2), 32.21 (CH; C-4), 34.06 (CH_2; C-4′), 39.46 (CH_2; C-5′), 47.30 (C; C-3), 111.36 (CH; C-8), 113.09 (C; C-4a), 117.84 (CH; C-5), 119.01 (CH; C-6), 121.17 (CH; C-7), 127.84 (C; C-4b), 132.84 (C; C-9a), 137.17 (C; C-8a), 182.94 (C; C-2′) ppm. MS (EI, 70 eV): m/z (%) = 254 (42) [M$^+$], 167 (12), 157 (100), 108 (20), 77 (9), 43 (10). IR (ATR): 3390 (s), 3249 (m), 3053 (w), 2987 (w), 1696 (vs), 1650 (vs), 1466 (s), 1430 (s), 1329 (m), 1273 (s), 1202 (s), 1140 (m), 1068 (m), 1037 (m), 747 (vs), 732 (vs) cm^{-1}. HRMS calcd. 254.1419 (for $C_{16}H_{18}N_2O$), found 254.1412 [M$^+$]. $C_{16}H_{18}N_2O$ (254.33).

Friedländer-synthesis with lactam 7a

2-Aminobenzaldehyde (225 mg, 1.86 mmol) was added to a solution of ketone **7a** (260 mg, 1.43 mmol) in glacial acetic acid (3.6 ml) and the mixture was stirred for 16 h at 100 °C. MTBE (30 ml) and 10% aqueous NaOH (15 ml) were added, and the layers separated. The aqueous layer was further extracted with MTBE (2 × 20 ml) and the combined organic layers were dried over $MgSO_4$. After filtration and evaporation of the solvent the residue was chromatographed on SiO_2 (toluene–acetone–NEt_3 50 : 50 : 1) to yield acridine **12a** (213 mg, 0.80 mmol, 56%) in the first fraction (R_f 0.21) and acridine **13a** (102 mg, 0.30 mmol, 21%) as the second fraction (R_f 0.14), both as colorless solids.

1,2,3,4-Tetrahydro-3-methylspiro[acridine-2,3′-pyrrolidine]-2′-one (12a)

Colorless solid, mp. 244–245 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD 1 : 1, 500 MHz): δ = 1.15 (d, J = 6.9 Hz, 3H; 3-Me), 1.99 (td, J = 13.3 Hz, J = 8.2 Hz, 1H; 4′-H), 2.11–2.21 (m, 2H; 3-H, 4′-H), 2.85 (d, J = 16.9 Hz, 1H; 1-H), 3.05 (dd, J = 17.8 Hz, 8.3 Hz, 1H; 4-H), 3.13 (dd, J = 17.8 Hz, 5.8 Hz, 1H; 4-H), 3.23–3.25 (m, 1H; 1-H), 3.26–3.30 (m, 2H; 2 × 5′-H), 7.36–7.40 (m, 1H; 7-H), 7.53–7.57 (m, 1H; 6-H), 7.67 (d, J = 8.2 Hz, 1H; 8-H), 7.83 (d, J = 8.6 Hz, 1H; 5-H), 7.85 (s, 1H; 9-H) ppm. ^{13}C{^{1}H}-NMR ($CDCl_3$–CD_3OD 1 : 1, 125 MHz): δ = 15.22 (CH_3; 3-Me), 33.39 (CH_2; C-4′), 34.34 (CH; C-3), 35.98 (CH_2; C-1), 37.60 (CH_2; C-4); 38.27 (CH_2; C-5′), 44.43 (C; C-2), 125.12 (CH; C-7), 126.06 (CH; C-5), 126.36 (CH; C-8), 126.74 (C; C-8a), 128.27 (CH; C-6), 128.37 (C; C-9a), 134.96 (CH; C-9), 145.29 (C; C-10a), 157.55 (C; C-4a), 179.79 (C; C-2′) ppm. MS (EI, 70 eV): m/z (%) = 266 (100) [M$^+$], 251 (90), 238 (32), 209 (33), 194 (55), 181 (40), 168 (23). IR (ATR): 3208 (m), 3086 (w), 2967 (m), 2872 (m), 1674 (vs), 1493 (s), 1288 (s), 1258 (s), 1142 (m), 924 (m), 786 (vs), 762 (vs), 696 (s) cm^{-1}. HRMS calcd. 266.1419 (for $C_{17}H_{18}N_2O$), found 266.1422 [M$^+$]. $C_{17}H_{18}N_2O$ (266.34).

1,2,3,4-Tetrahydro-1-methylspiro[acridine-2,3′-pyrrolidine]-2′-one (13a)

Colorless solid, mp. 190–191 °C. ^{1}H-NMR ($CDCl_3$–CD_3OD 1 : 1, 500 MHz): δ = 1.33 (d, J = 7.3 Hz, 3H; 1-Me), 1.73 (ddd, J = 13.6 Hz, J = 6.3 Hz, J = 4.2 Hz, 1H; 3-H), 1.90 (ddd, J = 12.8 Hz, J = 7.2 Hz, J = 3.0 Hz, 1H; 4′-H), 2.01 (td, J = 12.8 Hz, J = 8.4 Hz, 1H, 4′-H), 2.38 (ddd, J = 13.6 Hz, J = 10.8 Hz, J = 6.5 Hz, 1H; 3-H), 2.94–3.01 (m, 1H; 4-H), 3.09 (q, J = 7.3 Hz, 1H; 1-H), 3.20–3.29 (m, 2H; 4-H, 5′-H), 3.31–3.37 (m, 1H; 5′-H), 7.37–7.41 (m, 1H; 7-H), 7.54–7.58 (m, 1H; 6-H), 7.70 (d, J = 8.1 Hz, 1H; 8-H),

7.84 (d, $J = 8.5$ Hz, 1H; 5-H), 7.96 (s, 1H; 9-H) ppm. $^{13}C\{^1H\}$-NMR ($CDCl_3$–CD_3OD 1 : 1, 125 MHz): $\delta = 18.55$ (CH_3; 1-Me), 25.39 (CH_2; C-3), 28.25 (CH_2; C-4), 33.10 (CH_2; C-4′), 37.57 (CH; C-1), 37.92 (CH_2; C-5′), 44.82 (C; C-2), 125.38 (CH; C-7), 126.19 (CH; C-5), 126.61 (CH; C-8), 126.85 (C; C-8a), 128.77 (CH; C-6), 134.28 (C; C-9a), 136.11 (CH; C-9), 145.33 (C; C-10a), 156.64 (C; C-4a), 180.16 (C; C-2′) ppm. MS (EI, 70 eV): m/z (%) = 266 (100) [M^+], 251 (57), 237 (9), 223 (11), 209 (44), 194 (51), 180 (26), 168 (71). IR (ATR): 3191 (m), 3089 (w), 2922 (s), 2890 (m), 2853 (m), 1697 (vs), 1675 (vs), 1488 (s), 1377 (m), 1273 (s), 1080 (m), 908 (m), 786 (s), 753 (vs) cm^{-1}. HRMS calcd. 266.1419 (for $C_{17}H_{18}N_2O$), found 266.1424 [M^+]. $C_{17}H_{18}N_2O$ (266.34).

Acknowledgements

We gratefully acknowledge support from Boehringer-Ingelheim, Biberach. We are furthermore grateful to Ludmila Hermann and Elisabeth Jaskulska for assistance, to Irina Profir for initial experiments, to Detlev Haase for X-ray crystallography and Dr Herbert Frey for helping us with this manuscript. We acknowledge a generous donation of solvents from Dr Burkard Kreidler, Evonik Oxeno GmbH, Marl.

References

1 Reviews: (*a*) S. Kotha, A. C. Deb, K. Lahiri and E. Manivannan, *Synthesis*, 2009, 165–193; (*b*) S. Rosenberg and R. Leino, *Synthesis*, 2009, 2651–2673.
2 Examples: (*a*) W. Lin, A. Gupta, K. H. Kim, D. Mendel and M. J. Miller, *Org. Lett.*, 2009, **11**, 449–452; (*b*) Z. Guo, P. Orth, S.-C. Wong, B. J. Lavey, N.-Y. Shih, X. Niu, D. J. Lundell, V. Madison and J. A. Kozlowski, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 54–57; (*c*) L. Lomlim, J. Einsiedel, F. W. Heinemann, K. Meyer and P. Gmeiner, *J. Org. Chem.*, 2008, **73**, 3608–3611; (*d*) J. A. Pfefferkorn and C. Choi, *Tetrahedron Lett.*, 2008, **49**, 4372–4373; (*e*) A. Pasternak, S. D. Goble, G. A. Doss, N. N. Tsou, G. Butora, P. P. Vicario, J. M. Ayala, M. Struthers, J. A. DeMartino, S. G. Mills and L. Yang, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 1374–1377; (*f*) A. F. Gasiecki, J. L. Cross, R. F. Henry, V. Gracias and S. W. Djuric, *Tetrahedron Lett.*, 2008, **49**, 6286–6288; (*g*) D. S. Radchenko, O. O. Grygorenko and I. V. Komarov, *Tetrahedron: Asymmetry*, 2008, **19**, 2924–2930.
3 Recent examples: (*a*) L. Cheng, L. Liu, H. Jia, D. Wang and Y.-J. Chen, *J. Org. Chem.*, 2009, **74**, 4650–4653; (*b*) M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov and G. I. Nikishin, *Mol. Diversity*, 2009, **13**, 47–52; (*c*) K.-T. Yip, N.-Y. Zhu and D. Yang, *Org. Lett.*, 2009, **11**, 1911–1914; (*d*) G. Sirasani and R. B. Andrade, *Org. Lett.*, 2009, **11**, 2085–2088; (*e*) A. S. Girgis, *Eur. J. Med. Chem.*, 2009, **44**, 91–100; (*f*) K. S. Feldman and A. Y. Nuriye, *Tetrahedron Lett.*, 2009, **50**, 1914–1916; (*g*) H. Zuleta-Prada and L. D. Miranda, *Tetrahedron Lett.*, 2009, **50**, 5336–5339; (*h*) K. C. Majumdar, S. Alam and B. Chattopadhyay, *J. Heterocycl. Chem.*, 2009, **46**, 62–68.
4 Examples: (*a*) J. Barluenga, A. Mendoza, F. Rodriguez and F. J. Fananas, *Angew. Chem.*, 2008, **120**, 7152–7155, (*Angew. Chem., Int. Ed.*, 2008, **47**, 7044–7047); (*b*) I. Yavari, A. Mirzaei, L. Moradi and N. Hosseini, *Tetrahedron Lett.*, 2008, **49**, 2355–2358; (*c*) V. Nair, S. Devipriya and E. Suresh, *Synthesis*, 2008, 1065–1068; (*d*) A. V. Tverdokhlebov, A. P. Gorulya, A. A. Tolmachev, A. N. Kostyuk, A. N. Chernega and E. B. Rusanov, *Tetrahedron*, 2006, **62**, 9146–9152; (*e*) A. P. Kadutskii and N. G. Kozlov, *Russ. J. Org. Chem.*, 2006, **42**, 855–859.
5 Reviews: (*a*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209–2219; (*b*) C. V. Galliford and K. A. Scheidt, *Angew. Chem.*, 2007, **119**, 8902–8912, (*Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758).
6 (*a*) Review: G. R. Humphrey and J. T. Kuethe, *Chem. Rev.*, 2006, **106**, 2875–2911; (*b*) see also: B. Robinson, *"The Fischer Indole Synthesis"*, Wiley-Interscience, New York 1982.
7 Review: J. Marco-Contelles, E. Perez-Mayoral, A. Samadi, M. do Carmo Carreiras and E. Soriano, *Chem. Rev.*, 2009, **109**, 2652–2671.
8 Review: V. G. Nenajdenko, E. P. Zakurdaev and E. S. Balenkova, *Russ. Chem. Rev.*, 2009, **78**, 431–456.
9 (*a*) J. Christoffers, T. Werner, S. Unger and W. Frey, *Eur. J. Org. Chem.*, 2003, 425–431; (*b*) J. Christoffers, B. Kreidler, S. Unger and W. Frey, *Eur. J. Org. Chem.*, 2003, 2845–2853.
10 (*a*) E. Späth and J. Lintner, *Chem. Ber.*, 1936, **69**, 2727–2731; (*b*) J. Falbe and F. Korte, *Chem. Ber.*, 1965, **98**, 1928–1937; (*c*) K. Kulig, U. Holzgrabe and B. Malawska, *Tetrahedron: Asymmetry*, 2001, **12**, 2533–2536.
11 (*a*) C. Schultz-Fademrecht, P. H. Deshmukh, K. Malagu, P. A. Procopiou and A. G. M. Barrett, *Tetrahedron*, 2004, **60**, 7515–7524; (*b*) G. Kumaraswamy, A. Pitchaiah, G. Ramakrishna, D. S. Ramakrishna and K. Sadaiah, *Tetrahedron Lett.*, 2006, **47**, 2013–2015.
12 Reviews: (*a*) J. Christoffers, *Synlett*, 2001, 723–732; (*b*) J. Christoffers and H. Frey, *Chimica Oggi/Chem. Today Suppl.*, 2008, **26**, 26–28.
13 For regioselectivity of aldol-spirocyclizations see: J. Christoffers, H. Oertling and W. Frey, *Eur. J. Org. Chem.*, 2003, 1665–1671.
14 N. Ohmura, A. Nakamura, A. Hamasaki and M. Tokunaga, *Eur. J. Org. Chem.*, 2008, 5042–5045.
15 J. Christoffers, H. Scharl, W. Frey and A. Baro, *Eur. J. Org. Chem.*, 2004, 2701–2706.
16 (*a*) J. Christoffers, *Synlett*, 2006, 318–320; (*b*) C. L. Diedrich, W. Frey and J. Christoffers, *Eur. J. Org. Chem.*, 2007, 4731–4737.
17 CCDC 748342 (**10b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
18 (*a*) C. L. Diedrich, D. Haase, W. Saak and J. Christoffers, *Eur. J. Org. Chem.*, 2008, 1811–1816; (*b*) C. L. Diedrich, D. Haase and J. Christoffers, *Synthesis*, 2008, 2199–2210.

