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PAPER

Total synthesis of the monoterpenoid alkaloid (±)-tangutorine†

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A novel approach to a formal total synthesis of the monoterpenoid indole alkaloid (±)-tangutorine has been developed starting from an α,β-unsaturated cyclic dehydroamino ester. Synthesis of the rather unusual *trans*-substituted 2,3-indoloquinolizidine substructure was accomplished *via* Cu(II)-mediated conjugate addition and organozinc/copper coupling as the key steps, thereby setting the stage for ring-closing metathesis to produce the quinolone substructure. Finally, Bischler–Napieralski cyclization gave rise to the pentacyclic system of (±)-tangutorine thereby realizing a formal synthesis in an overall yield of 5.2% in eight consecutive steps.

Introduction

Monoterpenoid alkaloids are widespread in nature and possess diverse structures with often relevant biological properties.[1] β-Carbolines (*e.g.* **1–3**, Fig. 1) belong to this class and form one of the principal alkaloid groups in nature that are biosynthetically derived from tryptophan.[2] This class contains some of the most important alkaloids used in medicine such as reserpine (**3**).[3] In 1999, a novel racemic β-carboline named tangutorine (**1**) was isolated by Duan and colleagues from the leaves of the Chinese medical plant *Nitraria tangutorine*.[4] Although tangutorine (**1**) is structurally related to the more common yohimbine skeleton (*viz*. **2**), it is the only known β-carboline alkaloid containing an indoloquinolizidine substructure.

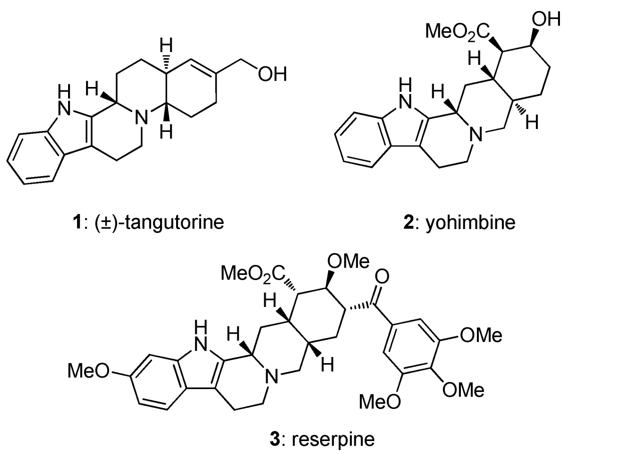

Fig. 1 Monoterpenoid indole alkaloids.

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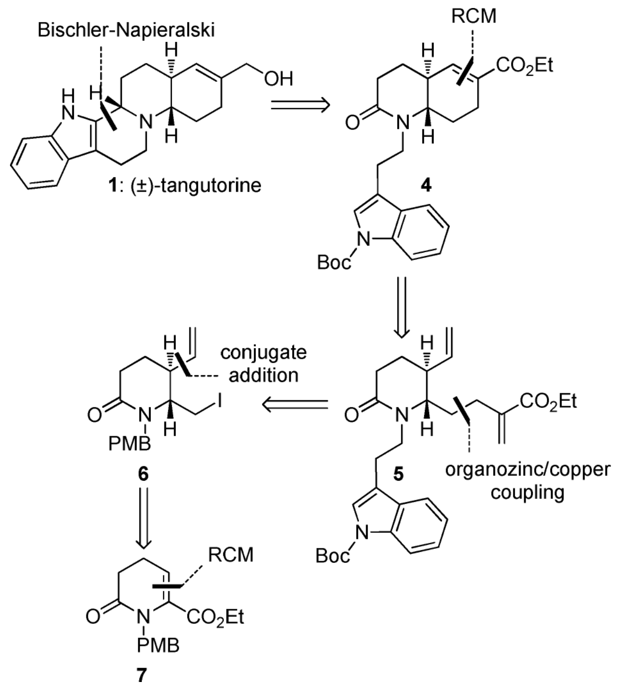
Tangutorine (**1**) shows interesting biological effects on the regulation of cell cycle and cellular morphology and therefore might serve as a lead compound for the design of new drugs.[5] Since its isolation in 1999, several syntheses of (±)-tangutorine (**1**) have been published,[6–10] one of which describes the synthesis of both optical antipodes.[11]

Following-up on previously developed methodology from our group on ring-closing metathesis (RCM) of (sterically hindered) enamides,[12,13] and its application in the synthesis of substituted piperidines,[14,15] we herewith describe a novel approach to racemic tangutorine (**1**) starting from key building block **7**.[16] As depicted in Scheme 1, a first disconnection of the pentacyclic

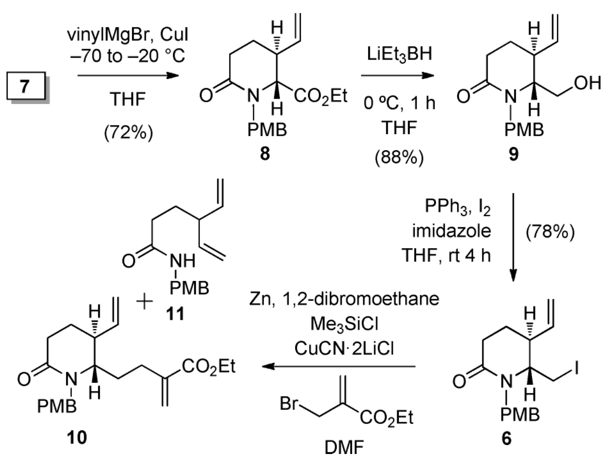


Scheme 1 Retrosynthesis of (±)-tangutorine (**1**).

tangutorine framework would involve a Bischler–Napieralski cyclization, followed by reduction giving rise to bicyclic precursor **4**. Subsequently, hexahydroquinolone **4** could be derived *via* RCM from the *trans*-5,6-disubstituted lactam **5**. We were hopeful that the primary iodide **6** would serve as a suitable precursor to deliver **5** *via* organozinc/copper-mediated coupling with ethyl 2-(bromomethyl)acrylate. Finally, diastereoselective copper-catalyzed 1,4-addition onto **7**, followed by some further functionalization was anticipated to lead to iodide **6**.

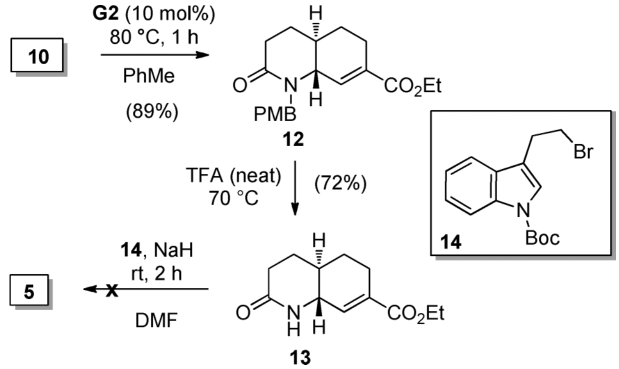
Results and discussion

Recently, we have shown that the unsaturated lactam **7** can be readily prepared from a linear enamide precursor through RCM.[15] Having lactam **7** thus available, diastereoselective copper-catalyzed 1,4-addition of vinylmagnesium bromide in the presence of CuI at −20 °C provided the *trans*-5,6-disubstituted lactam **8** in 72% yield as a single diastereoisomer (Scheme 2).[17] Next, conversion of the ester functionality into the corresponding primary iodide was aimed to provide a handle for introduction of the second double bond, thereby setting the stage for RCM formation of the second ring. Disappointingly, reduction with DIBAL-H at −78 °C was unproductive, and starting material was recovered. Use of $LiAlH_4$ also gave no product, but instead led to reduction of both the alcohol and the amide. Gratifyingly, reduction with $LiEt_3BH$ at 0 °C was efficient and yielded the desired alcohol **9** in 88%. Subsequent conversion into primary iodide **6** was accomplished with iodine in the presence of triphenylphosphine and imidazole in 78% yield. To prepare RCM precursor **10**, initially Grignard-mediated substitution of the iodide and the corresponding tosylate was investigated. In either case, however, no reaction was observed and only starting material was recovered. We then turned to an organozinc/copper coupling strategy to introduce the second olefin (Scheme 2).[18] Reaction of iodide **6** with activated zinc and ethyl 2-(bromomethyl)acrylate did result in the desired RCM-precursor **10** in 42% yield together with the undesired ring-opened product **11** (39%).



Scheme 2 Organozinc/copper coupling strategy.

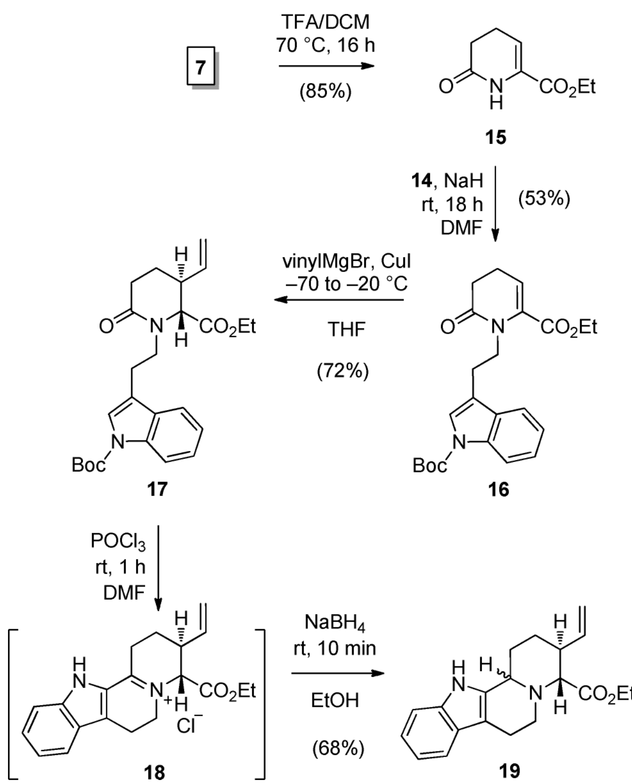
Having RCM-precursor **10** in hand, treatment with the Grubbs' second generation catalyst (**G2**, 10 mol%, toluene, 80 °C) led to hexahydroquinolone **12** in 89% yield (Scheme 3). To introduce the indole moiety, we initially turned to *N*-alkylation of quinolizidine



Scheme 3 Toward quinolone precursor **5**.

12 with Boc-protected tryptophyl bromide (**14**). To this end, the amide group had to be deprotected. PMB-deprotection of **12** proved to be somewhat less trivial than expected, however. Oxidation with ceric ammonium nitrate (CAN) in MeCN led to long reaction times despite using a large excess of reagents, eventually resulting in multiple products. Alternatively, treatment with DDQ in H_2O/CH_2Cl_2 mixtures did not show any conversion at all. Treatment with TFA at elevated temperatures on the other hand proceeded smoothly resulting in **13** in 72% yield. Unfortunately, alkylation of lactam **13** with bromide **14** and DIPEA at elevated temperature only resulted in degradation of the starting material.[19] Disappointingly, reaction with sodium hydride in DMF in the presence of **14** (and additional TBAI or KI) did not lead to any product either.

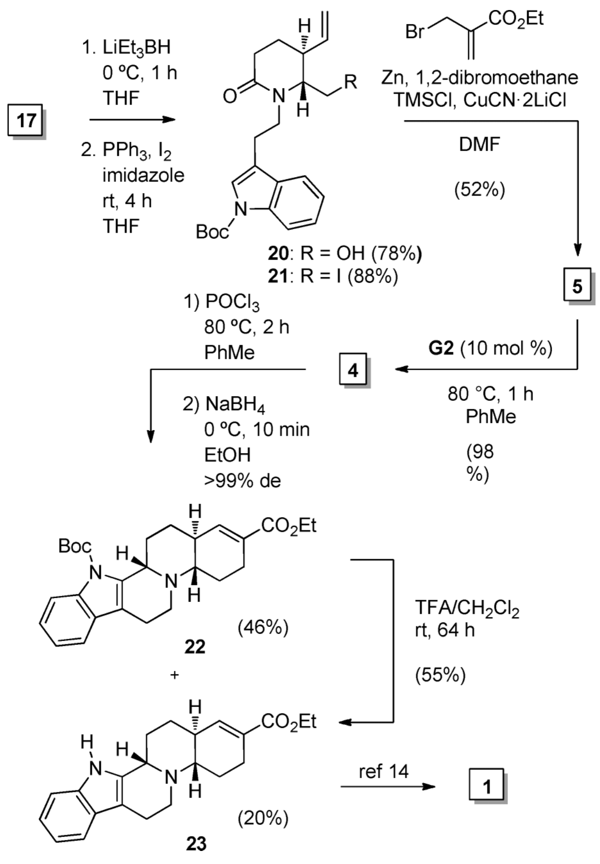
Introduction of the indole group was therefore envisioned to occur starting from the cyclic dehydroamino ester **7** (Scheme 4). PMB-deprotection of **7** using TFA yielded lactam **15** in 85% yield.



Scheme 4 Bischler–Napieralski cyclization.

Alkylation with Boc-protected tryptophyl bromide (**14**) in the presence of sodium hydride now resulted in the desired *N*-alkylated product, but the isolated yield never exceeded 10%. When sodium hydride was added portionwise (5 times 0.25 equiv) the yield was raised to an acceptable 53%. With **16** successfully synthesized, *trans*-selective 1,4-addition with vinylmagnesium bromide, followed by Bischler–Napieralski cyclization was thought to lead to the desired pentacycle.[20] Indeed, diastereoselective conjugate addition, and subsequent treatment of **17** with $POCl_3$ in DMF at elevated temperatures led to iminium-salt **18**, which was then reduced with sodium borohydride in ethanol to give an inseparable mixture of diastereoisomers **19** (86 : 14). Unfortunately, the Boc-group was cleaved during the cyclization so that reprotection was necessary to complete the synthesis.

To avoid the reprotection step, a slightly different strategy was pursued, in which the quinolizidine substructure was constructed from dehydroamino ester **17** in four consecutive steps (Scheme 5). The reduction/iodination protocol first yielded iodide **21** in 69% yield over two steps. Then, the organozinc/copper coupling afforded RCM precursor **5** in a moderate yield of 52%, again together with the undesired 1,4-diene (34%) as described previously. Finally, RCM proceeded uneventfully to give quinolone structure **4** in a near quantitative conversion. En route to completion of the synthesis, pentacycle **23** was produced in diastereomerically pure form *via* Bischler–Napieralski cyclization of lactam **4**. Surprisingly, the Boc-group was only partially removed during this reaction. Separation of both products and subsequent Boc-deprotection of **22** with TFA resulted in the known carboxylic ester **23** in an overall yield of 45%. Its spectral data were in agreement with values reported in literature.[4]



Scheme 5 Completion of tangutorine (**1**).

Conclusions

In conclusion, we have demonstrated the synthetic value of the dehydroamino ester building block **7** through application in the synthesis of (±)-tangutorine in eight consecutive steps in an overall yield of 5.2%. The pathway is characterized by a diastereoselective copper-catalyzed 1,4-addition onto the cyclic dehydroamino ester, an organozinc/copper coupling followed by ring-closing metathesis of the diolefin for the construction of the quinolone substructure and a diastereoselective Bischler–Napieralski cyclization.

Experimental

General

^{1}H-NMR spectra were recorded on a 400 MHz NMR spectrometer. ^{13}C-NMR spectra were recorded on a 75 MHz NMR spectrometer. Chemical shifts (δ) are reported in ppm and relative to a residual solvent peak (^{1}H-NMR: 7.26 in $CDCl_3$, ^{13}C-NMR: 77.0 in $CDCl_3$). IR spectra were recorded on an ATR IR-spectrometer. R_f values are obtained using thin layer chromatography (TLC) on silica gel-coated plates with the indicated eluents and compounds were detected with UV-light, potassium permanganate, *p*-anisaldehyde or ninhydrin.

1-[2-(1-*tert*-Butoxycarbonyl-1*H*-indol-3-yl)ethyl]-2-oxo-1,2,3,4,4a,5,6,8a-octahydroquinoline-7-carboxylic acid ethyl ester (4)

Compound **5** (28 mg, 0.056 mmol) was dissolved in toluene (1 mL) and argon was flushed through the solvent. The second generation Grubbs' catalyst (5 mg, 0.005 mmol) was added and the solution was heated to 80 °C. After 1 h, the solution was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **4** (26 mg, 98%) as a colorless oil. R_f 0.38 (EtOAc/heptane 2 : 1). FTIR (ATR) 2922, 1728, 1639, 1450, 1369, 1256, 1157 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, J = 7.0 Hz, 1H), 7.69 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 7.35–7.22 (m, 2H), 6.70 (d, J = 1.1 Hz, 1H), 4.21 (q, J = 6.9 Hz, 2H), 3.84–3.68 (m, 2H), 3.14 (ddd, J = 12.1, 9.7, 2.2 Hz, 1H), 3.09–3.00 (m, 1H), 2.83–2.73 (m, 1H), 2.69–2.53 (m, 3H), 2.46–2.36 (m, 2H), 2.34–2.23 (m, 1H), 2.04–1.96 (m, 1H), 1.67 (s, 9H), 1.63–1.50 (m, 2H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 170.2, 166.1, 149.3,m 138.7, 135.0, 130.0, 129.7, 128.5, 127.7, 124.8, 124.0, 122.4, 122.1, 118.7, 117.5, 114.8, 83.0, 60.2, 58.1, 42.3, 39.6, 32.5, 27.8, 26.8, 26.0, 24.1, 23.7, 13.8. HRMS (ESI) *m/z* calcd for $C_{27}H_{34}N_2O_5$ $(M + Na)^+$: 489.2368, found: 489.2365.

3-{2-[2-(3-Ethoxycarbonylbut-3-enyl)-6-oxo-3-vinylpiperidin-1-yl]ethyl}indole-1-carboxylic acid *tert*-butyl ester (5)

Zinc dust (42 mg, 0.65 mmol) was weighed into a Schlenk flask, which was flame dried and flushed with argon. 1,2-Dibromoethane (2.8 µL, 0.03 mmol) in dry DMF (0.2 mL) was added and the flask was heated to 60 °C for 1 h. Me_3SiCl (0.41 µL, 0.0031 mmol) was added and the mixture was stirred at 60 °C for 30 min.

Compound **21** (55 mg, 0.11 mmol) was dissolved in DMF (0.3 mL), added to the mixture and stirred for 10 min at 60 °C. CuCN (10 mg, 0.11 mmol) and LiCl (9.2 mg, 0.22 mmol) were heated to 150 °C under vacuum for 2 h and cooled to room temperature. Addition of DMF (0.3 mL) formed a soluble CuCN·2LiCL complex. After cooling, the organozinc reagent was cooled to −55 °C, the Cu-complex was added and the solution was warmed to 0 °C. After stirring for 10 min at 0 °C, the solution was cooled to −55 °C and ethyl 2-(bromomethyl)acrylate (18.2 µL, 0.13 mmol) was added. The solution was slowly warmed to room temperature and stirred overnight. The mixture was filtered over Celite, diluted with EtOAc (10 mL), washed with aqueous NH_4Cl (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording lactam **5** (28 mg, 52%) as a viscous oil. R_f 0.27 (EtOAc/heptane 1 : 1). FTIR (ATR) 2977, 1728, 1637, 1454, 1372, 1158 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.41 (s, 1H), 7.35–7.22 (m, 2H), 6.15 (s, 1H), 5.71 (ddd, J = 17.3, 10.3, 7.2 Hz, 1H), 5.51 (s, 1H), 5.16–5.06 (m, 2H), 4.19 (q, J = 6.9 Hz, 2H), 4.21–4.12 (m, 1H), 3.19–3.13 (m, 1H), 3.09–2.93 (m, 3H), 2.54–2.44 (m, 2H), 2.40–2.16 (m, 3H), 2.07–1.96 (m, 1H), 1.88–1.68 (m, 4H), 1.66 (s, 9H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 169.5, 166.3, 149.2, 139.3, 138.5, 135.0, 130.0, 124.8, 123.9, 122.8, 122.0, 118.7, 117.3, 115.6, 114.8, 82.9, 61.1, 60.3, 45.5, 38.4, 31.3, 28.6, 27.9, 27.8, 22.6, 22.2, 13.7. HRMS (ESI) m/z calcd for $C_{29}H_{38}N_2O_5$ (M + Na)$^+$: 517.2681, found: 517.2678.

6-Iodomethyl-1-(4-methoxybenzyl)-2-oxo-5-vinylpiperidine (6)

To a solution of compound **9** (105 mg, 0.38 mmol) in THF (4 mL), PPh_3 (120 mg, 0.46 mmol) and imidazole (39 mg, 0.57 mmol) were added. The reaction was heated to 70 °C and iodine (116 mg, 0.46 mmol) was added. After 30 min the reaction was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **6** (140 mg, 67%) as a viscous oil. R_f 0.82 (CH_2Cl_2/MeOH 9 : 1). FTIR (ATR) 2948, 1642, 1512, 1244, 519 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.59–5.49 (m, 1H), 5.51 (d, J = 15.0 Hz, 1H), 5.14–5.04 (m, 2H), 3.80 (s, 3H), 3.75 (d, J = 15.1 Hz, 1H), 3.36–3.33 (m, 2H), 2.94–2.89 (m, 1H), 2.68–2.60 (m, 1H), 2.60–2.41 (m, 2H), 1.95–1.86 (m, 1H), 1.78–1.66 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.9, 158.6, 137.8, 129.1, 127.9, 116.9, 113.7, 57.8, 54.8, 45.4, 41.4, 30.0, 23.2, 9.4. HRMS (ESI) m/z calcd for $C_{16}H_{20}INO_2Na$ (M + Na)$^+$: 408.0439, found: 408.0436.

1-(4-Methoxybenzyl)-6-oxo-3-vinylpiperidine-2-carboxylic acid ethyl ester (8)

To a cooled solution (−30 °C) of CuI (3.15 g, 16.6 mmol) in Et_2O (30 mL), a 1 M vinylmagnesium bromide solution in THF (8.3 mL, 8.3 mmol) was added. The solution was stirred for 20 min and was cooled to −70 °C. Then compound **7** (1.20 g, 4.15 mmol) dissolved in Et_2O (10 mL) was added and the temperature was slowly warmed to −10 °C. The reaction was quenched with 0.1 M HCl and washed with aqueous $Na_2S_2O_3$ (2 × 40 mL), $NaHCO_3$ (40 mL) and H_2O (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **8** (0.95 g, 72%) as a viscous oil. R_f 0.41 (EtOAc/heptane 1 : 1). FTIR (ATR) 2940, 1738, 1649, 1511 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.69–5.59 (m, 1H), 5.35 (d, J = 7.4 Hz, 1H), 5.08–4.91 (m, 2H), 4.22–4.12 (m, 2H), 3.89 (dd, J = 3.9, 1.0 Hz, 1H), 3.79 (s, 3H), 3.69 (d, J = 14.7, 1H), 2.83–2.77 (m, 1H), 2.54–2.47 (m, 2H), 2.00–1.90 (m, 1H), 1.78–1.71 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9, 169.3, 158.7, 136.2, 129.8, 127.9 116.3, 113.4, 61.9, 61.2 54.8, 48.1 38.6 28.3 22.9 13.7. HRMS (ESI) m/z calcd for $C_{18}H_{23}NO_4Na$ (M + Na)$^+$: 340.1537, found: 340.1525.

6-Hydroxymethyl-1-(4-methoxybenzyl)-2-oxo-5-vinylpiperidine (9)

To a cooled solution (0 °C) of compound **8** (0.95 g, 3.0 mmol) in THF (30 mL) $LiEt_3BH$ (9.0 mL, 9.0 mmol, 1 M solution in THF) was added. After 1.5 h of stirring at 0 °C another equivalent of $LiEt_3BH$ (1.0 mL, 1.0 mmol) was added and the reaction was stirred for 2 h. The reaction was then quenched with ice-water and the product was extracted with CH_2Cl_2 (2 × 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1 to CH_2Cl_2/MeOH 9 : 1) affording compound **9** (0.78 g, 95%) as a colorless oil. R_f 0.41 (CH_2Cl_2/MeOH 9 : 1). FTIR (ATR) 3376, 2948, 1613, 1512 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, J = 8.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 5.64–5.54 (m, 1H), 5.07–5.00 (m, 3H), 4.25 (d, J = 7.4 Hz, 1H), 3.79 (s, 3H), 3.79–3.73 (m, 1H), 3.64–3.56 (m, 1H), 3.21–3.16 (m, 1H), 2.72–2.63 (m, 1H), 2.58–2.37 (m, 2H), 2.05–1.95 (m, 2H), 1.72–1.60 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 158.5, 138.5, 129.2, 128.9, 116.0, 113.6, 61.1, 60.6, 54.8, 46.9, 38.3, 30.0, 23.8. HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_3Na$ (M + Na)$^+$: 298.1421, found: 298.1419.

4-[1-(4-Methoxybenzyl)-6-oxo-3-vinylpiperidin-2-yl]-2-methylenebutyric acid ethyl ester (10)

Zinc dust (52.3 mg, 0.81 mmol) was weighed into a Schlenk flask, which was evacuated under flame drying and flushed with argon. 1,2-Dibromoethane (3.3 µL, 0.04 mmol) in dry DMF (0.3 mL) was added and the flask was heated to 60 °C for 1 h. Me_3SiCl (0.5 µL, 0.004 mmol) was added and the mixture was stirred at 60 °C for 30 min. Compound **6** (50 mg, 0.13 mmol) was dissolved in DMF (0.4 mL), added to the mixture and stirred for 10 min at 60 °C. CuCN (11.6 mg, 0.13 mmol) and LiCl (11 mg, 0.26 mmol) were heated to 150 °C under vacuum for 2 h and cooled to room temperature. Addition of DMF (0.5 mL) formed a soluble CuCN·2LiCL complex. After cooling the organozinc reagent to −55 °C the Cu-complex was added and the solution was warmed to 0 °C. After stirring for 10 min at 0 °C the solution was cooled to −55 °C and ethyl 2-(bromomethyl)acrylate (21.8 µL, 0.156 mmol) was added. The solution was slowly warmed to room temperature and stirred for 16 h. The mixture was filtered over celite, diluted with EtOAc, washed with aqueous NH_4Cl and brine, dried over $MgSO_4$ and concentrated *in vacuo.* The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **10** (43 mg, 42%) as a viscous oil. R_f 0.25 (EtOAc/heptane 1 : 1). FTIR (ATR) 2936, 1712, 1635, 1512, 1245 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.18 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 6.16 (d, J = 1.2 Hz, 1H), 5.60–5.50 (m, 1H), 5.50 (d, J = 1.2 Hz, 1H), 5.42 (d, J = 14.6 Hz, 1H), 5.01–4.92 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.76 (d, J = 14.6 Hz, 1H), 3.18–3.13 (m, 1H), 2.58–2.45 (m, 2H), 2.44–2.34 (m, 1H), 2.33–2.17 (m, 2H), 2.06–1.95 (m, 1H), 1.90–1.63 (m, 3H), 1.32 (t, J = 7.1 Hz, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.7, 166.3, 158.4, 139.4, 138.4, 129.4, 128.9, 124.8, 115.6, 113.4, 60.3, 58.0, 54.8, 46.0, 39.3, 30.1, 28.9, 27.5, 22.5, 13.8. HRMS (ESI) m/z calcd for $C_{22}H_{29}NO_4Na$ (M + Na)$^+$: 394.1997, found: 394.1994.

4-Vinylhex-5-enoic acid 4-methoxybenzylamide (11)

Compound **11** (31 mg, 46%) was isolated as a side product from the organozinc/copper coupling with compound **6**. R_f 0.43 (EtOAc/heptane 1 : 1). FTIR (ATR) 3282, 3073, 2930, 1641, 1512, 1246 cm^{-1}.^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 5.75–5.64 (m, 2H), 5.62 (br s, 1H), 5.05–4.96 (m, 4H), 4.36 (d, J = 5.6 Hz, 2H), 3.80 (s, 3H), 2.71 (q, J = 7.4 Hz, 1H), 2.19 (t, J = 7.4 Hz, 2H), 1.79 (dt, J = 7.8, 7.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.9, 158.6, 139.9, 129.9, 128.8, 114.5, 113.6, 54.8, 46.9, 42.6, 33.8, 29.3. HRMS (ESI) m/z calcd for $C_{16}H_{21}NO_2Na$ (M + Na)$^+$: 282.1472, found: 282.1470.

1-(4-Methoxybenzyl)-2-oxo-1,2,3,4,4a,7,8,8a-octahydroquinoline-6-carboxylic acid ethyl ester (12)

Compound **10** (40 mg, 0.11 mmol) was dissolved in toluene (4 mL) and argon was flushed through the solvent. The second generation Grubbs' catalyst (9.2 mg, 0.01 mmol) was added and the solution was heated to 80 °C. After 1 h, the solution was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1 to 2 : 1) affording compound **12** (34 mg, 86%) as a colorless oil. R_f 0.16 (EtOAc/heptane 1 : 1). FTIR (ATR) 2933, 1708, 1639, 1512, 1244 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.13 (d, J = 8.8 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 1.3 Hz, 1H), 5.06 (d, J = 15.4 Hz, 1H), 4.42 (d, J = 15.4 Hz, 1H), 4.17 (q, J = 7.1, 7.0 Hz, 2H), 3.79 (s, 3H), 3.08 (ddd, J = 12.2, 9.8, 2.5 Hz, 1H), 2.76—2.59 (m, 2H), 2.55—2.31 (m, 3H), 2.23—2.09 (m, 1H), 2.05—1.97 (m, 1H), 1.60 (m, 1H), 1.42 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.5, 166.1, 158.1, 138.7, 129.3, 127.9, 126.7, 113.5, 60.1, 57.6, 54.8, 44.5, 39.5, 32.4, 26.4, 25.9, 24.0, 13.7. HRMS (ESI) m/z calcd for $C_{20}H_{25}NO_4Na$ (M + Na)$^+$: 366.1684, found: 366.1681.

6-Oxo-1,4,5,6-tetrahydropyridine-2-carboxylic acid ethyl ester (15)

Compound **7** (1.04 g, 3.6 mmol) was dissolved in a TFA/CH_2Cl_2 mixture (1 : 4, 36 mL) and stirred overnight at 50 °C. The reaction was quenched with $NaHCO_3$ and the organic compound was extracted with CH_2Cl_2 (2 × 40 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **15** (516 mg, 85%). R_f 0.14 (EtOAc/heptane 1 : 1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.58 (s, 1H), 6.29–6.26 (m, 1H), 4.29 (q, J = 7.1 Hz, 2H), 2.53–2.50 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 161.2, 128.4, 113.5, 61.4, 28.7, 20.3, 13.7.

3-[2-(6-Ethoxycarbonyl-2-oxo-3,4-dihydro-2*H*-pyridin-1-yl)ethyl]indole-1-carboxylic acid *tert*-butyl ester (16)

Lactam **15** (121 mg, 0.72 mmol) was dissolved in DMF (8 mL) and Boc-protected 3-(2-bromoethyl)indole (**14**, 347 mg, 1.07 mmol) was added. NaH (45 mg, 0.9 mmol) was gradually added to the mixture over 2.5 h. The reaction was then stirred overnight at room temperature, diluted with EtOAc/heptane 1 : 1 (10 mL), cooled to 0 °C and quenched with H_2O (10 mL). The organic layer was extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **16** (155 mg, 53%) as a viscous oil. R_f 0.40 (EtOAc/heptane 1 : 1). FTIR (ATR) 2977, 1724, 1678, 1367, 1255, 1157 cm^{-1}.^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 6.1 Hz, 1H), 7.62 (d, J = 7.7 Hz, 1H), 7.36 (s, 1H), 7.32–7.20 (m, 2H), 6.27 (t, J = 5.0 Hz, 1H), 4.11 (dq, J = 7.1, 0.5 Hz, 2H), 4.10–4.04 (m, 2H), 3.01–2.95 (m, 2H), 2.50 (t, J = 7.6 Hz, 2H), 2.35–2.26 (m, 2H), 1.66 (s, 9H), 1.25 (dt, J = 7.1, 0.5 Hz, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 162.1, 149.2, 135.1, 134.5, 130.0, 123.8, 122.8, 121.9, 119.9, 118.7, 117.2, 114.7, 82.9, 60.9, 42.9, 30.4, 27.8, 23.9, 19.4, 13.6. HRMS (ESI) m/z calcd for $C_{23}H_{28}N_2O_5Na$ (M + Na)$^+$: 435.1898, found: 435.1896.

3-[2-(2-Ethoxycarbonyl-6-oxo-3-vinylpiperidin-1-yl)ethyl]indole-1-carboxylic acid *tert*-butyl ester (17)

To a cooled solution (−30 °C) of CuI (0.3 g, 1.75 mmol) in Et_2O (2 mL), a 1 M vinylmagnesium bromide solution in THF (0.87 mL, 0.87 mmol) was added. The solution was stirred for 20 min and cooled to −70 °C. Then compound **16** (120 mg, 0.29 mmol) dissolved in Et_2O (1 mL) was added and the temperature was slowly warmed to −10 °C. The reaction was diluted with Et_2O, quenched with 0.1 M HCl (10 mL), washed with aqueous $Na_2S_2O_3$ (2 × 10 mL), $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **17** (0.95 g, 72%) as a viscous oil. R_f 0.26 (EtOAc/heptane 1 : 1). FTIR (ATR) 2977, 1731, 1650, 1454, 1373, 1158 cm^{-1}.^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.12 (d, J = 7.8 Hz, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.39 (s, 1H), 7.28 (m, 2H), 5.71 (ddd, J = 17.3, 10.4, 7.0 Hz, 1H), 5.19–5.10 (m, 2H), 4.22 (dq, J = 7.1, 0.6 Hz, 2H), 4.18–4.12 (m, 1H), 3.91 (d, J = 4.1 Hz, 1H), 3.10–2.86 (m, 3H), 2.85–2.77 (m, 1H), 2.56–2.38 (m, 2H), 1.98–1.87 (m, 1H), 1.78–1.69 (m, 1H), 1.66 (s, 9H), 1.27 (dt, J = 7.1, 0.7 Hz, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.0, 169.4, 149.2, 136.4, 135.0, 129.9, 123.9, 122.8, 122.1, 118.6, 117.1, 116.4, 114.8, 83.0, 65.0, 61.3, 47.3, 39.2, 28.5, 27.8, 23.2, 22.4, 13.8. HRMS (ESI) m/z calcd for $C_{25}H_{32}N_2O_5Na$ (M + Na)$^+$: 463.2211, found: 463.2209.

3-Vinyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-4-carboxylic acid ethyl ester (19)

Compound **17** (20 mg, 0.045 mmol) was dissolved in toluene (1 mL) and $POCl_3$ (42 µL, 0.45 mmol) was added. The solution was stirred at 70 °C for 2 h. The reaction was concentrated under reduced pressure, the residue was dissolved in EtOH (1 mL) and cooled to 0 °C. $NaBH_4$ (3.4 mg, 0.09 mmol) was added and the reaction was stirred for 10 min at 0 °C, diluted with CH_2Cl_2 (10 mL) and quenched with aqueous $NaHCO_3$

(10 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 2) affording compound **19** (13.0 mg, 68%) as a colorless oil. R_f 0.48 (EtOAc/heptane 1 : 1). FTIR (ATR) 3342, 2916, 1717, 1455, 611 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.69 (br s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.7 Hz, 1H), 7.11 (ddt, J = 15.9, 7.1, 1.2 Hz, 2H), 5.68 (m, 1H), 5.04 (dd, J = 10.2, 1.7 Hz, 1H), 4.30–4.20 (m, 2H), 3.40 (br d, J = 11.4 Hz, 1H), 3.06–2.97 (m, 2H), 2.95 (d, J = 10.3 Hz, 1H), 2.76–2.68 (m, 1H), 2.68–2.54 (m, 2H), 2.19–2.11 (m, 1H), 2.03–1.96 (m, 1H), 1.87–1.75 (m, 1H), 1.56–1.44 (m, 1H), 1.30 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.7, 137.9, 135.5, 133.5, 121.0, 119.0, 117.7, 116.1, 110.2, 108.0, 105.7, 72.6, 60.3, 58.8, 50.7, 44.6, 29.7, 28.3, 21.4, 13.9. HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_2$ $(M + H)^+$: 325.1918, found: 325.1916.

3-[2-(2-Hydroxymethyl-6-oxo-3-vinylpiperidin-1-yl)ethyl]indole-1-carboxylic acid *tert*-butyl ester (20)

To a cooled solution (0 °C) of compound **17** (93 mg, 0.21 mmol) in THF (2.5 mL) $LiEt_3BH$ (0.63 mL, 0.63 mmol, 1 M solution in THF) was added. After stirring for 2.5 h at 0 °C, the reaction was quenched with ice-water (25 mL) and the product was extracted with CH_2Cl_2 (2 × 40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/heptane 1 : 1 to CH_2Cl_2/MeOH 9 : 1) affording compound **20** (74 mg, 88%) as a viscous oil. R_f 0.35 (CH_2Cl_2/MeOH 9 : 1). FTIR (ATR) 3322, 1731, 1615, 1455, 1370 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.11 (d, J = 6.7 Hz, 1H), 7.69–7.60 (m, 1H), 7.39 (d, J = 3.3 Hz, 1H), 7.33–7.19 (m, 2H), 5.73–5.55 (m, 1H), 5.16–5.00 (m, 2H), 4.11–4.00 (m, 1H), 4.00–3.64 (m, 2H), 3.32–3.14 (m, 2H), 3.08–2.85 (m, 2H), 2.53–2.40 (m, 2H), 2.39–2.23 (m, 1H), 2.07–1.84 (m, 1H), 1.68–1.57 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.7, 170.4, 149.2, 138.5, 138.3, 135.0, 130.0, 130.0, 124.0, 123.9, 122.7, 122.1, 118.8, 118.6, 117.4, 117.3, 115.8, 115.7, 115.5, 114.8, 83.0, 82.9, 62.9, 62.0, 62.0, 61.9, 61.6, 46.0, 45.9, 45.8, 37.8, 37.7, 37.4, 29.4, 29.2, 29.0, 27.8, 23.1, 22.8, 22.7, 22.6. HRMS (ESI) m/z calcd for $C_{23}H_{30}N_2O_4Na$ $(M + Na)^+$: 421.2106, found: 421.2103.

3-[2-(2-Iodomethyl-6-oxo-3-vinyl-piperidin-1-yl)ethyl]-indole-1-carboxylic acid *tert*-butyl ester (21)

Compound **20** (20 mg, 0.125 mmol) was dissolved in THF (2 mL) and PPh_3 (50 mg, 0.19 mmol), imidazole (13 mg, 0.19 mmol) and iodine (48 mg, 0.19 mmol) were added and stirred at room temperature for 4 h. The reaction was diluted with CH_2Cl_2, washed with $Na_2S_2O_3$ (20 mL) and H_2O (20 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (heptane → EtOAc/heptane 1 : 3 to 1 : 2) affording compound **21** (50 mg, 78%). R_f 0.80 (CH_2Cl_2/MeOH 9 : 1). FTIR (ATR) 1975, 1731, 1646, 1455, 1373, 1157 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.13 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.35–7.23 (m, 3H), 5.67–5.56 (m, 1H), 5.23–5.10 (m, 2H), 4.20–2.11 (m, 1H), 3.43–3.37 (m, 1H), 3.36–3.29 (m, 1H), 3.16–2.91 (m, 4H), 2.72–2.64 (m, 1H), 2.55–2.36 (m, 2H), 1.95–1.85 (m, 1H), 1.75–1.63 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 149.2, 137.8, 135.0, 129.9, 124.0, 122.7, 122.1, 118.6, 117.2, 116.8, 114.8, 83.0, 60.9, 44.9, 40.9, 29.7, 27.8, 22.9, 22.6, 9.3. HRMS (ESI) m/z calcd for $C_{23}H_{29}IN_2O_3Na$ $(M + Na)^+$: 531.1123, found: 531.1121.

2,4a,5,6,11b,12,13,13a-Octahydro-1*H*-4b,11-diazaindeno[2,1-*a*]phenanthrene-3,11-dicarboxylic acid 11-*tert*-butyl ester 3-ethyl ester (22)

Compound **4** (26 mg, 0.056 mmol) was dissolved in toluene (1 mL) and $POCl_3$ (52 µL, 0.56 mmol) was added. The solution was stirred at 70 °C for 2 h, after which additional $POCl_3$ (27 µL, 0.27 mmol) was added and stirring was continued for another hour at 70 °C. The reaction was concentrated under reduced pressure, the residue was dissolved in EtOH (1 mL) and cooled to 0 °C. $NaBH_4$ (4.2 mg, 0.11 mmol) was added, the reaction was stirred for 10 min at 0 °C, diluted with CH_2Cl_2 (50 mL) and quenched with aqueous $NaHCO_3$ (50 mL). The organic layer was extracted, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 2) affording compound **22** (11.5 mg, 46%) as a viscous oil. R_f 0.63 (EtOAc/heptane 2 : 1). FTIR (ATR) 2933, 1725, 1477, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 8.16 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 7.2 Hz, 1H), 7.29–7.19 (m, 2H), 6.70 (s, 1H), 4.51 (d, J = 10.9 Hz, 1H), 4.21 (q, J = 7.2 Hz, 2H), 3.08–2.95 (m, 2H), 2.87–2.71 (m, 3H), 2.62 (dd, J = 15.8, 4.2 Hz, 1H), 2.39 (t, J = 10.7 Hz, 2H), 2.10–1.97 (m, 3H), 1.90–1.76 (m, 2H), 1.65 (s, 9H), 1.53–1.40 (m, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 149.6, 141.8, 136.4, 136.0, 129.4, 128.8, 123.4, 122.1, 117.4, 115.3, 114.5, 83.1, 63.3, 60.0, 58.2, 36.3, 33.3, 30.8, 27.8, 26.8, 25.8, 25.3, 21.7, 13.8. HRMS (ESI) m/z calcd for $C_{27}H_{34}N_2O_4$ $[M + H]^+$: 451.2599, found: 451.2597.

1,2,4a,5,6,11,11b,12,13,13a-Decahydro-4b,11-diazaindeno[2,1-*a*]phenanthrene-3-carboxylic acid ethyl ester (23)

Compound **23** (4 mg, 20%) was isolated as a side product of the Bischler–Napieralski reaction with compound **4**. R_f 0.54 (EtOAc/heptane 2 : 1). FTIR (ATR) 2919, 1700, 1648, 1255, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.70 (s, 1H), 7.39 (d, J = 7.9 Hz, H), 7.21 (d, J = 7.9 Hz, H), 7.16–7.06 (m, 2H), 6.68 (s, 1H), 4.21 (q, J = 7.2, 7.1 Hz, 2H), 3.62 (ddd, J = 10.4, 4.8, 2.1 Hz, 1H), 3.48 (d, J = 11.4 Hz, 1H), 2.98–2.88 (m, 1H), 2.79 (d, J = 15.5 Hz, 1H), 2.62 (dd, J = 16.1, 5.2 Hz, 1H), 2.45–2.27 (m, 4H), 2.25–2.14 (m, 2H), 2.09–2.02 (m, 1H), 1.82 (dq, J = 12.2, 3.6 Hz, 1H), 1.62–1.33 (m, 3H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.2, 141.6, 136.0, 135.1, 129.5, 127.3, 121.4, 119.4, 118.2, 110.7, 108.4, 64.0, 60.5, 60.4, 45.7, 40.7, 30.3, 30.0, 26.0, 25.0, 22.1, 14.3. HRMS (ESI) m/z calcd for $C_{22}H_{26}N_2O_2$ $[M + H]^+$: 351.2074, found: 351.2073.

Deprotection of 2,4a,5,6,11b,12,13,13a-octahydro-1*H*-4b,11-diazaindeno[2,1-*a*]phenanthrene-3,11-dicarboxylic acid 11-*tert*-butyl ester 3-ethyl ester (23)

Compound **22** (28 mg, 0.056 mmol) was dissolved in a mixture of TFA/CH_2Cl_2 (1 : 4) and stirred at room temperature. After 64 h the solution was concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/heptane 1 : 1) affording compound **23** (13 mg, 55%). R_f 0.21 (EtOAc/heptane 1 : 1).

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