Synthesis of Some New Optically Active Octahydro-6*H*-pyrido[4,3-*b*]-carbazole Derivatives

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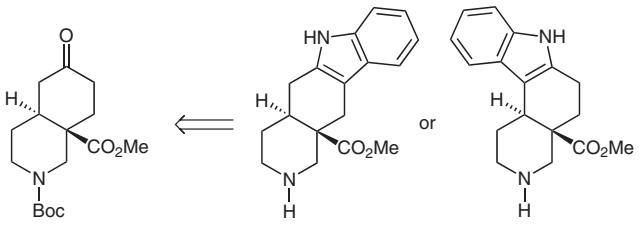
Abstract: An optically active octahydro-6*H*-pyrido[4.3-*b*]carbazole derivative was obtained by Fischer indolization of a decahydroisoquinolone with phenylhydrazine. The reaction proceeded with quantitative regioselectivity; no angular annulation products could be observed. The tetracyclic product was derivatized by sulfonamide, urea or carboxamide formation. Its linear constitution as well as relative and absolute configuration were established by single crystal X-ray crystallography of a derivative.

Key words: indoles, carbazoles, heterocycles, piperidines, amides

The indole ring system is a leading structural motif in drug discovery.[1] In most cases it appears annulated with other heterocyclic rings. For example, the 6*H*-pyrido[4,3-*b*]carbazole skeleton is the structural motif of ellipticine[2] and related indole alkaloids.[3] Octahydro-congeners like compound **2** have been reported to be potent pharmaceuticals, such as opioid receptor ligands[4] and melanin-concentrating hormone antagonists.[1a] We have previously reported on the preparation of building block **1** in optically active form on a large scale by copper-catalyzed asymmetric Michael reaction[5] and it has since been used as a starting material in medicinal chemistry.[6] In this work, we have used compound **1** as a starting material in Fischer indole synthesis.[7] We were expecting either linear octahydro-6*H*-pyrido[4,3-*b*]carbazole derivative **2** or angular annulation product **3** (Scheme 1).



Scheme 1 Synthetic plan for an octahydro-6*H*-pyrido[4,3-*b*]carbazole derivative **2** from optically active building block **1**

trans-Decahydroisoquinolone **1** was prepared in three steps (copper-catalyzed Michael-reaction, aldol-cyclization and catalytic hydrogenation) from L-valine-derived enaminoester **4** as reported before.[5] The stereochemical purity (>98% ee and de) was confirmed by GLC on a chiral phase, after conditions for appropriate baseline resolution was developed with the racemic material (Scheme 2).

In initial attempts at Fischer indolization, we decided to heat compound **1** in TFA–AcOH together with phenylhydrazine, in order to cleave the carbamate protective group in situ. However, we obtained a mixture of materials, which could be clearly identified as indoles by ^{1}H NMR of the crude reaction mixture, but showed molecular masses of m/z = 284 (compound **2**), m/z = 340 (three compounds) and m/z = 396 (one compound) upon GC-MS analysis. Obviously, isobutene generated by Boc-cleavage reacted with the indole moiety to generate several unspecifically *tert*-butylated compounds ($\Delta m/z$ = 56). For this reason, we performed the conversion stepwise as indicated in Scheme 2: The Boc-group was first cleaved with TFA at elevated temperature, then AcOH and phenylhydrazine were added to the reaction mixture. After some optimization of reaction times and temperatures, pyridocarbazole **2** was isolated in 54% yield.[8] By applying H,H-COSY, HMBC and HMQC experiments, we were able to assign almost all ^{1}H and ^{13}C resonances. The product constitution is therefore in accordance with structural formula **2**. We were not able to detect any product with angular constitution **3**.

Since we were planning to utilize the N-2 function for further derivatization (sulfonamide, urea and carboxyamide formation), we have prepared *para*-bromobenzene sulfonamide **5** (Scheme 3), which proceeded smoothly at 23 °C within two hours with triethylamine as an additional base.[9] As expected, we obtained compound **5** as a highly crystalline material and were able to grow single crystals that were suitable for a X-ray diffraction analysis. In the Supporting Information the molecular structure is shown, which confirms the linear annulation as already indicated by the 2D-NMR experiments. *trans*-Annulation of the two saturated six-membered rings is clearly visible. Furthermore, the bromine and sulfur atom in this compound allowed for anomalous dispersion giving the (4a*S*,11a*R*)-configuration as shown in the Supporting Information with an absolute structure parameter[10] of –0.0086(68).[11]

As mentioned, we were planning to prepare the urea and carboxamide derivatives at N-2. Conversion of carbazole derivative **2** with phenyl isocyanate proceeded slowly, but smoothly at ambient temperature to give the correspond-

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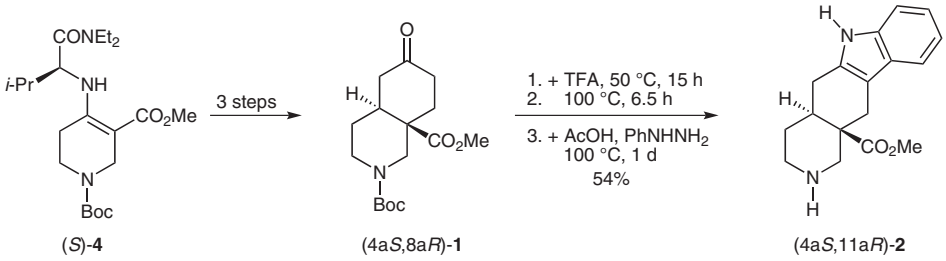
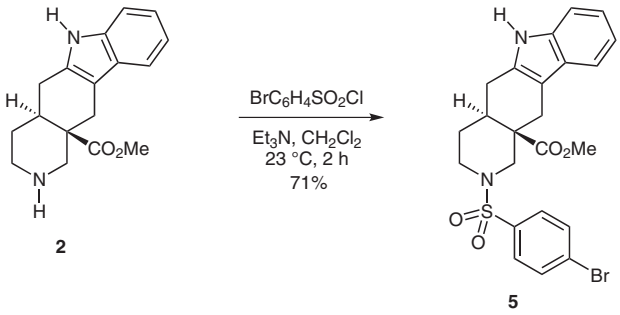


(*S*)-**4** (4a*S*,8a*R*)-**1** (4a*S*,11a*R*)-**2**

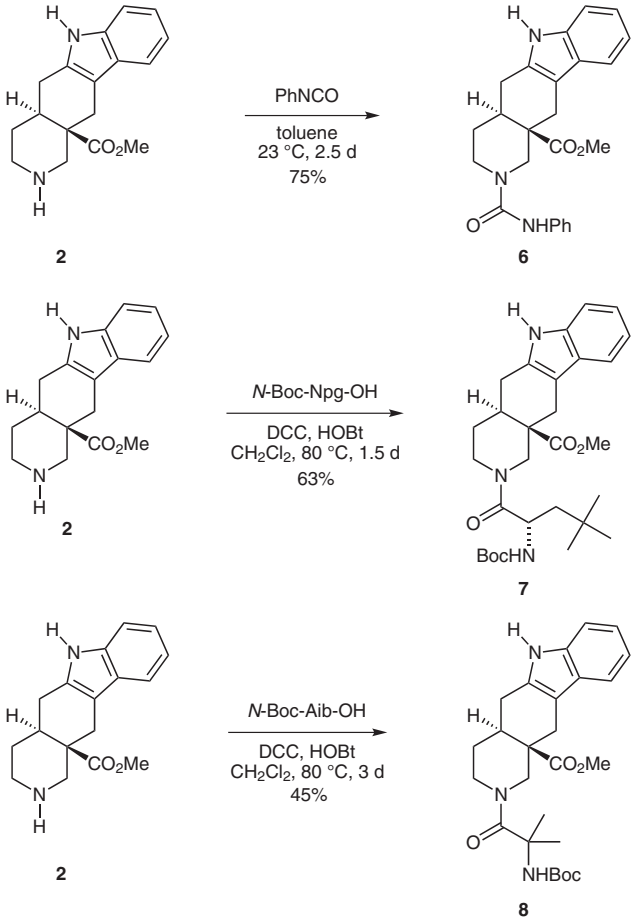
Scheme 2 Regioselective Fischer-indolization of decahydroisoquinolone **1**



Scheme 3 Preparation of sulfonamide **5** for the determination of constitution as well as relative and absolute configuration

ing urea derivative **6** (for experimental details see Supporting Information) in good yield (Scheme 4). Amidation at N-2 with *N*-Boc-protected neopentyl glycine (Npg)[12] was performed with DCC–HOBt. However, high reaction temperature was required in order to achieve full conversion of starting material **2**; compound **7** was obtained in satisfying yield (for experimental details see Supporting Information). Its NMR spectra showed doubled signal sets, presumably due to rotamers along the amide C–N bond (ratio 2:1). Conversion of the α-quaternary *N*-Boc aminoisobutyric acid (Aib)[13] under the same conditions required longer reaction times. Furthermore, the yield was low, because separation of product **8** from dicyclohexyl urea required two-fold chromatography (for experimental details see Supporting Information). At ambient temperature, the ^{1}H and ^{13}C NMR spectra show very broad signals. Two partly doubled, though still broad, signal sets appear when the spectra are recorded at 60 °C.

In summary, we conclude that Fischer indolization of isoquinolone derivative **1** proceeded with high regioselectivity to yield pyrido[4,3-*b*]carbazole derivative **2**. Further functionalization at N-2 by sulfonamide, urea, or carboxamide formation went smoothly.



Scheme 4 Synthesis of urea **6** and two carboxyamides **7** and **8** starting from carbazole derivative **2**

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

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References and Notes

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(8) (4a*S*,11a*R*)-Methyl 1,2,3,4,4a,5,11,11a-octahydro-6*H*-pyrido[4.3-*b*]carbazole-11a-carboxylate (**2**). TFA (1.0 mL, 1.5 g, 14 mmol) was added dropwise to the cooled (ice-water bath) isoquinolone **1** (347 mg, 1.11 mmol). The resulting solution was stirred for 15 h at 50 °C and then for 6.5 h at 100 °C. After cooling to ambient temperature, glacial AcOH (3 mL) and phenylhydrazine (240 mg, 2.22 mmol) were added. The mixture was again heated for 30 h at 100 °C and then poured onto ice (ca. 45 g). Aqueous KOH (5 mL, 50%) was added to the mixture until pH 14. Subsequently, CH_2Cl_2 (100 mL) was added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (100 mL) and dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue was purified by chromatography (SiO_2; CH_2Cl_2–MeOH, 2:1; R_f = 0.23) to yield the title compound **2** (170 mg, 0.60 mmol, 54%) as a yellow solid; mp 170–180 °C (dec.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.64 (d, *J* = 12.5 Hz, 1 H, 4-H), 1.93–2.21 (m, 1 H, 4a-H), 2.12 (dq, *J* = 4.5 Hz, *J* = 15.6 Hz, 2 H, 4-H and 2-NH), 2.47 (d, *J* = 15.7 Hz, 1 H, 11-H), 2.65 (d, *J* = 12.7 Hz, 2 H, 1-H and 5-H), 2.76 (dt, *J* = 12.3 Hz, *J* = 3.0 Hz, 1 H, 3-H), 3.08 (dd, *J* = 11.6 Hz, *J* = 14.9 Hz, 1 H, 5-H), 3.21 (d, *J* = 15.7 Hz, 2 H, 3-H and 11-H), 3.56 (s, 3 H, O*C*H$_3$), 3.60 (d, *J* = 12.4 Hz, 1 H, 1-H), 7.05–7.12 (m, 2 H, 8-H and 9-H), 7.23–7.26 (m, 1 H, 7-H), 7.42 (d, *J* = 7.0 Hz, 1 H, 10-H), 8.05 (s, 1 H, 6-NH). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ = 27.90 (CH_2, C-4), 29.73 (CH_2, C-5 or C-11), 30.26 (CH_2, C-11 or C-5), 40.13 (CH, C-4a), 46.89 (CH_2, C-3), 47.14 (C, C-11a), 51.66 (CH_3), 56.75 (CH_2, C-1), 107.17 (C, C-10b), 110.44 (CH, C-7), 117.66 (CH, C-10), 119.14 (CH, C-9), 121.16 (CH, C-8), 127.39 (C, C-10a), 133.26 (C, C-5a), 135.89 (C, C-6a), 174.72 (CO). IR (ATR): 3345 (m), 3140 (w), 3049 (w), 2922 (s), 2852 (m), 1705 (s), 1589 (m), 1451 (s), 1324 (m), 1194 (s), 741 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 284 (100) [M$^+$], 252 (40), 241 (12), 225 (50), 208 (70), 194 (60), 180 (54), 167 (56), 157 (20), 143 (52). HRMS (EI, 70 eV): *m*/*z* [M$^+$] calcd for $C_{17}H_{20}N_2O_2$: 284.1525; found: 284.1523. $[\alpha]_D^{20}$ +81 (*c* 1.3, $CHCl_3$).

(9) (4a*S*,11a*R*)-Methyl 2-(4-bromobenzenesulfonyl)-1,2,3,4,4a,5,11,11a-octahydro-6*H*-pyrido[4.3-*b*]carbazole-11a-carboxylate (**5**). Et_3N (57 mg, 0.56 mmol) and 4-$BrC_6H_4SO_2Cl$ (142 mg, 0.56 mmol) were subsequently added to a cooled (ice-water bath) solution of the carbazole **2** (79 mg, 0.28 mmol) in CH_2Cl_2 (0.6 mL). The resulting mixture was stirred for 2 h at 23 °C and then diluted with water (2 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated after filtration. Two-fold chromatography of the residue (SiO_2; hexane–MTBE, 1:2; R_f = 0.36; then hexane–EtOAc, 1:2) gave the title compound **5** (100 mg, 0.200 mmol, 71%) as a brown solid; mp 165–175 °C (dec.). Single crystals were obtained by slow evaporation of a solution in $CHCl_3$. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.72–1.82 (m, 2 H), 2.23 (d, *J* = 11.5 Hz, 1 H), 2.30–2.48 (m, 3 H), 2.64–2.70 (dd, *J* = 5.4 Hz, *J* = 16.0 Hz, 1 H), 3.18–3.39 (m, 2 H), 3.58 (s, 3 H), 3.90–3.94 (m, 1 H), 4.35 (dd, *J* = 1.7 Hz, *J* = 11.5 Hz, 1 H), 7.04–7.08 (m, 1 H), 7.08–7.13 (m, 1 H), 7.23–7.27 (m, 1 H), 7.39 (d, *J* = 7.8 Hz, 1 H), 7.63–7.66 (m, 2 H), 7.70–7.71 (m, 2 H), 7.74 (s, 1 H). ^{13}C{^{1}H} NMR ($CDCl_3$, 126 MHz): δ = 27.05 (CH_2), 28.35 (CH_2), 29.91 (CH_2), 39.27 (CH), 46.63 (C), 47.05 (CH_2), 51.93 (CH_3), 55.76 (CH_2), 106.00 (C), 110.54 (CH), 117.55 (CH), 119.26 (CH), 121.39 (CH), 127.03 (C), 127.90 (C), 129.11 (2 × CH), 132.42 (2 × CH), 132.96 (C), 135.56 (C), 135.89 (C), 172.61 (C). IR (ATR): 3370 (s), 2953 (w), 2915 (m), 2853 (m), 1719 (s), 1575 (m), 1469 (m), 1454 (m), 1389 (m), 1339 (s), 1324 (m), 1234 (vs), 1159 (vs), 1090 (s), 1011 (m), 943 (m), 916 (vs), 747 (vs), 732 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 502 (42) [M$^+$], 283 (69), 251 (100), 223 (29), 194 (58), 143 (38), 97 (27). HRMS (EI, 70 eV): *m*/*z* [M$^+$] calcd for $C_{23}H_{23}BrN_2O_4S$: 502.0562; found: 502.0566. $[\alpha]_D^{20}$ –46 (*c* 0.9, CH_2Cl_2).

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(11) CCDC 742770 (**5**) 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

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