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# Regioselectivity of Friedländer Quinoline Syntheses

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*Dedicated to Professor Jürgen Martens on the occasion of his 60th birthday*

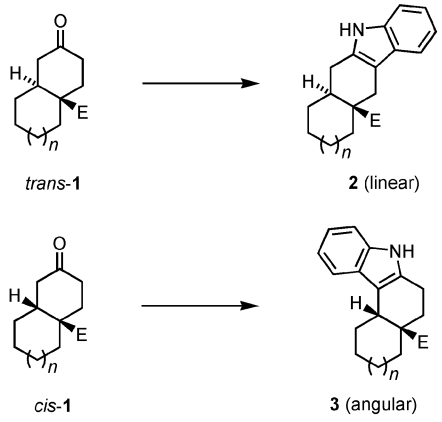
**Keywords:** Annulation / Quinoline derivatives / Heterocycles / Regioselectivity / Friedländer synthesis

Optically active, bicyclic ketones were submitted to Friedländer quinoline syntheses with 2-aminobenzaldehyde to yield regioisomeric linear or angular products. When starting from *trans*-configured ketones, the linear products are the major isomers (ratios ranging from 76:24 to >98/2). With *cis*-configured ketones the angular products are predominantly formed, although with lower regioselectivity.



## Introduction

Quinoline derivatives are among the most important pharmaceuticals and bioactive natural products.[1] An important example are chinchona alkaloids and related antimalarial drugs.[2] When annulated with one or more rings, again a vast number of natural and synthetic compounds with high potential for medicinal applications are known. The most prominent example in this area is camptothecin and related inhibitors of DNA topoisomerases.[3] The condensation of 2-aminobenzaldehyde and an aliphatic ketone was named after its inventor[4] and is still the most efficient route to quinoline derivatives.[5] The acridine skeleton is accessed, if cyclohexanone is used as the aliphatic ketone in the Friedländer reaction. With substituted cyclohexanone derivatives a regioselectivity problem can arise during the annulation reaction. We have recently reported on Fischer indole syntheses starting from bicyclic cyclohexanones **1** (Scheme 1).[6] The regioselectivity of this annulation turned out to be strictly dependent on the relative configuration of the starting materials **1**: *trans*-annulated ketones **1** gave exclusively linear annulated carbazole derivatives **2**, whereas relative *cis* configuration of ketones **1** led to angular products **3**. Starting materials *cis*-**1** and *trans*-**1** with one five-, six- or seven-membered ring ($n$ = 0, 1, 2) were readily available in optically active form by a three-step sequence starting with an asymmetric Michael reaction of methyl vinyl ketone with β-oxo esters,[7] followed by aldol condensation (Robinson annulation)[8] and final catalytic C=C double-bond hydrogenation. The latter gave a mixture of both ketones, *trans*-**1** and *cis*-**1**, which were separable by column chromatography. In this work we would like to report on the regioselectivity of Friedländer quinoline syntheses starting from these optically active bicyclic cyclohexanone derivatives *cis*-**1** and *trans*-**1**.




Scheme 1. Linear or angular indole annulation of bicyclic cyclohexanones. E = $CO_2Et$ or $CO_2Me$; $n$ = 0, 1, 2.

## Results and Discussion

Protocols for Friedländer reaction require either Brönsted-basic or Brönsted- or Lewis-acidic catalysts. The main drawback of most protocols is the low stability of aminobenzaldehyde **7**, which tends to self-condensation reactions. It has been suggested in the literature, to prepare this aldehyde **7** by in situ reduction of nitrobenzaldehyde **6** with excess $SnCl_2$, which seems attractive on the first glance, since $Sn^{IV}$ species generated under these reaction conditions are acidic catalysts for the Friedländer reac-

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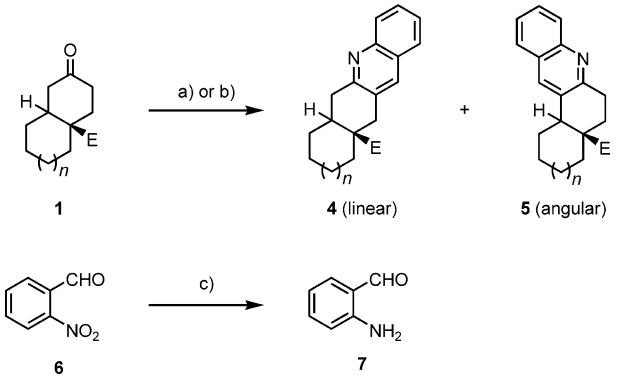
Table 1. Starting materials (*n*, E), products, regioselectivities and yields.

| | Starting material | *n* | E | Method | Products | Ratio[a] | Yield |
|---|---|---|---|---|---|---|---|
| 1 | *trans*-**1a** | 0 | $CO_2Et$ | "Sn" | *trans*-**4a**, *trans*-**5a** | 95:5 | 74% |
| 2 | *trans*-**1b** | 1 | $CO_2Et$ | "Sn" | *trans*-**4b**, *trans*-**5b** | 74:26 | 78% |
| 3 | *trans*-**1c** | 2 | $CO_2Me$ | "Sn" | *trans*-**4c**, *trans*-**5c** | 69:31 | 81% |
| 4 | *cis*-**1a** | 0 | $CO_2Et$ | "Sn" | *cis*-**4a**, *cis*-**5a** | 45:55 | 50% |
| 5 | *trans*-**1a** | 0 | $CO_2Et$ | "Fe" | *trans*-**4a**, *trans*-**5a** | >98:2 | 85% |
| 6 | *trans*-**1b** | 1 | $CO_2Et$ | "Fe" | *trans*-**4b**, *trans*-**5b** | 80:20 | 93% |
| 7 | *trans*-**1c** | 2 | $CO_2Me$ | "Fe" | *trans*-**4c**, *trans*-**5c** | 76:24 | 96% |
| 8 | *cis*-**1a** | 0 | $CO_2Et$ | "Fe" | *cis*-**4a**, *cis*-**5a** | 46:54 | 98% |
| 9 | *cis*-**1b** | 1 | $CO_2Et$ | "Fe" | *cis*-**4b**, *cis*-**5b** | 44:56 | 90% |
| 10 | *cis*-**1c** | 2 | $CO_2Me$ | "Fe" | *cis*-**4c**, *cis*-**5c** | 38:62 | 78% |

[a] Calcd. from isolated compounds.

tion.[9] We investigated this one-pot protocol for the conversion of starting materials *trans*-**1a**–**1c** and *cis*-**1a** (Scheme 2; Table 1, Entries 1–4, method "Sn"). Yields of products **4** and **5** were in the range of 50–81%. The regioselectivity for starting materials *trans*-**1a**–**1c** was good to moderate (95:5 to 69:31; Entries 1–3) with linear annulation products *trans*-**4a**–**4c** as the major products. For starting material *cis*-**1a** almost no regioselectivity was observed (*cis*-**4a**/*cis*-**5a** = 45:55), and the yield was low (50%). The most severe problem with this procedure was, however, the separation of the products from tin-containing materials, which made workup and extraction very tedious. For this reason, we left the idea of in situ preparation of aminobenzaldehyde **7**.




Scheme 2. Friedländer synthesis starting from nitrobenzaldehyde **6** (method "Sn") or from aminobenzaldehyde **7** (method "Fe"); reagents and conditions: (a) method "Sn", 1 equiv. of aldehyde **6**, 3 equiv. of $SnCl_2 \cdot 2H_2O$, EtOH, 115 °C, 16 h; (b) method "Fe", 1.3 equiv. of aldehyde **7**, 1 equiv. of *p*TosOH·$H_2O$, 110 °C, 1.5 h; (c) 10 equiv. of Fe powder, cat. HCl, $H_2O$/EtOH, 100 °C, 1.5 h, 87%. For E, *n* and yields see Table 1.

For further investigations, we prepared aminobenzaldehyde **7** freshly by reduction of nitrobenzaldehyde **6** with Fe/HCl/$H_2O$ (method "Fe").[10] Product **7** was purified each time by column chromatography (yield ca. 87%) and directly submitted to an acid-catalyzed Friedländer reaction. With this approach, yields (78–98%) and regioselectivites were improved (Entries 5–10). Moreover, the workup was significantly simplified. For starting materials *trans*-**1a**–**1c** again the linear annulation products *trans*-**4a**–**4c** are the major products (yields 85–96%), with decreasing selectivity when increasing the ring size *n* (Entries 5–7). For *n* = 1, no angular product *trans*-**5a** was detectable. For the six- and

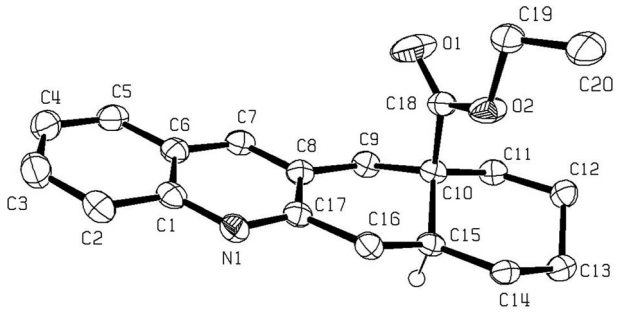



Figure 1. ORTEP representation of the structure of compound *trans*-**4b** in the solid state.

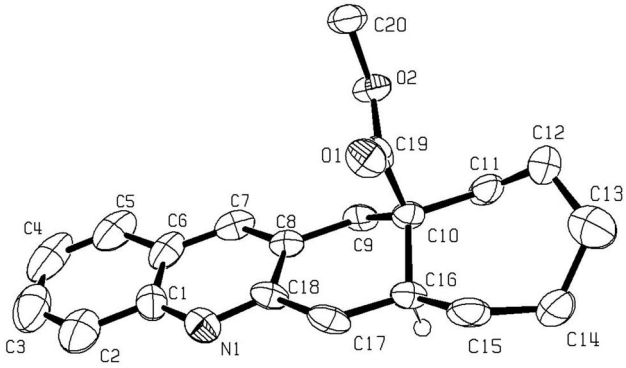



Figure 2. ORTEP representation of the structure of compound *trans*-**4c** in the solid state.

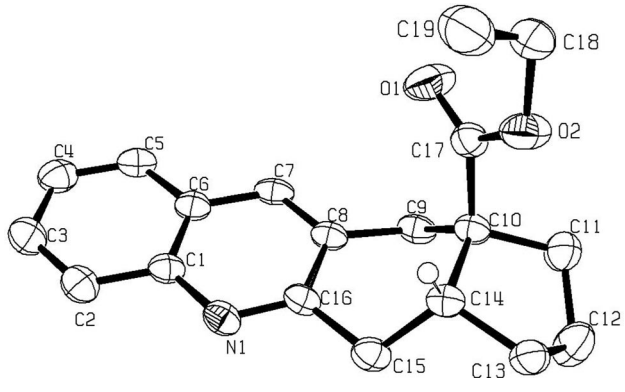



Figure 3. ORTEP representation of the structure of compound *cis*-**4a** in the solid state.

the seven-membered ring annulation, selectivities were 80:20 ($n$ = 1) and 76:24 ($n$ = 2), respectively. When starting with *cis*-annulated ketones *cis*-**1a**–**1c** (Entries 8–10), the regioselectivities were generally lower and increased with increasing ring size: 45:55 ($n$ = 0), 43:57 ($n$ = 1), and 38:62 ($n$ = 2). In all these cases, the angularly annulated products *cis*-**5a**–**5c** were the major isomer. In all six cases, the regioisomers **4** and **5** could be separated by column chromatography.

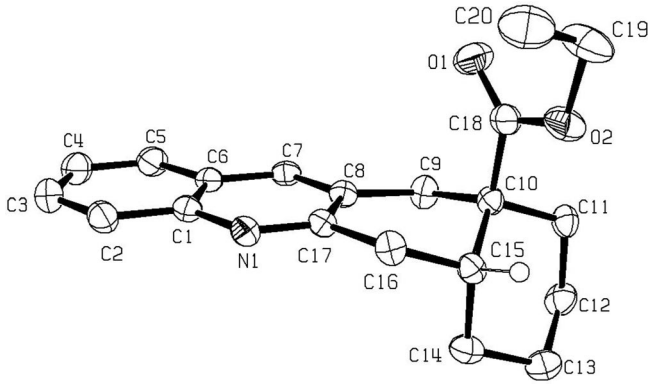



Figure 4. ORTEP representation of the structure of compound *cis*-**4b** in the solid state.

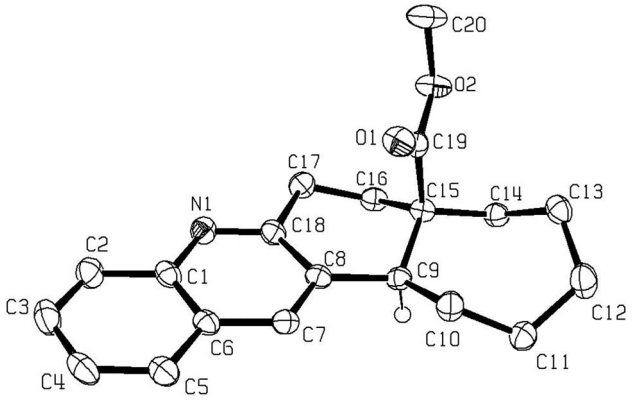



Figure 5. ORTEP representation of the structure of compound *trans*-**5c** in the solid state.

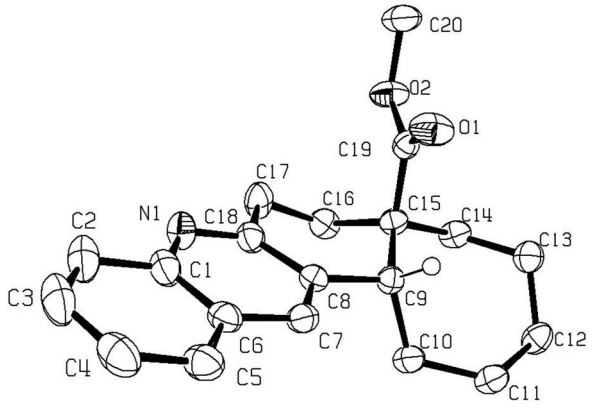



Figure 6. ORTEP representation of the structure of compound *cis*-**5c** in the solid state.

All twelve compounds *cis*- and *trans*-**4a**–**4c**, *cis*- and *trans*-**5a**–**5c** are new, and their constitution could be elucidated by 2D NMR spectroscopy (H,H- and C,H-COSY, HMQC, and HMBC). In six cases, single crystals could be grown, which were suitable for X-ray structure analysis. ORTEP representations of the molecular structures are given in Figures 1, 2, 3, 4, 5 and 6.[11] In all six cases the ester groups E (E = $CO_2Et$ or $CO_2Me$) occupy an axial position at the C/D ring junction.

## Conclusions

Bicyclic ketones **1a**–**1c** are readily available in optically active form with relative *trans* or *cis* configuration. Friedländer quinoline synthesis with aminobenzaldehyde **7** yields regioisomeric linear or angular products. In the cases of *trans*-annulated starting materials *trans*-**1**, the linear isomers predominate the product mixtures with selectivities from 76:24 to >98:2. Ketones *cis*-**1** with relative *cis* configuration lead to angular isomers, although the selectivities are lower in these cases. Mixtures of regioisomers can be separated by column chromatography and all twelve new tetracyclic products were fully characterized, in six cases by single-crystal X-ray structure analysis.

We recommend to use freshly prepared aminobenzaldehyde **7** in acid-catalyzed Friedländer reactions. In situ reduction of nitroaldehyde **6** with $SnCl_2$ leads to hardly separable tin-containing byproducts, and yields and selectivities are lower.

## Experimental Section

**General Methods:** Preparative column chromatography was carried out using Merck $SiO_2$ (0.035–0.070 mm, type 60 A) with hexanes (b.p. 40–60 °C) (PE), and ethyl acetate (EA) as eluents. TLC was performed on Merck $SiO_2$ $F_{254}$ plates on aluminium sheets. $^1H$ and $^{13}C$ NMR spectra were recorded with Bruker Avance DRX 500 and Avance DPX 300 instruments. Multiplicities were determined with DEPT experiments. EI-MS, CI-MS and HRMS data 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 from Fisons Instruments. Ketones **1** were prepared according to procedures reported previously.[6] All other starting materials were commercially available.

**Preparation of Aminobenzaldehyde 7:** Iron powder (5.55 g, 99.3 mmol, 10 equiv.) and concd. hydrochloric acid (ca. 50 mg) were added to a solution of nitroaldehyde **6** (1.50 g, 9.93 mmol) in EtOH (30 mL) and water (7.5 mL), and the mixture was heated to reflux for 90 min. EtOAc (150 mL) was added to the mixture, and it was dried with $MgSO_4$. After filtration and evaporation of the solvent, the residue was purified by chromatography ($SiO_2$; PE/EA, 7:1; $R_f$ = 0.32) to give 1.05 g (8.67 mmol, 87%) of aminoaldehyde **7** as a yellow solid (m.p. 38–40 °C).

**Preparation of Quinolines. General Procedure "Fe":** Freshly prepared aminoaldehyde **7** (1.3 equiv.) was added to 1.0 equiv. of *p*TosOH·$H_2O$ and 1.0 equiv. of the corresponding oxo ester **1**. The mixture was stirred without solvent at 110 °C for 90 min. After cooling to 23 °C, $CH_2Cl_2$ (20 mL) was added and the solution washed with aqueous $NaHCO_3$ solution (2 × 10 mL) and brine (1 × 10 mL). After drying ($MgSO_4$), filtration and evaporation of

the solvent, the residue was purified by chromatography ($SiO_2$; PE/EA).

**Conversion of Ketone *trans*-1a to Quinoline *trans*-4a According to General Procedure "Fe":** A mixture of *trans*-**1a** (480 mg, 2.28 mmol), *p*TosOH·$H_2O$ (424 mg, 2.23 mmol) and aminoaldehyde **7** (350 mg, 2.90 mmol) gave, after purification by chromatography on $SiO_2$ (PE/EA, 2:1; $R_f$ = 0.56), *trans*-**4a** (560 mg, 1.90 mmol, 85%) as a colorless solid (mp. 98–99 °C). Isomer *trans*-**5a** could only be detected in traces.

**Conversion of Ketone *trans*-1a to Quinolines *trans*-4a/*trans*-5a. Procedure "Sn":** A mixture of ketone *trans*-**1a** (500 mg, 2.38 mmol), nitroaldehyde **6** (359 mg, 2.38 mmol), $SnCl_2$·$2H_2O$ (1.61 g, 7.14 mmol, 3 equiv.) and EtOH (0.5 mL) was heated in a tightly closed reaction flask to 115 °C for 16 h. The resulting black mixture was poured into aqueous $NaHCO_3$ solution (30 mL) and extracted with EtOAc (2 × 30 mL). After drying with $MgSO_4$, filtration and evaporation of the solvent, the residue was purified by chromatography on $SiO_2$ (PE/EA, 2:1) to give *trans*-**4a** (490 mg, 1.66 mmol, 70%) in the first fraction ($R_f$ = 0.56) as a colorless solid (m.p. 98–99 °C). The second fraction ($R_f$ = 0.46) contained *trans*-**5a** (30 mg, 0.10 mmol, 4%, light yellow resin).

**(+)-Ethyl (3a*S*,11a*R*)-2,3,3a,4,11,11a-Hexahydro-1*H*-cyclopenta[*b*]-acridine-11a-carboxylate (*trans*-4a):** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.03 (t, $J$ = 7.1 Hz, 3 H, $OCH_2CH_3$), 1.61 (ddd, $J$ = 8.7, $J$ = 9.9, $J$ = 12.9 Hz, 1 H, 1-H), 1.82–1.95 (m, 2 H, 2-H, 3-H), 1.96–2.07 (m, 2 H, 2-H, 3-H), 2.16–2.25 (m, 1 H, 3a-H), 2.27–2.34 (m, 1 H, 1-H), 2.81 (d, $J$ = 15.9 Hz, 1 H, 11-H), 3.08 (dd, $J$ = 13.4, $J$ = 17.5 Hz, 1 H, 4-H), 3.35 (dd, $J$ = 5.3, $J$ = 17.5 Hz, 1 H, 4-H), 3.64 (d, $J$ = 15.9 Hz, 1 H, 11-H), 3.97 (q, $J$ = 7.1 Hz, 2 H, $OCH_2CH_3$), 7.41–7.46 (m, 1 H, 7-H or 8-H), 7.58–7.63 (m, 1 H, 8-H or 7-H), 7.70 (d, $J$ = 7.9 Hz, 1 H, 9-H), 7.84 (s, 1 H, 10-H), 7.97 (d, $J$ = 8.5 Hz, 1 H, 6-H) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.99 ($CH_3$, $OCH_2CH_3$), 22.75 ($CH_2$, C-2), 28.79 ($CH_2$, C-3), 36.22 ($CH_2$, C-4), 36.67 ($CH_2$, C-1), 40.20 ($CH_2$, C-11), 46.64 (CH, C-3a), 52.11 (C, C-11a), 60.16 ($CH_2$, $OCH_2CH_3$), 125.61 (CH, C-8 or C-7), 126.89 (C, C-9a), 126.90 (CH, C-9), 128.32 (CH, C-6), 128.51 (CH, C-7 or C-8), 130.27 (C, C-10a), 135.13 (CH, C-10), 146.44 (C, C-5a), 158.69 (C, C-4a), 175.08 (C, $CO_2$Et) ppm. IR (ATR): $\tilde{\nu}$ = 2966 (m), 2873 (w), 1710 (vs), 1415 (m), 1179 (s), 1140 (s) 756 (s) cm$^{-1}$. MS (EI): *m*/*z* (%) = 295 (32) [M$^+$], 221 (100), 193 (21). HR-MS: calcd. for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572. $[\alpha]_D^{20}$ = +157 ($c$ = 7.75 in $CDCl_3$). M.p. 98–99 °C. $C_{19}H_{21}NO_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.43, H 7.20, N 4.74.

**(–)-Ethyl (3a*R*,11b*S*)-2,3,3a,4,5,11b-Hexahydro-1*H*-cyclopenta[*a*]-acridine-3a-carboxylate (*trans*-5a):** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 0.94 (t, $J$ = 7.2 Hz, 3 H, $OCH_2CH_3$), 1.62–1.70 (m, 1 H, 1-H), 1.91–2.03 (m, 3 H, 4-H, 2 2-H), 2.21 (dq, $J$ = 6.8, $J$ = 11.5 Hz, 1 H, 3-H), 2.26–2.34 (m, 2 H, 1-H, 3-H), 2.69 (ddd, $J$ = 1.8, $J$ = 8.0, $J$ = 13.1 Hz, 1 H, 4-H), 3.04 (dd, $J$ = 8.8, $J$ = 10.4 Hz, 1 H, 11b-H), 3.21 (ddd, $J$ = 8.0, $J$ = 10.6, $J$ = 18.7 Hz, 1 H, 5-H), 3.32 (ddd, $J$ = 1.8, $J$ = 8.2, $J$ = 18.7 Hz, 1 H, 5-H), 3.85–3.92 (m, 2 H, $OCH_2CH_3$), 7.43 (t, $J$ = 7.1 Hz, 1 H, 8-H), 7.57–7.62 (m, 1 H, 9-H), 7.72 (d, $J$ = 8.0 Hz, 1 H, 7-H), 7.75 (s, 1 H, 11-H), 7.95 (d, $J$ = 8.4 Hz, 1 H, 10-H) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.86 ($CH_3$, $OCH_2CH_3$), 22.62 ($CH_2$, C-2), 25.21 ($CH_2$, C-3), 31.48 ($CH_2$, C-5), 32.19 ($CH_2$, C-4), 36.58 ($CH_2$, C-1), 50.18 (CH, C-11b), 53.78 (C, C-3a), 60.06 ($CH_2$, $OCH_2CH_3$), 125.48 (CH, C-8), 127.08 (CH, C-7), 127.13 (C, C-10a), 128.25 (CH, C-10), 128.26 (CH, C-9), 130.62 (CH, C-11), 133.97 (C, C-11a), 146.26 (C, C-6a), 158.82 (C, C-5a), 174.79 (C, $CO_2$Et) ppm. IR (ATR): $\tilde{\nu}$ = 3054 (vw), 2955 (m), 2872 (w), 1715 (vs), 1491 (w), 1456 (w), 1225 (w), 1174 (vs), 1025 (m), 750 (s) cm$^{-1}$. MS (EI): *m*/*z* (%) = 295 (37) [M$^+$], 221 (100), 193 (18), 180 (20). HR-MS: calcd. for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572. $[\alpha]_D^{20}$ = –113 ($c$ = 2.3 in $CDCl_3$). $C_{19}H_{21}NO_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.25, H 7.18, N 4.78.

**Conversion of Ketone *trans*-1b to Quinolines *trans*-4b/*trans*-5b According to General Procedure "Fe":** A mixture of *trans*-**1b** (500 mg, 2.23 mmol), *p*TosOH·$H_2O$ (424 mg, 2.23 mmol) and aminoaldehyde **7** (360 mg, 2.97 mmol) gave after chromatography ($SiO_2$; PE/EA, 3:1) compound *trans*-**4b** (510 mg, 1.65 mmol, 74%) in the first fraction ($R_f$ = 0.70) as a colorless solid (m.p. 106–107 °C). The second fraction ($R_f$ = 0.53) contained compound *trans*-**5b** (130 mg, 0.42 mmol, 19%, light yellow solid, m.p. 76–77 °C).

**(+)-Ethyl (6a*S*,10a*R*)-6,6a,7,8,9,10,10a,11-Octahydrobenzo[*b*]acridine-10a-carboxylate (*trans*-4b):** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.03 (t, $J$ = 7.1 Hz, 3 H), 1.28–1.52 (m, 3 H), 1.63–1.78 (m, 2 H), 1.82–2.02 (m, 3 H), 2.32 (d, $J$ = 13.1 Hz, 1 H), 2.78 (d, $J$ = 16.0 Hz, 1 H), 3.15 (dd, $J$ = 6.1, $J$ = 18.4 Hz, 1 H), 3.31 (dd, $J$ = 12.0, $J$ = 18.4 Hz, 1 H), 3.35 (d, $J$ = 16.0 Hz, 1 H), 3.97 (q, $J$ = 7.0 Hz, 2 H), 7.43 (t, $J$ = 7.5 Hz, 1 H), 7.61 (t, $J$ = 7.5 Hz, 1 H), 7.69 (d, $J$ = 8.1 Hz, 1 H), 7.78 (s, 1 H), 7.97 (d, $J$ = 8.5 Hz, 1 H) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.84 ($CH_3$), 22.89 ($CH_2$), 25.77 ($CH_2$), 28.86 ($CH_2$), 37.35 ($CH_2$), 37.66 ($CH_2$), 40.80 (CH), 42.19 ($CH_2$), 45.73 (C), 59.72 ($CH_2$), 125.24 (CH), 126.68 (C), 126.70 (CH), 128.10 (CH), 128.33 (CH), 128.66 (C), 134.32 (CH), 146.65 (C), 158.51 (C), 174.18 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2992 (w), 2937 (m), 2858 (w), 2360 (w), 2340 (w), 1704 (vs), 1490 (w), 1441 (w), 1416 (m), 1210 (s), 1188 (s) cm$^{-1}$. MS (EI): *m*/*z* (%) = 309 (28) [M$^+$], 236 (42), 235 (100), 193 (25). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1728. $[\alpha]_D^{20}$ = +95 ($c$ = 5.02 in $CDCl_3$). M.p. 106–107 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.98, H 77.47, N 4.52.

**(–)-Ethyl (4a*R*,12b*S*)-1,2,3,4,4a,5,6,12b-Octahydrobenzo[*a*]acridine-4a-carboxylate (*trans*-5b):** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.04 (t, $J$ = 7.1 Hz, 3 H), 1.28–1.42 (m, 2 H), 1.42–1.54 (m, 1 H), 1.74 (d, $J$ = 13.0 Hz, 1 H), 1.89–2.06 (m, 3 H), 2.30–2.49 (m, 3 H), 2.74 (d, $J$ = 11.3 Hz, 1 H), 3.02 (ddd, $J$ = 6.5, $J$ = 13.0, $J$ = 18.5 Hz, 1 H), 3.26 (dd, $J$ = 5.9, $J$ = 18.5 Hz, 1 H), 3.92 (q, $J$ = 7.1 Hz, 2 H), 7.43 (t, $J$ = 7.5 Hz, 1 H), 7.59 (t, $J$ = 7.6 Hz, 1 H), 7.71 (d, $J$ = 8.1 Hz, 1 H), 7.92–7.95 (m, 2 H) ppm. $^{13}$C{$^1$H} NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.84 ($CH_3$), 22.80 ($CH_2$), 24.97 ($CH_2$), 25.77 ($CH_2$), 30.79 ($CH_2$), 34.97 ($CH_2$), 37.28 ($CH_2$), 44.56 (CH), 46.98 (C), 59.81 ($CH_2$), 125.20 (CH), 127.06 (C), 127.13 (CH), 127.79 (CH), 128.14 (CH), 130.17 (CH), 134.11 (C), 145.71 (C), 157.35 (C), 174.15 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2925 (s), 2855 (m), 1720 (vs), 1454 (w), 1376 (w), 1191 (m) cm$^{-1}$. MS (EI): *m*/*z* (%) = 309 (31) [M$^+$], 236 (50), 235 (100), 193 (19). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1728. $[\alpha]_D^{20}$ = –109 ($c$ = 4.75 in $CDCl_3$). M.p. 76–77 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.25, H 7.49, N 4.46.

**Conversion of Ketone *trans*-1c to Quinolines *trans*-4c/*trans*-5c According to General Procedure "Fe":** A mixture of *trans*-**1c** (500 mg, 2.23 mmol), *p*TosOH·$H_2O$ (424 mg, 2.23 mmol) and aminoaldehyde **7** (360 mg, 2.97 mmol) gave after chromatography ($SiO_2$; PE/EA, 5:1) compound *trans*-**4c** (500 mg, 1.62 mmol, 73%) in the first fraction ($R_f$ = 0.42) as a colorless solid (m.p. 144–145 °C). The second fraction ($R_f$ = 0.25) contained compound *trans*-**5c** (160 mg, 0.52 mmol, 23%, light yellow solid, m.p. 117–118 °C).

**(+)-Methyl (6a*S*,11a*R*)-6a,7,8,9,10,11,11a,12-Octahydro-6*H*-cyclohepta[*b*]acridine-11a-carboxylate (*trans*-4c):** $^1$H NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.38–1.52 (m, 2 H), 1.53–1.76 (m, 3 H), 1.80–1.98 (m, 3 H), 1.98–2.06 (m, 1 H), 2.06–2.24 (m, 2 H), 3.12–3.20 (m, 2

H), 2.95 (d, $J$ = 16.1 Hz, 1 H), 3.32 (d, $J$ = 16.1 Hz, 1 H), 3.53 (s, 3 H), 7.42 (t, $J$ = 7.3 Hz, 1 H), 7.60 (t, $J$ = 7.6 Hz, 1 H), 7.69 (d, $J$ = 8.0 Hz, 1 H), 7.82 (s, 1 H), 7.96 (d, $J$ = 8.4 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 22.73 ($CH_2$), 28.64 ($CH_2$), 28.92 ($CH_2$), 31.59 ($CH_2$), 38.36 ($CH_2$), 39.74 ($CH_2$), 41.41 ($CH_2$), 44.00 (CH), 49.29 (C), 51.44 ($CH_3$), 125.54 (CH), 126.91 (CH), 127.02 (C), 128.28 (CH), 128.59 (CH), 129.51 (C), 134.79 (CH), 146.69 (C), 158.70 (C), 176.14 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2922 (m), 2860 (w), 2359 (w), 2340 (w), 1723 (vs), 1492 (m), 1446 (m), 1431 (m), 1416 (m), 1188 (s) $cm^{-1}$. MS (EI): $m/z$ (%) = 309 (30) [$M^+$], 250 (50), 249 (100), 193 (28). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1729. $[a]_D^{20}$ = +108 ($c$ = 2.76 in $CDCl_3$). M.p. 144–145 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.85, H 7.45, N 4.54.

**(–)-Methyl (5a*R*,13b*S*)-2,3,4,5,5a,6,7,13b-Octahydro-1*H*-cyclohepta[*a*]acridine-5a-carboxylate (*trans*-5c):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.62–1.79 (m, 7 H), 2.00 (ddd, $J$ = 6.3, $J$ = 11.8, $J$ = 13.4 Hz, 1 H), 2.54–2.62 (m, 1 H), 2.08–2.18 (m, 1 H), 2.22–2.28 (m, 2 H), 2.93 (dd, $J$ = 4.4, $J$ = 9.5 Hz, 1 H), 3.04 (ddd, $J$ = 6.2, $J$ = 11.7, $J$ = 17.7 Hz, 1 H), 3.15 (ddd, $J$ = 3.5, $J$ = 6.3, $J$ = 17.7 Hz, 1 H), 3.52 (s, 3 H), 7.40–7.45 (m, 1 H), 7.57–7.62 (m, 1 H), 7.72 (d, $J$ = 8.1 Hz, 1 H), 7.95 (d, $J$ = 8.4 Hz, 1 H), 8.04 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 25.10 ($CH_2$), 26.59 ($CH_2$), 26.94 ($CH_2$), 30.47 ($CH_2$), 31.18 ($CH_2$), 36.46 ($CH_2$), 40.14 ($CH_2$), 45.91 (CH), 49.40 (C), 51.27 ($CH_3$), 125.38 (CH), 127.29 (C), 127.31 (CH), 127.90 (CH), 128.49 (CH), 132.15 (CH), 135.19 (C), 145.75 (C), 158.00 (C), 175.70 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2927 (m), 2860 (w), 2360 (w), 2342 (w), 1724 (vs), 1455 (m), 1415 (m), 1259 (m) 1015 (s) $cm^{-1}$. MS (EI): $m/z$ (%) = 309 (67) [$M^+$], 249 (100), 180 (23), 168 (45). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1729. $[a]_D^{20}$ = –272 ($c$ = 0.90 in $CDCl_3$). M.p. 117–118 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.81, H 7.46, N 4.54.

**Conversion of Ketone *cis*-1a to Quinolines *cis*-4a/*cis*-5a According to General Procedure "Fe":** A mixture of *cis*-**1a** (500 mg, 2.38 mmol), *p*TosOH·$H_2O$ (452 mg, 2.38 mmol) and aminoaldehyde **7** (350 mg, 2.89 mmol) gave after chromatography ($SiO_2$; PE/EA, 2:1) compound *cis*-**4a** (317 mg, 1.07 mmol, 45%) in the first fraction ($R_f$ = 0.57) as a light yellow solid (m.p. 80–81 °C). The second fraction ($R_f$ = 0.50) contained compound *cis*-**5a** (373 mg, 1.26 mmol, 53%, colorless oil).

**(+)-Ethyl (3a*R*,11a*R*)-2,3,3a,4,11,11a-Hexahydro-1*H*-cyclopenta[*b*]acridine-11a-carboxylate (*cis*-4a):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.08–1.17 (m, 1 H, 3-H), 1.23 (t, $J$ = 7.2 Hz, 3 H, $OCH_2CH_3$), 1.40 (ddd, $J$ = 6.4, $J$ = 10.0, $J$ = 12.7 Hz, 1 H, 1-H), 1.46–1.54 (m, 1 H, 2-H), 1.54–1.62 (m, 1 H, 2-H), 1.97–2.04 (m, 1 H, 3-H), 2.18–2.25 (m, 1 H, 1-H), 2.84 (d, $J$ = 14.6 Hz, 1 H, 11-H), 2.93 (dd, $J$ = 5.3, $J$ = 14.4 Hz, 1 H, 4-H), 2.99 (ddd, $J$ = 5.6, $J$ = 8.0, $J$ = 13.9 Hz, 1 H, 3a-H), 3.18 (dd, $J$ = 5.9, $J$ = 14.4 Hz, 1 H, 4-H), 3.30 (d, $J$ = 14.6 Hz, 1 H, 11-H), 4.10–4.16 (m, 2 H, $OCH_2CH_3$), 7.46–7.50 (m, 1 H, 8-H), 7.62–7.67 (m, 1 H, 7-H), 7.75 (d, $J$ = 7.5 Hz, 1 H, 9-H), 7.83 (s, 1 H, 10-H), 8.03 (d, $J$ = 8.4 Hz, 1 H, 6-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 14.15 ($OCH_2CH_3$), 25.11 ($CH_2$, C-2), 33.95 ($CH_2$, C-3), 36.94 ($CH_2$, C-11 or C-4), 37.26 ($CH_2$, C-4 or C-11), 38.42 ($CH_2$, C-1), 42.30 (CH, C-3a), 52.70 (C, C-11a), 60.75 ($OCH_2CH_3$), 125.69 (CH, C-8), 127.12 (CH, C-9), 127.72 (C, C-9a), 128.58 (CH, C-6), 128.59 (CH, C-7), 130.16 (C, C-10a), 133.94 (CH, C-10), 146.99 (C, C-5a), 160.63 (C, C-4a), 177.76 (C, $CO_2Et$) ppm. IR (ATR): $\tilde{\nu}$ = 3058 (w), 2954 (m), 2867 (w), 1715 (vs), 1420 (m), 1277 (s), 1184 (vs), 1145 (s), 755 (vs) $cm^{-1}$. MS (EI): $m/z$ (%) = 295 (25) [$M^+$], 221 (100), 180 (18), 167 (10). HR-MS: calcd. for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572. $[a]_D^{20}$ = +69 ($c$ = 3.65 in $CDCl_3$). M.p. 80–81 °C. $C_{19}H_{21}NO_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.04, H 7.19, N 4.69.

**(+)-Ethyl (3a*R*,11b*R*)-2,3,3a,4,5,11b-Hexahydro-1*H*-cyclopenta[*a*]acridine-3a-carboxylate (*cis*-5a):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.22 (t, $J$ = 7.1 Hz, 3 H, $OCH_2CH_3$), 1.62–1.70 (m, 1 H, 1-H), 1.73–1.91 (m, 3 H, 2-H, 3-H), 1.98 (ddd, $J$ = 4.7, $J$ = 10.7, $J$ = 24.3 Hz, 1 H, 4-H), 2.24–2.85 (m, 3 H, 3-H, 4-H, 1-H), 3.01 (ddd, $J$ = 4.7, $J$ = 10.7, $J$ = 17.2 Hz, 1 H, 5-H), 3.10 (dt, $J$ = 17.2, $J$ = 5.2 Hz, 1 H, 5-H), 3.85 (dd, $J$ = 9.2, $J$ = 9.6 Hz, 1 H, 11b-H), 4.08–4.20 (m, 2 H, $OCH_2CH_3$), 7.41–7.47 (m, 1 H, 9-H), 7.59–7.64 (m, 1 H, 8-H), 7.72 (d, $J$ = 4.9 Hz, 1 H, 10-H), 7.91 (s, 1 H, 11-H), 7.97 (d, $J$ = 8.5 Hz, 1 H, 7-H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 14.12 ($OCH_2CH_3$), 23.96 ($CH_2$, C-2), 29.93 ($CH_2$, C-4), 30.99 ($CH_2$, C-5), 36.57 ($CH_2$, C-1), 38.07 ($CH_2$, C-3), 45.27 (CH, C-11b), 51.23 (C, C-3a), 60.70 ($OCH_2CH_3$), 125.55 (CH, C-9), 126.94 (CH, C-10), 127.37 (C, C-10a), 128.25 (CH, C-8), 128.61 (CH, C-7), 132.90 (C, C-11a), 135.24 (CH, C-11), 146.33 (C, C-6a), 158.02 (C, C-5a), 176.97 (C, $CO_2Et$) ppm. IR (ATR): $\tilde{\nu}$ = 3057 (w), 2952 (m), 2870 (w), 1715 (s), 1491 (m), 1419 (m), 1250 (s), 1172 (s), 1161 (s), 751 (s) $cm^{-1}$. MS (EI): $m/z$ (%) = 295 (20) [$M^+$], 266 (14), 221 (100), 180 (18), 167 (8). HR-MS: calcd. for $C_{19}H_{21}NO_2$ 295.1572, found 295.1572. $[a]_D^{20}$ = +26 ($c$ = 7.5 in $CDCl_3$). $C_{19}H_{21}NO_2$ (295.38): calcd. C 77.26, H 7.17, N 4.74; found C 77.52, H 7.12, N 4.78.

**Conversion of Ketone *cis*-1b to Quinolines *cis*-4b/*cis*-5b According to General Procedure "Fe":** A mixture of *cis*-**1b** (500 mg, 2.23 mmol), *p*TosOH·$H_2O$ (424 mg, 2.23 mmol) and aminoaldehyde **7** (410 mg, 3.40 mmol) gave after chromatography ($SiO_2$; PE/EA, 3:1) compound *cis*-**4b** (271 mg, 0.88 mmol, 40%) in the first fraction ($R_f$ = 0.39) as a colorless solid (m.p. 87–88 °C). The second fraction ($R_f$ = 0.30) contained *cis*-**5b** (349 mg, 1.13 mmol, 51%, m.p. 59–60 °C).

**(+)-Ethyl (6a*R*,10a*R*)-6,6a,7,8,9,10,10a,11-Octahydrobenzo[*b*]acridine-10a-carboxylate (*cis*-4b):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.16 (t, $J$ = 7.1 Hz, 3 H), 1.33 (dq, $J$ = 3.4, $J$ = 15.6 Hz, 1 H), 1.41–1.52 (m, 1 H), 1.52–1.62 (m, 1 H), 1.64–1.73 (m, 2 H), 1.73–1.80 (m, 2 H), 1.88 (ddd, $J$ = 4.4, $J$ = 12.0, $J$ = 13.2 Hz, 1 H), 2.53–2.60 (m, 1 H), 2.96 (dd, $J$ = 2.9, $J$ = 18.3 Hz, 1 H), 3.24 (d, $J$ = 17.1 Hz, 1 H), 3.25 (dd, $J$ = 6.5, $J$ = 18.2 Hz, 1 H), 3.32 (d, $J$ = 17.1 Hz, 1 H), 4.05–4.16 (m, 2 H), 7.41–7.46 (m, 1 H), 7.58–63 (m, 1 H), 7.72 (d, $J$ = 8.0 Hz, 1 H), 7.87 (s, 1 H), 7.95 (d, $J$ = 8.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.95 ($CH_3$), 21.10 ($CH_2$), 24.62 ($CH_2$), 28.02 ($CH_2$), 30.64 ($CH_2$), 33.15 ($CH_2$), 35.63 (CH), 37.18 ($CH_2$), 45.57 (C), 60.46 ($CH_2$), 125.36 (CH), 126.74 (CH), 127.06 (C), 128.03 (CH), 128.08 (C), 128.36 (CH), 134.87 (CH), 146.74 (C), 156.76 (C), 176.65 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2977 (w), 2928 (m), 2856 (w), 1720 (vs), 1493 (m), 1450 (m), 1424 (m), 1288 (m), 1215 (s), 1185 (s), 750 (s) $cm^{-1}$. MS (EI): $m/z$ (%) = 309 (24) [$M^+$], 235 (100), 193 (19), 180 (15), 168 (13). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1728. $[a]_D^{20}$ = +95 ($c$ = 7.5 in $CDCl_3$). M.p. 87–88 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.82, H 7.46, N 4.56.

**(–)-Ethyl (4a*R*,12b*R*)-1,2,3,4,4a,5,6,12b-Octahydrobenzo[*a*]acridine-4a-carboxylate (*cis*-5b):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.14 (t, $J$ = 7.1 Hz, 3 H), 1.41–1.61 (m, 3 H), 1.61–1.70 (m, 1 H), 1.71–1.80 (m, 2 H), 1.81–1.89 (m, 1 H), 1.90–1.96 (m, 1 H), 2.12–2.19 (m, 1 H), 2.40 (ddd, $J$ = 6.7, $J$ = 11.5, $J$ = 13.4 Hz, 1 H), 3.12 (ddd, $J$ = 7.0, $J$ = 11.5, $J$ = 18.5 Hz, 1 H), 3.23 (ddd, $J$ = 2.7, $J$ = 6.7, $J$ = 18.5 Hz, 1 H), 3.45 (dd, $J$ = 4.6, $J$ = 11.6 Hz, 1 H), 4.05 (dq, $J$ = 2.1, $J$ = 7.1 Hz, 2 H), 7.43 (t, $J$ = 7.2 Hz, 1 H), 7.58–7.62 (m, 1 H), 7.72 (d, $J$ = 7.9 Hz, 1 H), 7.89 (s, 1 H), 7.95 (d, $J$ = 8.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 13.94 ($CH_3$), 20.95 ($CH_2$), 24.61 ($CH_2$), 25.18 ($CH_2$), 30.31 ($CH_2$), 32.78 ($CH_2$),

34.29 ($CH_2$), 41.02 (CH), 45.27 (C), 60.30 ($CH_2$), 125.29 (CH), 126.92 (CH), 127.14 (C), 127.98 (CH), 128.44 (CH), 134.85 (C), 134.86 (CH), 146.56 (C), 156.91 (C), 176.53 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2931 (m), 2856 (m), 1721 (s), 1491 (w), 1418 (w), 1239 (s), 1226 (s), 909 (s), 727 (vs) $cm^{-1}$. MS (EI): *m*/*z* (%) = 309 (27) [$M^+$], 280 (12), 235 (100), 193 (12), 180 (13). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1727. $[\alpha]_D^{20}$ = –67 (*c* = 7.0 in $CDCl_3$). $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.70, H 7.48, N 4.51.

**Conversion of Ketone *cis*-1c to Quinolines *cis*-4c/*cis*-5c According to General Procedure "Fe":** A mixture of *cis*-**1c** (500 mg, 2.23 mmol), *p*TosOH·$H_2O$ (424 mg, 2.23 mmol) and aminoaldehyde **7** (410 mg, 3.40 mmol) gave after chromatography ($SiO_2$; PE/EA, 3:1) compound *cis*-**4c** (210 mg, 0.68 mmol, 30%) in the first fraction ($R_f$ = 0.45) as a light yellow solid (m.p. 64–64 °C). The second fraction ($R_f$ = 0.34) contained *cis*-**5c** (330 mg, 1.07 mmol, 48%, m.p. 101–102 °C).

**(+)-Methyl (6a*R*,11a*R*)-6a,7,8,9,10,11,11a,12-Octahydro-6*H*-cyclohepta[*b*]acridine-11a-carboxylate (*cis*-4c):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.30–1.39 (m, 1 H), 1.42–1.53 (m, 3 H), 1.62–1.74 (m, 3 H), 1.76–1.84 (m, 2 H), 2.12–2.20 (m, 1 H), 2.85–2.87 (m, 1 H), 2.87–2.91 (m, 2 H), 3.09–3.17 (m, 1 H), 3.25 (d, *J* = 15.3 Hz, 1 H), 3.59 (s, 3 H), 7.42–7.45 (m, 1 H), 7.60–7.64 (m, 1 H), 7.72 (d, *J* = 8.1 Hz, 1 H), 7.80 (s, 1 H), 8.00 (d, *J* = 8.5 Hz, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 24.84 ($CH_2$), 27.85 ($CH_2$), 29.66 ($CH_2$), 32.81 ($CH_2$), 37.23 ($CH_2$), 38.65 ($CH_2$), 38.69 (CH), 39.90 ($CH_2$), 50.59 (C), 52.04 ($CH_3$), 125.55 (CH), 127.07 (CH), 127.49 (C), 128.45 (CH), 128.54 (CH), 129.35 (C), 133.46 (CH), 146.94 (C), 159.75 (C), 177.77 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2924 (m), 2855 (w), 1726 (vs), 1495 (w), 1459 (w), 1427 (m), 1194 (m), 751 (m) $cm^{-1}$. MS (EI): *m*/*z* (%) = 309 (38) [$M^+$], 266 (9), 250 (100), 206 (22), 193 (26), 180 (23). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1729. $[\alpha]_D^{20}$ = +23 (*c* = 8.0 in $CDCl_3$). M.p. 64–65 °C.

**(–)-Methyl (5a*R*,13b*R*)-2,3,4,5,5a,6,7,13b-Octahydro-1*H*-cyclohepta[*a*]acridine-5a-carboxylate (*cis*-5c):** $^1H$ NMR ($CDCl_3$, 500 MHz): $\delta$ = 1.20–1.31 (m, 1 H), 1.45–1.57 (m, 2 H), 1.64–1.78 (m, 3 H), 1.78–1.86 (m, 1 H), 1.86–1.94 (m, 2 H), 1.94–2.02 (m, 1 H), 2.23–2.33 (m, 2 H), 2.94 (ddd, *J* = 5.9, *J* = 13.0, *J* = 18.6 Hz, 1 H), 3.21 (ddd, *J* = 2.1, *J* = 5.6, *J* = 18.3 Hz, 1 H), 3.59 (s, 3 H), 3.78 (d, *J* = 9.6 Hz, 1 H), 7.37–7.43 (m, 1 H), 7.56–7.61 (m, 1 H), 7.71 (d, *J* = 8.1 Hz, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.97 (s, 1 H) ppm. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): $\delta$ = 23.15 ($CH_2$), 30.19 ($CH_2$), 31.19 ($CH_2$), 31.35 ($CH_2$), 31.52 ($CH_2$), 36.71 ($CH_2$), 39.79 ($CH_2$), 45.23 (CH), 49.23 (C), 52.49 ($CH_3$), 125.92 (CH), 127.52 (CH), 128.02 (C), 128.58 (CH), 129.19 (CH), 136.69 (C), 137.11 (CH), 147.12 (C), 157.35 (C), 177.63 (C) ppm. IR (ATR): $\tilde{\nu}$ = 2925 (m), 2855 (w), 1722 (vs), 1490 (m), 1420 (m), 1244 (s), 1195 (s), 1166 (vs), 749 (s), 731 (s) $cm^{-1}$. MS (EI): *m*/*z* (%) = 309 (20) [$M^+$], 249 (100), 220 (9), 206 (17), 194 (18), 180 (24). HR-MS: calcd. for $C_{20}H_{23}NO_2$ 309.1729, found 309.1728. $[\alpha]_D^{20}$ = –101 (*c* = 17.5 in $CDCl_3$). M.p. 101–102 °C. $C_{20}H_{23}NO_2$ (309.40): calcd. C 77.64, H 7.49, N 4.53; found C 77.63, H 7.45, N 4.56.

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