DOI: 10.1002/ejoc.200700351

Linear versus Angular Fischer Indole Annulation: Relative Configuration Determines Regioselectivity

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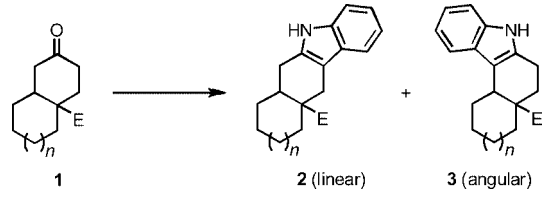
Keywords: Annulation / Indole derivatives / Heterocycles / Regioselectivity / Carbazole derivatives

Fischer indole synthesis with bicyclic ketones yields regioselectively linear annulated tetracyclic products when starting from ketones with a relative *trans* configuration. On the other hand, starting materials with a relative *cis* configuration give exclusively angular annulated indole derivatives. The starting materials were prepared in optically active form in three steps by a sequence of asymmetric Michael reaction, aldol condensation, and catalytic hydrogenation. The last step yields a mixture of *cis* and *trans* diastereoisomers which can be separated by column chromatography.

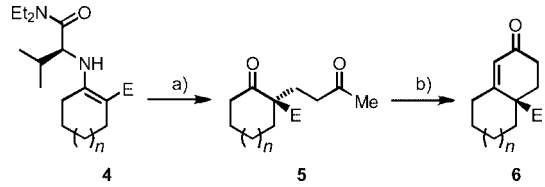
Introduction

The annulated indole nucleus is a structural component of a vast number of biologically active natural compounds.[1] The synthesis and functionalization of indoles has been the object of research for over 100 years and a variety of well-established classical methods are now available,[2] to name only a few of them, Bartoli,[3] Blechert,[4] Fürstner,[5] Larock,[6] Leimgruber–Batcho,[7] Madelung,[8] Nenitzescu,[9] Reissert,[10] and Wittig indole syntheses.[11] Still the most important and most frequently reported, however, is the transformation of aryl hydrazones according to Emil Fischer.[12] A regioselectivity problem can arise when the Fischer indole synthesis is applied to unsymmetric ketones.[13] For example, annulated cyclohexanones **1** can give either linear indole annulation (**2**) or angular products (**3**) (Scheme 1). The 2-decalone system (bicyclo[4.4.0]decan-3-one scaffold, structure **1** with $n = 1$) has been previously reported to only give linear annulation products irrespective of whether the decaline has a relative *cis* or *trans* configuration.[14]

We have recently developed a copper-catalyzed asymmetric reaction of optically active enamines **4** (derived from L-valine) with methyl vinyl ketone furnishing 1,5-diketones **5** with 96–99% *ee* (Scheme 2).[15] The key feature of this method is the formation of quaternary stereocenters at ambient temperatures and under extraordinarily simple conditions.[16] In order to determine the enantiopurity of compounds **5** by GLC on a chiral phase it was necessary to transform these diketones **5** into bicyclic enones **6**.[17] Compounds **6** and their hydrogenation products **1** are precursors of indoles **2** and **3** (Scheme 1). In a preliminary study of a racemic series, we found an interesting dependence of the regiochemistry (linear vs. angular) on the relative configuration of the starting materials **1** (*cis* vs. *trans* annulation).[18] In this full paper we wish to report on the regioselective preparation of enantiopure indoles **2** and **3** starting from optically active precursors **1** and **6**.



Scheme 1. Linear or angular indole annulation of bicyclic cyclohexanones: E = CO_2Et or CO_2Me.



Scheme 2. Asymmetric Michael reaction of enamines **4** followed by annulation of intermediate products **5** to bicyclic cyclohexenones **6**: $n = 0$, 1, or 2; E = CO_2Et or CO_2Me. Reagents and conditions: a) 1. cat. $Cu(OAc)_2 \cdot H_2O$, methyl vinyl ketone, acetone, 23 °C; 2. HCl/H_2O; b) pyrrolidine/AcOH.

Results and Discussion

Michael addition products **5** were prepared in an optically active form (>99% *ee* for **5a**, **5b**; 90% *ee* for **5c**) and subsequently cyclized to bicyclic enones **6** with pyrrolidine/

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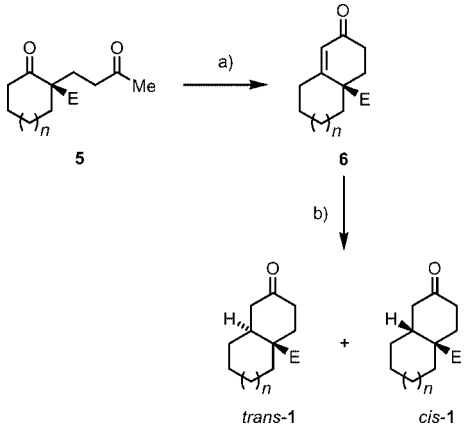
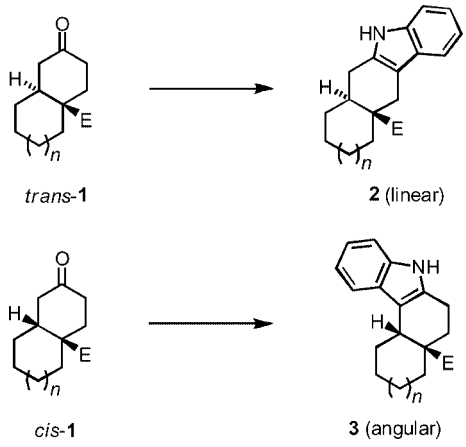
AcOH (Scheme 3). Compounds **6a**,[19] **6b**,[19c,20] and **6c**[17] have been reported before; the spectroscopic and analytical data were found to be in accordance with literature values. The C–C double bonds of the enones **6** were hydrogenated under ambient conditions with Pd on charcoal to yield mixtures of the *trans* and *cis* isomers of **1** (for the ratios, see Table 1). Isopropyl alcohol was used as the solvent in order to avoid acetal formation, as we observed earlier when using EtOH or MeOH.[15f] The reaction rates are somewhat dependent on the geometry of the flask and the scale of the reaction as three phases are involved (solid catalyst, solution, gas phase). This might have an influence on the yields. The *cis* and *trans* diastereoisomers of compounds **1a**–**1c** are separable by column chromatography. For compound **1a**, the *cis*-configured hydrogenation product is the major isomer, which is in agreement with the literature.[19a] For **1b** and **1c**, the *trans* isomers dominate the mixtures. All the compounds **1a**,[19a,21] **1b**,[20a,22] and **1c**[23] have been reported several times before, but without full characterization data in most cases. For compounds **1a** and **1b** the relative *cis* and *trans* configurations have been correlated to ^{13}C NMR spectroscopic data by Rao et al.,[22d] and later references refer to this work. However, compared with our data, the *cis* and *trans* diastereoisomers of **1a** have obviously been mixed up by Rao et al. We have proved the relative configuration of *trans*-**1a**–**1c** by single-crystal X-ray structure analysis of the corresponding indoles **2a**–**2c** prepared from these materials (vide infra).[18] Similarly, Rao et al. assigned data to a *cis* isomer that is *trans*-**1b** in our hands. Data for our *cis*-**1b** do not match at all the data of another compound supposed by Rao et al. to be the *trans* isomer. Data for **1c** have not been reported before. Moreover, Rao et al. recommend the use of a transfer-hydrogenation process to invert the *cis*/*trans* ratio of the hydrogenation product[22c] which would be very welcome in our eyes in order to obtain larger amounts of *cis*-**1b** and *cis*-**1c**, which were the minor isomers in our hydrogenation reactions. Unfortunately, the inversion of the *cis*/*trans* ratio was not observed when we adopted the transfer-hydrogenation protocol reported by Rao et al.; we again obtained the *trans* isomers as the major products.



Scheme 3. Two-step preparation of bicyclic ketones **1** from starting materials **5** (for E, *n* and yields, see Table 1). Reagents and conditions: a) pyrrolidine/AcOH, for details, see Table 1; b) Pd/C, H_2 (1 atm), *i*PrOH, 23 °C, 16 h (for **6a**, **6b**), 40 h (for **6c**).

Bicyclic ketones **1** were treated with a small excess of $PhNHNH_2$ in a mixture of TFA and AcOH at 100 °C for 1–3 d in a tightly closed reaction flask to yield the optically active indole derivatives **2** and **3** as single isomers after chromatography. Starting with the *trans* diastereoisomers of **1a**–**1c**, compounds **2a**–**2c** were obtained in 55–70% yields (Scheme 4, Table 2). Although no other unique materials were obtained as byproducts, chromatographic purification was performed in order to separate several other unspecific components in the mixture. Repeated chromatography was necessary; therefore, the yields are lower than those reported in our preliminary communication.[18] These crystalline materials turned out to be linear annulated tetracycles,



Scheme 4. Linear (products **2a**–**2c**) versus angular (products **3a**–**3c**) indole annulation. Reaction conditions: $PhNHNH_2$, TFA, AcOH, 100 °C, 1–3 d. For E, *n*, and the yields, see Table 2.

Table 2. Starting materials, products, and the yields of indoles **2** and **3**.

Starting material	E	*n*	Indole	% Yield
trans-**1a**	CO_2Et	0	**2a**	70
trans-**1b**	CO_2Et	1	**2b**	58
trans-**1c**	CO_2Me	2	**2c**	55
cis-**1a**	CO_2Et	0	**3a**	72
cis-**1b**	CO_2Et	1	**3b**	42
cis-**1c**	CO_2Me	2	**3c**	72

Table 1. Constitutions, conditions, and yields for the preparation of ketones **1** via enones **6**.

	E	*n*	Conditions for synthesis of **6**	% Yield of **6**	% Yield of *trans*-**1**	% Yield of *cis*-**1**
5a	CO_2Et	0	23 °C, 16 h, EA	83 (**6a**)	35 (*trans*-**1a**)	50 (*cis*-**1a**)
5b	CO_2Et	1	30 °C, 16 h, EA	72 (**6b**)	42 (*trans*-**1b**)	13 (*cis*-**1b**)
5c	CO_2Me	2	30 °C, 3 d, CH_2Cl_2	75 (**6c**)	79 (*trans*-**1c**)	8 (*cis*-**1c**)

which was confirmed by single-crystal X-ray structure analysis of these compounds. The structures of **2a** and **2c** (both as racemates) have been reported previously in our preliminary communication.[18] The X-ray structure of optically active **2b** was first reported in this article and its ORTEP representation is given in Figure 1.[24] The structures of compounds **2a**–**2c** were furthermore evidenced by an AX system in their ^{1}H NMR spectra, which appears at $\delta_A \approx 2.5$ and $\delta_X \approx 3.6$ ppm with $^2J_{AX} = 15$ Hz in all three cases and can be assigned to the isolated methylene groups at C-4 (**2a**), C-11 (**2b**), and C-12 (**2c**), respectively (for the compound numbering, see Figure 2). These AX systems show no further ^3J couplings, but fine splittings due to ^4J couplings of around 1 Hz.

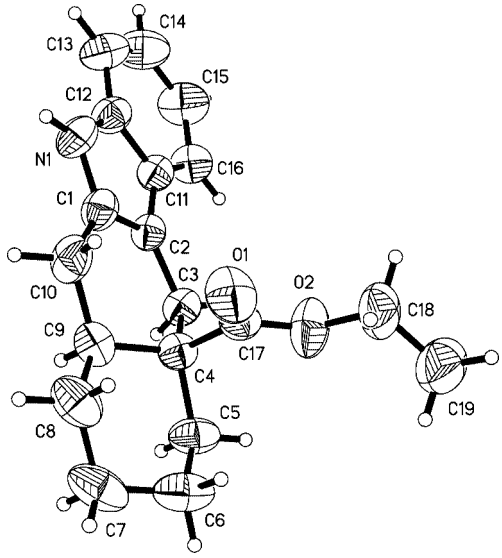


Figure 1. ORTEP representation of the structure of compound **2b** in the solid state.

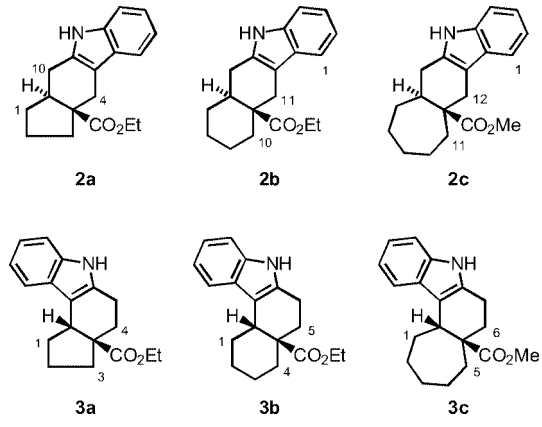


Figure 2. Compound numbering of indole derivatives.

On the other hand, optically active angular annulation products **3a**–**3c** were obtained as oily materials in 42–72% yields exclusively from the *cis* diastereoisomers of **1a**–**1c**. Again, no other unique byproducts could be isolated after column chromatography, although repeated chromatography was necessary in order to obtain pure compounds, which again had the effect of course of lowering the yields. Structure elucidation was based on the methine resonance (10c-H in **3a**, 11c-H in **3b**, 12c-H in compound **3c**) appearing at around 3.6–3.8 ppm, which clearly only shows up to two ^3J couplings and no further ^3J or ^4J coupling constants. Moreover, the methylene group next to the pyrrole ring (H_2C-5 in **3a**, H_2C-6 in **3b**, H_2C-7 in compound **3c**) is found as an AB part of an ABXY system as two ddd at $\delta_A \approx 2.6$ and $\delta_B \approx 2.8$ ppm and with $^2J_{AB} = 16$ Hz in all three cases. In the case of compound **3c** the structure was further confirmed by H,H-COSY, HMBC, and HMQC experiments. This allowed the complete assignment of all the proton resonances. Carbon resonances have also been assigned, except for those of C-1, C-2, and C-3. Key to the structural elucidation is C-12c. In the HMBC experiment, correlations between 12c-H and C-5, C-5a, C-6, C-7a, C-12a, C-12b are clearly visible. Moreover, 12c-H has only one coupling partner in the H,H-COSY spectrum, which is 1-H. No correlation between 12c-H and 7-H was observed, proving the angular annulation.

Finally, the question of the origin of this remarkable regioselectivity remains to be answered. It is of course generally accepted that the reaction starts with an imine–enamine tautomerism which is already determining the structure of the final product. Performed under thermodynamic conditions, there is some analogy to the enolization of 2-decalone derivatives. The regiochemistry of the latter has been the subject of experimental and theoretical investigations[25] from which it can be concluded that rather complex combinations of torsional effects, nonbonded interactions, and angle strain are the origin of the relative stabilities of isomeric bicyclic enolates.

However, our approach allows the regio-, diastereo-, and enantioselective construction of tetracyclic carbazole derivatives, an important structural motif of several biologically active alkaloids.[1] We are particularly interested in those that form flat polycyclic structures which intercalate with DNA and thus are important in both mutagenesis and tumor therapy. We are therefore looking forward to obtaining data on the biological activity of enantiopure compounds **2a**–**2c** and **3a**–**3c** and are furthermore working on derivatives with more elaborate substitution patterns.

Experimental Section

General Methods: Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EA) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets; we recommend to visualize spots with molybdophosphoric acid reagent. ^{1}H and ^{13}C-NMR spectra were recorded with Bruker Avance DRX 500 and Avance DPX 300 spectrometers. Multiplicities were determined by DEPT experiments. EI-MS, CI-MS, and HRMS spectra were obtained with a Finnigan MAT 95 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were measured with an EA 1108 apparatus from Fisons Instruments. GLC analyses were either performed with a HRGC 5300 (Carlo–Erba Strumentazione) instrument with FID using a Bondex unβ

(20 m × 0.3 mm, chiral phase), Amidex C (20 m × 0.3 mm, chiral phase), DB5 (30 m × 0.3 mm, achiral phase), or PSO 86 (20 m × 0.3 mm, achiral phase) column with hydrogen as the carrier gas (0.4 bar) or with a Focus/Triplus (Thermo Electron) instrument with FID using a Lipodex E (25 m × 0.25 mm, chiral phase) or CP Sil 19 (30 m × 0.25 mm, achiral phase) column with hydrogen as the carrier gas (0.4 bar). All starting materials were commercially available.

Ethyl (+)-(*R*)-6-Oxo-1,2,3,4,5,6-hexahydro-3a*H*-indene-3a-carboxylate (6a):[19] A mixture of Michael product **5a** (1.80 g, 8.00 mmol), AcOH (0.60 g, 8.00 mmol), and pyrrolidine (0.57 g, 8.0 mmol) in EA (5 mL) was stirred for 16 h at 23 °C. Subsequently, all volatile materials were removed in vacuo and the residue purified by chromatography on SiO_2 (PE/EA, 2:1, R_f = 0.36) to give the title compound **6a** (1.38 g, 6.60 mmol, 83%) as a brown oil. GLC, Amidex C (40–200 °C at 2.5 K min^{-1}): $t(S)$ = 44.3 min, $t(R)$ = 44.5 min; >99% *ee*. $[\alpha]_D^{20}$ = +185 (c = 5.3 in $CHCl_3$).

Ethyl (+)-(*R*)-2-Oxo-3,4,5,6,7,8-hexahydronaphthalene-4a(2*H*)-carboxylate (6b):[19c,20] A mixture of Michael product **5b** (3.10 g, 12.9 mmol), AcOH (0.96 g, 12.9 mmol), and pyrrolidine (0.92 g, 12.9 mmol) in EA (25 mL) was stirred for 16 h at 30 °C. Subsequently, all volatile materials were removed in vacuo and the residue purified by chromatography on SiO_2 (PE/EA, 2:1, R_f = 0.43) to give the title compound **6b** (6.70 g, 51.7 mmol, 72%) as a colorless oil. GLC, Bondex (40–200 °C at 2.5 K min^{-1}): $t(S)$ = 45.9 min, $t(R)$ = 46.2 min; >99% *ee*. $[\alpha]_D^{20}$ = +198 (c = 4.9 in $CHCl_3$).

Methyl (+)-(*R*)-2-Oxo-2,3,4,5,6,7,8,9-octahydro-4a*H*-benzocycloheptene-4a-carboxylate (6c):[17] A mixture of Michael product **5c** (6.77 g, 28.2 mmol), AcOH (2.00 g, 28.2 mmol), and pyrrolidine (1.69 g, 28.2 mmol) in CH_2Cl_2 (10 mL) was stirred for 3 d at 30 °C. Subsequently, all volatile materials were removed in vacuo and the residue purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.25) to give the title compound **6c** (4.74 g, 21.3 mmol, 75%) as a colorless oil. GLC, Lipodex E (115–160 °C at 0.33 K min^{-1}): $t(S)$ = 72.6 min, $t(R)$ = 76.0 min; 90% *ee*. $[\alpha]_D^{20}$ = +186 (c = 8.5 in $CHCl_3$).

Ethyl 6-Oxoindane-3a-carboxylate (1a):[19a,21] A mixture of **6a** (1.35 g, 6.49 mmol), Pd/C (170 mg, 5% Pd), and *i*PrOH (10 mL) was degassed (three cycles freeze–pump–thaw), then stirred at 23 °C for 16 h under H_2 (1 atm, balloon). After filtration, the solvent was evaporated and the crude product purified by chromatography on SiO_2 (PE/EA, 5:1) to give compounds *trans*-**1a** (469 mg, 2.23 mmol, 35%) as the first fraction (R_f = 0.32) and *cis*-**1a** (670 mg, 3.19 mmol, 50%) as the second fraction (R_f = 0.27), both as colorless liquids. GLC, DB5 (40–300 °C at 10 K min^{-1}): t(*trans*-**1a**) = 16.7 min, t(*cis*-**1a**) = 17.1 min.

(+)-(3a*R*,7a*S*)-1a (*trans*-1a): $[\alpha]_D^{20}$ = +49.5 (c = 5.2 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.28 (t, J = 7.1 Hz, 3 H), 1.44 (dt, J = 13.3, J = 9.0 Hz, 1 H), 1.53–1.63 (m, 1 H), 1.73–1.94 (m, 5 H), 2.17–2.23 (m, 1 H), 2.35–2.44 (m, 2 H), 2.48–2.58 (m, 2 H), 2.82 (dd, J = 13.8, J = 15.4 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.24 (CH_3), 22.75 (CH_2), 27.92 (CH_2), 33.27 (CH_2), 36.19 (CH_2), 38.67 (CH_2), 43.05 (CH_2), 48.75 (CH), 52.62 (C), 60.43 (CH_2), 175.00 (C), 211.36 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2953 (m), 2872 (m), 1714 (vs), 1241 (m), 1179 (m), 1153 (m), 1116 (m), 1052 (m), 1023 (m) cm^{-1}. MS (EI, 70 eV): m/z = 210 (14) $[M]^+$, 164 (26), 136 (100), 119 (10), 95 (18). $C_{12}H_{18}O_3$ (210.27): calcd. C 68.55, H 8.63; found C 68.41, H 8.53.

(+)-(3a*R*,7a*R*)-1a (*cis*-1a): $[\alpha]_D^{20}$ = +26.3 (c = 1.5 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (t, J = 7.2 Hz, 3 H), 1.32–1.45 (m, 1 H), 1.65–1.89 (m, 4 H), 1.81–2.04 (m, 2 H), 2.04–2.16 (m, 1 H), 2.21–2.41 (m, 3 H), 2.60 (dd, J = 6.3, J = 15.2 Hz, 1 H), 2.77–2.92 (m, 1 H), 4.20 (q, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.25 (CH_3), 22.86 (CH_2), 29.86 (CH_2), 32.08 (CH_2), 37.13 (CH_2), 37.36 (CH_2), 42.23 (CH_2), 42.48 (CH), 50.94 (C), 60.87 (CH_2), 176.86 (C), 212.25 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2953 (m), 2872 (m), 1714 (vs), 1240 (m), 1178 (m), 1154 (m) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{12}H_{19}O_3$ $[MH]^+$ 211.1334; found 211.1334.

Ethyl 2-Oxoperhydronaphthalene-4a(2*H*)-carboxylate (1b):[20a,22] A mixture of **6b** (1.30 g, 5.85 mmol), Pd/C (55 mg, 5% Pd), and *i*PrOH (8.5 mL) was degassed (three freeze–pump–thaw cycles), then stirred at 23 °C for 16 h under H_2 (1 atm, balloon). After filtration, the solvent was evaporated and the crude product purified by chromatography on SiO_2 (PE/EA, 5:1) to give compounds *trans*-**1b** (560 mg, 2.50 mmol, 42%) as the first fraction (R_f = 0.32) and *cis*-**1b** (180 mg, 0.80 mmol, 13%) as the second fraction (R_f = 0.26), both as colorless liquids. GLC, PSO 86 (40–300 °C at 10 K min^{-1}): t(*trans*-**1b**) = 18.0 min, t(*cis*-**1b**) = 18.6 min.

(+)-(4a*R*,8a*S*)-1b (*trans*-1b): $[\alpha]_D^{20}$ = +2.0 (c = 6.2 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.16 (dt, J = 3.2, J = 13.2 Hz, 1 H), 1.21–1.27 (m, 2 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.40–1.47 (m, 1 H), 1.52–1.69 (m, 3 H), 1.75–1.81 (m, 1 H), 1.87 (dq, J = 4.1, J = 12.7 Hz, 1 H), 2.17–2.37 (5 H), 2.98 (dd, J = 14.4, J = 14.6 Hz, 1 H), 4.18–4.25 (m, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.27 (CH_3), 23.26 (CH_2), 25.73 (CH_2), 29.16 (CH_2), 37.22 (CH_2), 37.34 (CH_2), 39.16 (CH_2), 44.60 (CH), 45.38 (CH_2), 47.21 (C), 60.30 (CH_2), 174.59 (C), 210.96 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2929 (s), 2858 (s), 1713 (vs), 1449 (s), 1422 (s), 1370 (s), 1299 (s), 1282 (s), 1226 (s), 1189 (s), 1134 (s), 1020 (s), 942 (s) cm^{-1}. MS (EI, 70 eV): m/z (%) = 224 (47) $[M]^+$, 196 (21), 178 (40), 150 (100). $C_{13}H_{20}O_3$ (224.30): calcd. C 69.61, H 8.99; found C 69.76, H 8.98.

(+)-(4a*R*,8a*R*)-1b (*cis*-1b): $[\alpha]_D^{20}$ = +13 (c = 2.9 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.25–1.33 (m, 2 H), 1.30 (t, J = 7.1 Hz, 3 H), 1.42–1.51 (m, 1 H), 1.53–1.60 (m, 2 H), 1.65–1.79 (m, 3 H), 2.11–2.18 (m, 2 H), 2.19–2.36 (m, 2 H), 2.41 (ddd, J = 8.0, J = 10.7, J = 14.7 Hz, 1 H), 2.56–2.59 (m, 2 H), 4.24 (q, J = 7.1 Hz, 2 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 14.23 (CH_3), 21.13 (CH_2), 24.77 (CH_2), 27.83 (CH_2), 28.19 (CH_2), 33.47 (CH_2), 38.44 (CH_2), 38.82 (CH), 45.19 (CH_2), 46.36 (C), 60.80 (CH_2), 176.70 (C), 211.18 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2927 (s), 2858 (s), 1712 (vs), 1449 (s), 1421 (s), 1372 (s), 1320 (s), 1281 (s), 1236 (s), 1218 (s), 1188 (s), 1134 (s), 1106 (s), 1034 (s), 1021 (s), 983 (w), 941 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{13}H_{20}O_3$ $[M]^+$ 224.1412; found 224.1412. $C_{13}H_{20}O_3$ (224.30): calcd. C 69.61, H 8.99; found C 69.61, H 8.96.

Methyl 2-Oxoperhydro-4a*H*-benzocycloheptene-4a-carboxylate (1c):[23] A mixture of **6c** (4.00 g, 18.0 mmol) and Pd/C (200 mg, 5% Pd) in *i*PrOH (40 mL) was degassed (three cycles freeze–pump–thaw), then stirred at 23 °C for 40 h under H_2 (1 atm, balloon). After filtration, the solvent was evaporated and the crude product purified by chromatography on SiO_2 (PE/EA, 5:1) to give the title compound *trans*-**1c** (3.21 g, 14.3 mmol, 79%, R_f = 0.54) in the first fraction as a colorless liquid. A second fraction (R_f = 0.50) contained *cis*-**1c** (310 mg, 1.4 mmol, 8%) as a colorless oil. GLC, CP Sil 19 (50–250 °C at 10 K min^{-1}): t(*trans*-**1c**) = 17.98 min, t(*cis*-**1c**) = 18.13 min.

(–)-(4a*R*,8a*S*)-1c (*trans*-1c): $[\alpha]_D^{20}$ = –3.7 (c = 8.5 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 1.39–1.78 (m, 10 H), 1.91–2.01 (m, 1 H), 2.06 (dd, J = 5.1, J = 10.3 Hz, 1 H), 2.18–2.34 (m, 4 H), 2.85 (dd, J = 14.4, J = 14.5 Hz, 1 H), 3.76 (s, 3 H) ppm. ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ = 23.28 (CH_2), 26.30 (CH_2), 26.47 (CH_2), 33.23 (CH_2), 38.29 (CH_2), 38.31 (CH_2), 38.42 (CH_2), 46.44 (CH_2), 47.13 (CH), 49.39 (C), 51.43 (CH_3), 175.48 (C), 211.04 (C) ppm.

IR (ATR): $\tilde{\nu}$ = 2925 (m), 1715 (s), 1193 (m) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{13}H_{20}O_3$ $[M]^+$ 224.1412; found 224.1412. $C_{13}H_{20}O_3$ (224.30): calcd. C 69.61, H 8.99; found C 69.76, H 9.02.

(+)-(4a*R*,8a*R*)-1c (*cis*-1c): $[\alpha]_D^{20}$ = +8.7 (c = 7.3 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.40–1.68 (m, 6 H), 1.72–1.90 (m, 4 H), 2.05–2.11 (m, 1 H), 2.18 (ddd, J = 1.9, J = 4.8, J = 14.4 Hz, 1 H), 2.22–2.28 (m, 1 H), 2.29–2.40 (m, 2 H), 2.48 (dd, J = 6.0, J = 14.5 Hz, 1 H), 2.79–2.87 (m, 1 H), 3.77 (s, 3 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 23.14 (CH_2), 28.49 (CH_2), 30.19 (CH_2), 31.17 (CH_2), 32.97 (CH_2), 38.29 (CH_2), 38.32 (CH_2), 41.69 (CH), 46.87 (CH_2), 48.82 (C), 52.17 (CH_3), 177.42 (C), 211.63 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2925 (m), 1716 (vs), 1459 (m), 1433 (m), 1194 (s) cm^{-1}. HRMS (CI, isobutane): calcd. for $C_{13}H_{21}O_3$ $[MH]^+$ 225.1490; found 225.1491.

Ethyl (+)-(3a*R*,10a*S*)-1,2,4,9,10,10a-Hexahydro-9-azacyclopenta[*b*]fluorene-3a(3*H*)-carboxylate (2a): A mixture of *trans*-**1a** (200 mg, 0.95 mmol), phenylhydrazine (260 mg, 2.40 mmol), TFA (0.8 mL), and HOAc (2.3 mL) was stirred for 3 d at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (5 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with hydrochloric acid (5 mL, 1 mol dm^{-3}) and water (5 mL) and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.21) to give **2a** (190 mg, 0.67 mmol, 70%) as a colorless solid, m.p. 170–171 °C. $[\alpha]_D^{20}$ = +184 (c = 3.3 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.07 (t, J = 7.1 Hz, 3 H), 1.70 (dt, J = 9.8, J = 12.7 Hz, 1 H), 1.79–1.90 (m, 2 H), 1.90–2.20 (m, 2 H), 2.14–2.24 (m, 2 H), 2.50 (ddd, ^4J = 1.6, ^4J = 2.5, ^2J = 15.0 Hz, 1 H, 4-H_{ax}), 2.82 (ddd, J = 1.4, J = 5.8, J = 15.8 Hz, 1 H), 3.03–3.11 (m, 1 H), 3.58 (dd, ^4J = 1.0, ^2J = 15.0 Hz, 1 H, 4-H_{eq}), 3.91 (dq, J = 10.9, J = 7.1 Hz, 1 H, OC*H*H), 4.00 (dq, J = 10.9, J = 7.1 Hz, 1 H, OCH*H*), 7.05 (dt, J = 1.3, J = 7.3 Hz, 1 H), 7.09 (dt, J = 1.4, J = 7.1 Hz, 1 H), 7.23 (br. d, J = 8.0 Hz, 1 H), 7.45 (br. d, J = 7.5 Hz, 1 H), 7.70 (s, 1 H) ppm. IR (ATR): $\tilde{\nu}$ = 3367 (m), 2944 (w), 1700 (s), 2463 (m), 1451 (m), 1430 (m), 1023 (m), 1007 (w), 743 (s), 659 (m), 606 (m) cm^{-1}. ^{13}C NMR and MS data have been reported previously.[18]

Ethyl (+)-(6a*S*,10a*R*)-5,6,6a,7,8,9,10,11-Hexahydro-10a*H*-benzo[*b*]carbazole-10a-carboxylate (2b): A mixture of *trans*-**1b** (600 mg, 2.68 mmol), phenylhydrazine (723 mg, 6.70 mmol), TFA (2.3 mL), and HOAc (6.7 mL) was stirred for 16 h at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (15 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with hydrochloric acid (15 mL, 1 mol dm^{-3}) and water (15 mL) and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.34) to give **2b** (460 mg, 1.55 mmol, 58%) as a colorless solid, m.p. 163–164 °C. Single crystals were obtained from MeOH/H_2O at 5 °C. $[\alpha]_D^{20}$ = +100 (c = 4.6 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.08 (t, J = 7.1 Hz, 3 H), 1.24–1.44 (m, 3 H), 1.66–1.70 (m, 2 H), 1.82–1.91 (m, 2 H), 1.98 (dq, J = 4.1, J = 12.7 Hz, 1 H), 2.34 (dq, J = 13.4, J = 1.8 Hz, 1 H), 2.49 (dt, ^2J = 15.4, ^4J = 1.9 Hz, 1 H, 11-H_{ax}), 2.62 (ddd, J = 1.0, J = 6.0, J = 16.2 Hz, 1 H), 3.08 (ddd, J = 1.6, J = 4.9, J = 16.2 Hz, 1 H), 3.31 (d, ^2J = 15.4 Hz, 1 H, 11-H_{eq}), 3.91 (dq, J = 10.8, J = 7.1 Hz, 1 H, OC*H*H), 4.01 (dq, J = 10.8, J = 7.1 Hz, 1 H, OCH*H*), 7.03–7.10 (m, 2 H), 7.22 (d, J = 7.4 Hz, 1 H), 7.42 (d, J = 7.5 Hz, 1 H), 7.67 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.09 (CH_3), 23.58 (CH_2), 26.41 (CH_2), 28.25 (CH_2), 29.63 (CH_2), 34.19 (CH_2), 38.22 (CH_2), 41.01 (CH), 47.02 (C), 59.76 (CH_2), 107.84 (C), 110.32 (CH), 117.61 (CH), 118.93 (CH), 120.84 (CH), 127.43 (C), 133.99 (C), 135.86 (C), 175.15 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3369 (s), 2940 (m), 2848 (m), 1702 (s), 1466 (m), 1447 (m), 1430 (m), 1311 (m), 1198 (s), 1129 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{19}H_{23}NO_2$ $[M]^+$ 297.1729; found 297.1729.

Methyl (+)-(6a*S*,11a*R*)-5,6,6a,7,8,9,10,12-Octahydro-5*H*-cyclohepta[*b*]carbazole-11a(11*H*)-carboxylate (2c): A mixture of *trans*-**1c** (400 mg, 1.78 mmol), phenylhydrazine (385 mg, 3.57 mmol), TFA (1.4 mL), and HOAc (4 mL) was stirred for 16 h at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with hydrochloric acid (10 mL, 1 mol dm^{-3}) and water (10 mL) and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.45) to give **2c** (290 mg 0.98 mmol, 55%) as a light-yellow solid, m.p. 172–173 °C. $[\alpha]_D^{20}$ = +107 (c = 2.15 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.37–1.46 (m, 2 H), 1.61–1.65 (m, 3 H), 1.76–2.04 (m, 5 H), 2.12–2.22 (m, 1 H), 2.62 (d, ^2J = 15 Hz, 1 H, 12-H_{ax}), 2.64 (dd, J = 4.8, J = 16.7 Hz, 1 H), 3.05 (t, J = 5.4 Hz, 1 H), 3.25 (d, ^2J = 15 Hz, 1 H, 12-H_{eq}), 3.49 (s, 3 H, OMe), 7.02–7.12 (m, 2 H), 7.20–7.25 (m, 1 H), 7.44 (d, J = 7.5 Hz, 1 H), 7.63 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 22.54 (CH_2), 28.58 (CH_2), 28.76 (CH_2), 29.82 (CH_2), 31.80 (CH_2), 33.57 (CH_2), 38.47 (CH_2), 44.49 (CH), 49.99 (C), 51.28 (CH_3), 108.99 (C), 110.36 (CH), 117.76 (CH), 118.96 (CH), 120.95 (CH), 127.44 (C), 134.25 (C), 136.10 (C), 176.58 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3377 (s), 2926 (m), 1712 (s), 744 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{19}H_{23}NO_2$ $[M]^+$ 297.1729; found 297.1729. $C_{19}H_{23}NO_2$ (297.40): calcd. C 76.74, H 7.80, N 4.71; found C 76.67, H 7.78, N 4.71.

Ethyl (+)-(3a*R*,10c*R*)-1,2,4,5,6,10c-Hexahydrocyclopenta[*c*]carbazole-3a(3*H*)-carboxylate (3a): A mixture of *cis*-**1a** (400 mg, 1.90 mmol), phenylhydrazine (410 mg, 3.80 mmol), TFA (2 mL), and HOAc (6 mL) was stirred for 3 d at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with hydrochloric acid (10 mL, 1 mol dm^{-3}) and water (10 mL) and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.36) to give **3a** (390 mg, 1.37 mmol, 72%) as a light-yellow oil. $[\alpha]_D^{20}$ = +76 (c = 3.4 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.22 (t, J = 7.1 Hz, 3 H), 1.65 (dq, J = 12.4, J = 8.5 Hz, 1 H), 1.70–1.75 (m, 1 H), 1.76–1.86 (m, 2 H), 1.87–1.93 (m, 1 H), 2.17 (ddd, J = 8.7, J = 6.1, J = 13.2 Hz, 1 H), 2.28 (dt, J = 13.3, J = 4.7 Hz, 1 H), 2.42 (dtd, J = 4.7, J = 7.6, J = 12.4 Hz, 1 H), 2.64 (dt, J = 16.3, J = 4.8 Hz, 1 H, 5-H), 2.81 (dddd, J = 1.2, J = 5.1, J = 10.0, J = 16.4 Hz, 1 H, 5-H), 3.76 (t, ^3J = 8.4 Hz, 1 H, 10c-H), 4.07 (dq, J = 10.8, J = 7.1 Hz, 1 H, OC*H*H), 4.15 (dq, J = 10.9, J = 7.2 Hz, 1 H, OCH*H*), 7.07 (dt, J = 1.0, J = 7.9 Hz, 1 H), 7.10 (dt, J = 1.1, J = 7.3 Hz, 1 H), 7.23 (d, J = 7.7 Hz, 1 H), 7.51 (d, J = 7.5 Hz, 1 H), 7.70 (s, 1 H) ppm. IR (ATR): $\tilde{\nu}$ = 3394 (m), 2951 (m), 2869 (m), 1702 (s), 1464 (m), 1452 (m), 1255 (m), 1231 (m), 1161 (s), 1011 (s), 737 (s) cm^{-1}. ^{13}C NMR and MS data have been reported previously.[18]

Ethyl (+)-(4a*R*,11c*R*)-1,2,3,4,5,6,7,11c-Octahydro-4a*H*-benzo[*c*]carbazole-4a-carboxylate (3b): A mixture of *cis*-**1b** (320 mg, 1.44 mmol), phenylhydrazine (311 mg, 2.88 mmol), TFA (1.5 mL), and HOAc (4.5 mL) was stirred for 2 d at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (10 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was washed with hydrochloric acid (10 mL, 1 mol dm^{-3}) and water (10 mL) and dried with $MgSO_4$. After filtration, the sol-

vent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 7:1, R_f = 0.26) to give **3b** (170 mg, 0.57 mmol, 42%) as a light-yellow oil. $[\alpha]_D^{20}$ = –42 (*c* = 6.0 in C_6D_6). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.13 (t, *J* = 7.1 Hz, 3 H), 1.42–1.56 (m, 3 H), 1.61–1.74 (m, 2 H), 1.82–1.90 (m, 2 H), 2.06 (ddd, *J* = 1.5, *J* = 6.6, *J* = 13.2 Hz, 1 H), 2.14–2.21 (m, 1 H), 2.29 (ddd, *J* = 6.8, *J* = 10.1, *J* = 13.1 Hz, 1 H), 2.75 (ddd, *J* = 2.0, *J* = 6.4, *J* = 16.6 Hz, 1 H, 6-H), 2.93 (ddd, *J* = 6.9, *J* = 9.9, *J* = 16.6 Hz, 1 H, 6-H), 3.56 (dd, ^3J = 4.1, ^3J = 10.0 Hz, 1 H, 11c-H), 4.01 (dq, *J* = 10.8, *J* = 7.1 Hz, 1 H, OC*H*H), 4.08 (dq, *J* = 10.8, *J* = 7.1 Hz, 1 H, OCH*H*), 7.05–7.13 (m, 2 H), 7.21 (d, *J* = 7.0 Hz, 1 H), 7.55 (d, *J* = 7.1 Hz, 1 H), 7.75 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 14.08 (CH_3), 20.73 (CH_2), 21.67 (CH_2), 25.07 (2 CH_2), 30.73 (CH_2), 34.42 (CH), 35.29 (CH_2), 46.59 (C), 60.19 (CH_2), 114.87 (C), 116.42 (CH), 118.02 (CH), 118.80 (CH), 120.78 (CH), 127.00 (C), 132.04 (C), 136.22 (C), 177.38 (C) ppm. IR (ATR): $\tilde{\nu}$ = 3398 (m), 2929 (s), 2855 (m), 1713 (s), 1463 (m), 1229 (s), 736 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{19}H_{23}NO_2$ $[M]^+$ 297.1729; found 297.1728.

Methyl (–)-(5a*R*,12c*R*)-2,3,4,5,6,7,8,12c-Octahydro-1*H*-cyclohepta[*c*]carbazole-5a-carboxylate (3c): A mixture of *cis*-**1c** (300 mg, 1.34 mmol), phenylhydrazine (289 mg, 2.67 mmol), TFA (1.20 mL), and HOAc (3.40 mL) was stirred for 16 h at 100 °C in a tightly closed reaction vial. It was then poured into ice/water (5 mL) and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic layer was washed with hydrochloric acid (5 mL, 1 mol dm^{-3}) and water (5 mL) and dried with $MgSO_4$. After filtration, the solvent was removed in vacuo. The crude material was purified by chromatography on SiO_2 (PE/EA, 5:1, R_f = 0.29) to give **3c** (290 mg, 0.97 mmol, 72%) as a light-yellow oil which slowly crystallized, m.p. 35–38 °C. $[\alpha]_D^{20}$ = –62 (*c* = 5.30 in $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 1.19–1.30 (m, 1 H, 3-H), 1.46–1.85 (m, 2 H, 5-H, 1-H), 1.61–1.69 (m, 2 H, 2 × 4-H), 1.72–1.78 (m, 1 H, 2-H), 1.83 (ddd, ^3J = 6.0, ^3J = 12.1, ^2J = 13.0 Hz, 1 H, 6-H), 1.90–2.03 (m, 3 H, 1-H, 2-H, 3-H), 2.11–2.33 (m, 2 H, 6-H, 5-H), 2.62 (ddd, ^3J = 1.1, ^3J = 5.8, ^2J = 16.5 Hz, 1 H, 7-H), 2.78 (dddd, ^4J = 0.9, ^3J = 5.8, ^3J = 11.9, ^2J = 16.6 Hz, 1 H, 7-H), 3.58 (s, 3 H, OMe), 3.72 (d, ^3J = 9.9 Hz, 1 H, 12c-H), 7.06 (dt, *J* = 1.3, *J* = 7.3 Hz, 1 H, 11-H), 7.10 (dt, *J* = 1.3, *J* = 7.3 Hz, 1 H, 10-H), 7.23 (d, *J* = 7.2 Hz, 1 H, 9-H), 7.47 (d, *J* = 7.2 Hz, 1 H, 12-H), 7.59 (s, 1 H, NH) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ = 21.03 (CH_2; C-7), 22.83 (CH_2; C-4), 29.82 (CH_2; C-6), 30.96 (CH_2), 31.55 (CH_2), 31.64 (CH_2), 38.00 (CH; C-12c), 40.20 (CH_2; C-5), 49.71 (C; C-5a), 51.84 (CH_3; OMe), 110.46 (CH; C-9), 115.17 (C; C-12b), 118.04 (CH; C-12), 118.95 (CH; C-11), 121.12 (CH; C-10), 127.22 (C; C-12a), 132.29 (C; C-7a), 136.44 (C; C-8a), 177.57 (C; CO_2Me) ppm. IR (ATR): $\tilde{\nu}$ = 3398 (m, br.), 2923 (m), 1706 (s), 1463 (m), 1164 (s) cm^{-1}. HRMS (EI, 70 eV): calcd. for $C_{19}H_{23}NO_2$ $[M]^+$ 297.1729; found 297.1729.

Acknowledgments

This work was generously supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

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Received: April 20, 2007
Published Online: July 25, 2007

