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Syntheses of aza-analogous *iso*-ergoline scaffolds using carbene mediated C–H insertion

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ABSTRACT

A novel direct, flexible, and robust approach to the *iso*-ergoline tetracyclic system in which a five or six-membered ring is established by intramolecular carbene C–H insertion is reported. The protocol involves a two step conversion of an aromatic aldehyde to the corresponding hydrazone and without purification further conversion to the diazo-compound followed by thermal carbene formation and C–H insertion α to a nitrogen.

1. Introduction

The ergot alkaloids first isolated from the parasitic fungus Claviceps, are found as metabolites in several fungi and plants including penicillium and aspergillus. The ergot alkaloids are derivatives of the ergoline ring system (**1**) (Fig. 1) and are divided in three main groups, the clavine type derived from agroclavine (**2**) (Fig. 1), the water-soluble lysergic acid type, and the water-insoluble lysergic acid type or peptide ergot alkaloids. The ergot alkaloids display a diverse spectrum of pharmacological properties, which include central, peripheral, and neurohormonal activity due to binding to adrenergic, dopaminergic, and serotonergic receptor sites.[1] For example, pergolide (**3**) from the clavine group act as a partial agonist at the dopamine receptor and have been used in the treatment of Parkinson's disease.[2] The semi-synthetic ergolines of the lysergic acid type counts members like the hallucinogenic LSD (**4**) but also Lisuride (**5**), which is a drug used in the treatment of Parkinsons disease. The synthetic 7-aza isomeric ergolines represented by compound **6** are potent neuroleptic dopaminergic ligands.[3] We therefore reasoned that the synthesis of the novel 10-aza-isoergoline ring system (**7**, Scheme 1) might give access to pharmaceutically interesting compounds with modified physical chemical-properties, since introduction of an additional nitrogen atom into the ergoline ring system renders the indole part more electron-rich. Moreover, it increases the polar surface area, while decreasing lipophilicity and basicity.

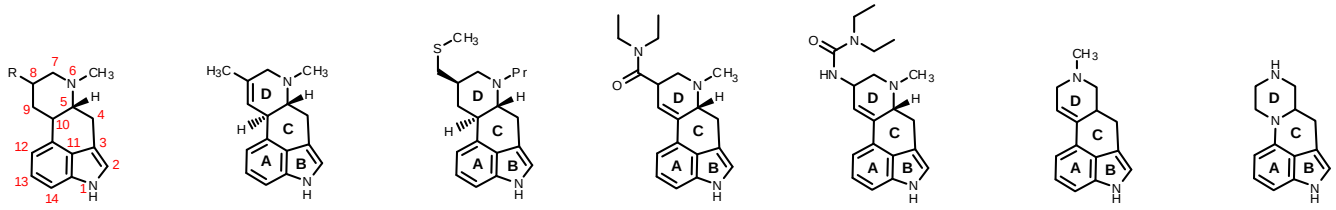

Fig. 1. Different ergolines and analogous structures.

In recent years, the insertion of carbenes into a carbon–hydrogen bond has attracted considerable interest because of its potential for carbon–carbon bond formation. During the last twenty years, one method of modifying the reactivity of the

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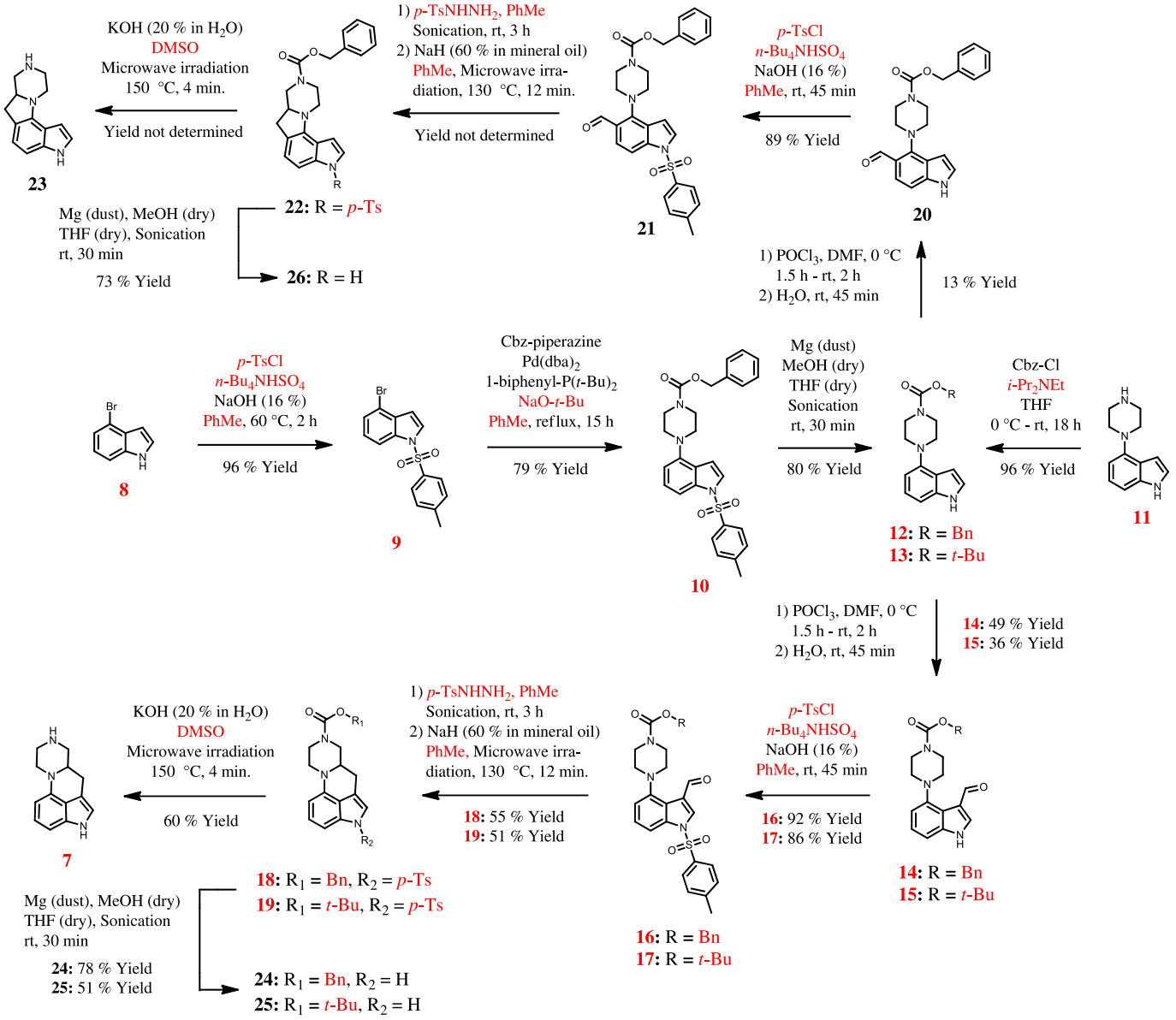


Scheme 1. Synthesis of the novel tetracyclic scaffolds.

carbene, whilst still maintaining its reactivity toward carbon–hydrogen insertion, has been the application of transition metal carbenes, especially rhodium.[4] Thermally generated carbenes were initially considered to be unselective in insertion reactions except when intramolecular cyclisation was favored. In this paper C–H insertion reactions using thermally generated carbenes are applied successfully to intramolecular cyclisation reactions forming five-membered and six-membered rings. Due to its similarity with the bioactive ergolines and presence of the 4-piperazinoindole scaffold in several neuroactive compounds,[5] the novel, tetracyclic *iso*-ergoline derived scaffold may give access to pharmaceutically interesting compounds.

2. Results and discussion

The synthesis of the novel 10-aza-ergolines **7** and **23** is shown in Scheme 1, notably using as a key synthetic-step an intramolecular carbene mediated C–H insertion.

The synthesis starts from 4-bromoindole (**8**), which was first protected by tosylation using phase-transfer conditions to give excellent yields (96%) of 1-tosyl-4-bromoindole **9**.[6] Benzyloxycarbonyl-protected piperazine was then introduced at the 4-position of the indole by cross-coupling using Buchwald–Hartwig palladium catalysis conditions to give compound **10**.[7] All attempts to perform the Buchwald–Hartwig coupling without tosyl protection failed. Good yields could be obtained in the Buchwald–Hartwig coupling, however, strict control of reaction temperature was required for minimisation of an undesired side product resulting from detosylation of product **10** and subsequent coupling with another molecule of substrate **9**. The tosyl group was easily and selectively removed under mild conditions by reduction with magnesium to give the benzyloxycarbonyl protected 4-piperazinoindole **12**.[8] Cbz protection of commercially available 4-piperazinoindole **11** offered a simple one-pot synthesis of compound **12**, but due to the commercial price of compound **11**, the alternative route starting from less expensive 4-bromoindole **8** was used. Formylation of the 3-position of piperazinoindole **12** was accomplished using Vilsmeier–Haack conditions to give the indole aldehyde **14**.[9] Detosylation prior to formylation was essential, since it was not possible to formylate the tosyl protected **10**. Although

both the 5- and 7-position in piperazinoindole **12** are activated toward electrophilic attack the 3-formyl isomer **14** was the main product.

Highly reactive carbenes are generated in situ from a precursor, most often a diazo compound.[10] The synthetic protocols for the preparation of diazo compounds are numerous, but a common procedure involves conversion of a ketone or an aldehyde to the corresponding tosylhydrazone, followed by deprotonation and thermal elimination of sulfinate to yield the diazo compound.[10] In our case, the respective tosylhydrazone intermediates were prepared by sonication in toluene of a mixture of either aldehyde **16** or aldehyde **21** and tosylhydrazide.[11] After drying ($MgSO_4$) and filtration, the corresponding tosylhydrazones were used directly without further purification to form the diazo intermediates by deprotonation using sodium hydride followed by heating using microwave irradiation to 135 °C. Further heating at 135 °C led to the in situ generation of the carbene by thermal decomposition of the diazo compound. The carbene reacted selectively with C–H insertion into the piperazine fragment. We observed that purification of the intermediary hydrazones by recrystallisation did not improve overall yields, therefore, the isolation and purification of intermediates was omitted. The tetracyclic compound **18** was deprotected by exposure to microwave irradiation at 150 °C for 4 min in a solution of KOH in DMSO and H_2O.[12] In the same fashion the regioisomeric 5-formyl compound **20** could be converted to the tetracyclic structure **22**, however, C–H insertion leads to a five-membered ring in this case. Moreover, the deprotected derivatives **23** and **26** turned out to be more unstable than **7**, and decomposed over time. Notably, the diprotected tetracyclic structures **22** and **18** could also be selective detosylated under similar conditions as described for compound **10**. The Cbz protection group could be replaced with the Boc group without significant decrease in yields. In this case Boc-protected 4-piperazinoindole (**13**), which is commercially available, was used as starting material.

The novel aza-ergoline **7** was characterized using ^{1}H, ^{13}C, ^{13}C-APT, COSY, HSQC, and HMBC. Notably, the normally symmetrical signal from protons of unsubstituted piperazines was significantly distorted reflecting the presence of a chiral centre and pronounced conformational restriction of the molecule (Fig. 2).

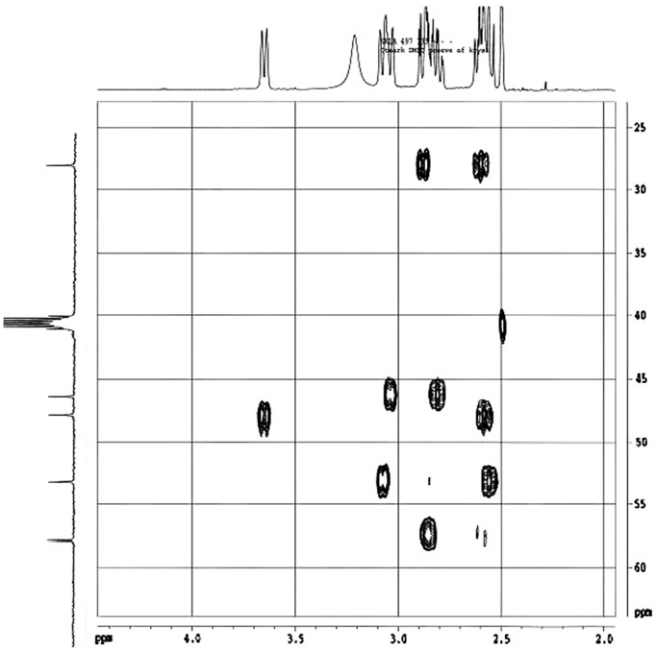
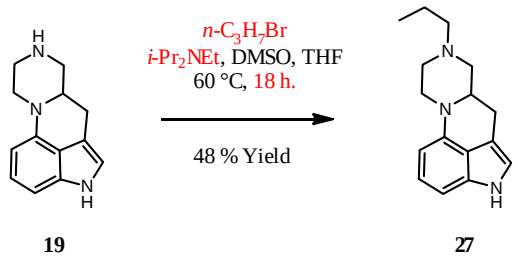


Fig. 2. The aliphatic area of the HSQC spectrum of compound **7**.

An attempt to provide structural confirmation by X-ray crystallography of compound **7** failed since a suitable crystal could not be prepared. Instead, the aza-ergoline **7** was converted to the *n*-propyl derivative **27** (Scheme 2), which after enantiomeric separation by chiral HPLC afforded a suitable crystal X-ray crystallography confirmed the structure of compound **27** (Fig. 3).



Scheme 2. Synthesis of the *n*-propyl derivative **27** from compound **7**.

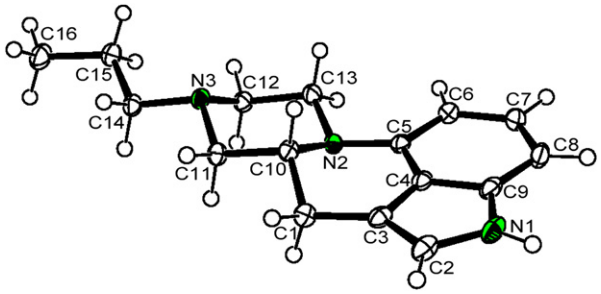


Fig. 3. Perspective drawing (ORTEP)[13] of the tetracyclic compound **27** determined by X-ray crystallography. CCDC 783989.

3. Conclusion

In conclusion, the synthesis of a novel, tetracyclic *iso*-ergoline analogue **7** has been developed. The key step is a quick, versatile carbene mediated intramolecular C–H insertion alpha to a nitrogen atom. No purification of the intermediates is needed, when the tetracyclic structure is generated from aldehyde **16** or **17** as substrates. The carbene mediated C–H insertion step is sufficiently robust to tolerate microwave irradiation at elevated temperatures (135 °C in toluene for 10 min).

4. Experimental section

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance AV-500 at 500 MHz for H nuclei and 125 MHz for C nuclei. Microwave-assisted reactions were performed using the following instruments: Emrys Optimizer (300 w), Emrys Synthesizer (300 w), Biotage Initiater (400 w) and Biotage Advancer (300 w). The solvents applied were deuterated chloroform ($CDCl_3$), DMSO ($(CD_3)_2SO$), methanol (CD_3OD) or water (D_2O). Tetramethylsilane (TMS) was used as internal reference in the chloroform and DMSO. In case of CD_3OD and D_2O the residual solvent peak was used as reference. Multiplicities of ^{1}H NMR signals are given as follows: s, singlet; br s, broad singlet; m(s), multiplet that appears as a singlet; d, doublet; br d, broad doublet; t, triplet; q, quartet; quin, quintet; se, sextet; h, heptet; o, octet; n, nonet. The purification by chromatography were performed either manually or using one of the following instruments: FlashMasterII (FM) from JonesChromatography with

prepacked IST (international sorbent technology) columns, ISCO Companion 4X (ISCO), Reactions and product mixtures were analyzed by thin layer chromatography (TLC) on silica gel precoated 0.25 mm silica gel plates and visualized under UV light or by use of an analytical LC–MS system. LC–MS spectra were recorded on either a Sciex API150ex or Sciex API300 apparatus. In-house HRMS spectra were recorded on an Agilent/Bruker Daltonics LC-SPE-MS apparatus.

4.2. General procedure for formylation of the indole (method A)

Compound **12** (9.20 g, 27.4 mmol) was dissolved in DMF (30 mL), purged with and placed under argon, and cooled to 0 °C. $POCl_3$ (2.80 mL, 30.0 mmol) was added dropwise under argon to the reaction mixture over 15 min. The mixture was left at 0 °C for 1.5 h and then stirred at room temperature for another 1 h. Additional $POCl_3$ (0.28 mL, 3.00 mmol) was added and the reaction mixture stirred at room temperature for 1 h. To the reaction mixture was slowly added water (12 mL) and the mixture stirred at room temperature for 45 min. The mixture was then carefully poured into a large separation funnel and added a mixture of Et_2O (400 mL), satd $NaHCO_3$ (200 mL), and ice (handful) (Warning! Quenching of $POCl_3$ can be violent). The aqueous phase was extracted with Et_2O (200 mL). The combined organic phases were washed with brine/water (1:1) (200 mL), brine (200 mL), dried over $MgSO_4$, filtered, concentrated in vacuo on Celite, and purified by flash chromatography (ISCO).

4.3. General procedure for formylation of the indole (method B)

DMF (10 mL) was cooled to 0 °C and dropwise added $POCl_3$ (3.71 mL, 39.8 mmol). The mixture was then stirred at room temperature for 30 min. In another flask **13** (10 g, 33.1 mmol) was dissolved in DMF (25 mL), cooled to 0 °C, an argon atmosphere applied, and dropwise added the solution containing the preformed formamidinium chloride for 15 min. The mixture was stirred at 0 °C for 2 h. To the mixture was added carefully 2 M NaOH (15 mL) and the mixture stirred at room temperature for 30 min. The mixture was transferred to a large separation funnel containing EtOAc (200 mL), satd $NaHCO_3$ (200 mL), and ice (handful) (Warning! Quenching of $POCl_3$ can be violent). After the gas production had ceased Et_2O (400 mL) was added. The aqueous phase was re-extracted with Et_2O (200 mL). The combined organic phases were washed twice with brine/water (1:1) (200 mL), brine (200 mL), dried over $MgSO_4$, filtered, and purified by flash chromatography (ISCO).

4.4. General procedure for magnesium assisted detosylation of the indole (method C)

p-Tosylindole (2.50 mmol) was dissolved in dry THF (5 mL), added dry MeOH (15 mL), cooled to 0 °C, and added magnesium powder (300 mg, 12.3 mmol). The mixture was removed from the ice-bath and sonicated for 30 min. During the first 15 min the mixture was removed several times from the sonification and placed in an ice-bath for short periods of time due to a raise in the temperature that caused reflux of the solvent. The mixture was filtered through Celite and concentrated in vacuo (concentration stopped before white gel formation). The reaction mixture was transferred to a separation funnel containing 0.1 M HCl (100 mL) and Et_2O (100 mL). The aqueous phase was extracted three times with Et_2O (75 mL). The combined organic phases were washed with satd $NaHCO_3$ (150 mL), brine (150 mL), dried over $MgSO_4$, filtered, and purified by flash chromatography (FM).

*4.4.1. 6,6a,7,8,9,10-Hexahydro-4H-pyrazino[1,2-a]pyrrolo[4,3,2-de] quinoline (**7**).* Compound **18** (245 mg, 0.49 mmol) was dissolved in DMSO (3 mL) and 20% KOH (1.5 mL) added. The mixture was heated using microwave irradiation at 150 °C for 4 min and then added a large amount of EtOAc (300 mL). The organic phase was washed with a combination of satd NH_4Cl (75 mL) and satd $NaHCO_3$ (75 mL), then twice with brine (150 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The pale light-brown solid was further dried at 60 °C in high vacuum to give 63 mg (60%) of an amorphous solid. LC–MS: UV=100% (t_R=0.29 min), ELS=100% (t_R=0.35 min), m/z=214.1 (100%) (t_R=0.34 min, ESI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.53–2.64 (3H, m), 2.77–2.91 (3H, m), 3.01–3.11 (2H, m), 3.2 (1H, br s), 3.65 (1H, dm, J=12 Hz), 6.18 (1H, d, J=8 Hz), 6.69 (1H, d, J=8 Hz), 6.77 (1H, m), 6.88 (1H, t, J=8 Hz), 10.49 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 27.7, 45.3, 46.7, 52.2, 56.8, 97.8, 101.9, 107.7, 115.4, 117.7, 122.9, 134.0, 142.4. HRMS: ($M+H^+$: $C_{13}H_{16}N_3$) calculated: 214.1339, found: 214.1341, deviation: 0.9 ppm. TLC: R_f=0.32 (EtOAc/MeOH: TEA, 3:2:1) (Excessive heating of TLC plate results in a black spot).

*4.4.2. 4-Bromo-1-(toluene-4-sulfonyl)-1H-indole (**9**).* Compound **8** (14.8 g, 75.2 mmol), *p*-tosyl chloride (17.2 g, 90.2 mmol), and tetrabutylammonium hydrogensulfate (1.25 g, 3.69 mmol) were dissolved in toluene (90 mL) and 28% NaOH (90 mL) and water (30 mL) added. The mixture was stirred for 10 min at room temperature before the temperature was raised to 60 °C for 2.5 h. The mixture was stirred vigorously through the entire reaction period. The reaction mixture was then diluted with toluene (400 mL) and water (250 mL) and the phases were separated. The organic phase was washed with water (250 mL), brine (250 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The brownish solid was crystallised from EtOAc and a small amount of MeOH with heptane to yield 23.4 g (89%) of slightly off white solid. LC–MS: UV=100% (t_R=1.84), ELS=100% (t_R=1.90), m/z=351.4 (95%)/349.1 (100%) (t_R=1.89 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.35 (3H, s), 6.72 (1H, d, J=3.5 Hz), 7.17 (1H, t, J=8 Hz), 7.24 (2H, t, J=9 Hz), 7.38 (1H, d, J=7.5 Hz), 7.62 (1H, d, J=3.5 Hz), 7.75 (2H, d, J=8 Hz), 7.94 (1H, d, J=8.5 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 22.0, 109.2, 113.0, 115.4, 125.9, 126.6, 127.3, 130.4, 131.8, 135.4, 145.8. TLC: R_f=0.32 (EtOAc/heptane, 1:10).

*4.4.3. Benzyl 4-[1-(toluene-4-sulfonyl)-1H-indol-4-yl]-piperazine-1-carboxylate (**10**).* Compound **9** (2.01 g, 5.74 mmol), benzyl (1-piperazinyl)carboxylate (1.27 mL, 6.58 mmol), and sodium *tert*-butylate (680 mg, 7.07 mmol) were suspended in toluene (20 mL) and argon was bubbled through the suspension for 20 min. $Pd(dba)_2$ (125 mg, 0.22 mmol) and 1-biphenyl-P(t-Bu)$_2$ (117 mg, 0.39 mmol) were added and suspension purged with argon for another 10 min before the vial (35 mL capacity) was sealed and heated to 85 °C for 18 h. The yellow/reddish suspension was filtered through a plug of Celite®. The vial was washed three times with EtOAc (20 mL), which were afterward passed through the plug. The solution was concentrated in vacuo, dissolved in acetone, pre-adsorbed on Celite® (545 coarse) in vacuo and purified by flash chromatography (FM) to yield 2.21 g (79%) of light brownish foam. LC–MS: UV=100% (t_R=1.88 min), ELS=100% (t_R=1.94), m/z=490.5 (t_R=1.92 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.33 (3H, s), 3.08 (4H, m), 3.70 (4H, m), 5.16 (2H, s), 6.65 (1H, d, J=5 Hz), 6.70 (1H, d, J=8 Hz), 7.20 (3H, m), 7.30–7.40 (5H, m), 7.54 (1H, d, J=4 Hz), 7.67 (1H, d, J=9 Hz), 7.75 (2H, m). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 21.5, 44.1, 52.4, 67.3, 106.9, 108.4, 111.0, 124.3, 125.1, 125.4, 126.9, 128.0, 128.1, 128.5, 129.9, 135.2, 135.9, 136.6, 145.0, 145.7, 155.3. HRMS: ($M+H^+$: $C_{27}H_{28}N_3O_4S$) calculated: 490.1795, found: 490.1803, deviation: 1.6 ppm. ($M+Na^+$: $C_{27}H_{27}N_3NaO_4S$) calculated: 512.1615, found: 512.1636, deviation: 4.1 ppm. TLC: R_f=0.42 (EtOAc/heptane, 1:1).

*4.4.4. Benzyl 4-(1H-indol-4-yl)-piperazine-1-carboxylate (**12**).* Prepared using *method C*. Clear, colorless oil (658 mg, 80%).

Alternative method: 4-piperazin-1-yl-1*H*-indole dihydrochloride **11** (8.00 g, 29.2 mmol) was dissolved in THF (120 mL), added *i*-Pr_2NEt (16.5 mL, 94.7 mmol), purged with and placed under argon, and cooled to 0 °C. Cbz-Cl (4.6 mL, 32.2 mmol) was dropwise added for 15 min. The reaction mixture was left in an ice-bath for another 15 min before being removed and stirred at room temperature for 18 h. The reaction mixture was added Et_2O (150 mL) and wash with satd $NaHCO_3$ (150 mL). The aqueous phase was re-extracted with Et_2O (150 mL) and the combined organic phases were washed with brine (250 mL), dried over $MgSO_4$, filtered, pre-adsorbed on SiO_2 in vacuo, and purified by flash chromatography (ISCO) to yield 9.23 g (94%) of clear, colorless oil. LC–MS: UV=100% (t_R=1.14), ELS=100% (t_R=1.20), *m*/*z*=336.6 (t_R=1.19 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 3.18 (4H, br s), 3.74 (4H, br t, *J*=5 Hz), 5.18 (2H, s), 6.50 (1H, m), 6.56 (1H, dm, *J*=8 Hz), 7.06 (1H, dm, *J*=8 Hz), 7.10 (1H, t, *J*=8 Hz), 7.11 (1H, t, *J*=3 Hz), 7.3–7.4 (5H, m), 8.33 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 44.2, 51.0, 67.2, 100.4, 106.5, 106.7, 121.2, 122.3, 123.1, 127.8, 128.0, 128.5, 136.5, 136.9, 145.1, 155.4. HRMS: (M^+: $C_{20}H_{21}N_3O_2$) calculated: 335.1628, found: 335.1631, deviation: 0.9 ppm. ($M+H^+$: $C_{20}H_{22}N_3O_2$) calculated: 336.1707, found: 336.1701, deviation: 1.8 ppm. ($M+Na^+$: $C_{20}H_{21}N_3NaO_2$) calculated: 358.1526, found: 358.1532, deviation: 1.7 ppm. TLC: R_f=0.30 (EtOAc/heptane, 1:2).

*4.4.5. Benzyl 4-(3-formyl-1H-indol-4-yl)-piperazine-1-carboxylate (**14**).* Prepared using *method A*. Clear, colorless oil/foam (4.49 g, 12.36 mmol, 45%). LC–MS: UV=99.1% (t_R=0.75), ELS=100% (t_R=0.80), *m*/*z*=364.7 (100%) (t_R=0.80 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.9–3.2 (4H, br s), 3.3–4.2 (4H, vbr s), 5.18 (2H, s), 6.91 (1H, dd, *J*=7 Hz, 2 Hz), 7.18–23 (2H, m), 7.3–7.4 (5H, m), 7.94 (1H, d, *J*=3 Hz), 9.49 (1H, br s), 10.50 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 44.1, 52.3, 67.4, 108.8, 112.1, 119.1, 119.9, 124.2, 127.9, 128.2, 128.6, 131.9, 136.5, 138.4, 147.0, 155.5, 187.5. HRMS: ($M+H^+$: $C_{21}H_{22}N_3O_3$) calculated: 364.1656, found: 364.1654, deviation: 0.6 ppm. ($M+Na^+$: $C_{21}H_{21}N_3NaO_3$) calculated: 386.1475, found: 386.1488, deviation: 3.4 ppm. TLC: R_f=0.30 (EtOAc/heptane, 1:2).

*4.4.6. Benzyl 4-(3-formyl-1H-indol-4-yl)-piperazine-1-carboxylate (**15**).* Prepared using *method B*. Clear, colorless oil/foam (36%). LC–MS: UV=99.5% (t_R=0.66 min), ELS=100% (t_R=0.72 min), *m*/*z*=330.4 (100%), 274.4 (81%), 230.6 (52%) (t_R=0.74 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 1.49 (9H, s), 2.9–3.2 (4H, br s), 3.2–4.2 (4H, br s), 6.92 (1H, m), 7.18–7.24 (2H, m), 7.95 (1H, d, *J*=3 Hz), 9.75 (1H, br s), 10.51 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 28.5, 43.4, 44.4, 52.2, 80.2, 108.7, 111.9, 118.9, 119.9, 124.1, 132.2, 138.5, 147.0, 155.0, 187.5. HRMS: ($M+H^+$: $C_{18}H_{23}N_3O_3$) calculated: 330.1812, found: 330.1819, deviation: 2.20 ppm. TLC: R_f=0.10 (EtOAc/heptane, 1:1).

*4.4.7. Benzyl 4-[3-formyl-1-(toluene-4-sulfonyl)-1H-indol-4-yl]-piperazine-1-carboxylate (**16**).* Compound **14** (450 mg, 1.19 mmol), *p*-tosyl chloride (300 mg, 1.57 mmol), and benzyltriethylammonium chloride (20 mg, 0.09 mmol) were dissolved in toluene (10 mL) and water (5 mL) and NaOH (28%) (5 mL) added. The mixture was stirred vigorously for 45 min at room temperature. The mixture was then diluted with EtOAc (50 mL) and poured into water (50 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered, pre-adsorbed on Celite® (545 coarse) in vacuo, and purified by flash chromatography (FM) to yield 563 mg (92%) of clear colorless oil/white foam. LC–MS: UV=98.9% (t_R=1.51), ELS=100% (t_R=1.57), *m*/*z*=518.5 (100%) (t_R=1.56 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.36 (3H, s), 2.99 (4H, br s), 3.0–4.6 (4H, vbr s), 5.16 (2H, s), 6.99 (1H, d, *J*=8 Hz), 7.25–7.38 (8H, m), 7.75 (1H, d, *J*=8 Hz), 7.84 (2H, d, *J*=9 Hz), 8.31 (1H, s), 10.60 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 21.5, 43.8, 52.3, 67.1, 109.7, 114.6, 121.90, 121.93, 126.2, 127.2, 127.8, 128.0, 128.4, 130.2, 130.5, 134.1, 136.2, 136.5, 146.0, 147.3, 155.1, 187.4. HRMS: ($M+H^+$: $C_{28}H_{28}N_3O_5S$) calculated: 518.1744, found: 518.1728, deviation: 2.9 ppm. ($M+Na^+$: $C_{28}H_{27}N_3NaO_5S$) calculated: 540.1564, found: 540.1556, deviation: 1.5 ppm TLC: R_f=0.31 (EtOAc/heptane, 1:1).

*4.4.8. tert-Butyl 4-(3-formyl-1-tosyl-1H-indol-4-yl)piperazine-1-carboxylate (**17**).* Compound **15** (1.29 g, 3.90 mmol), *p*-tosyl chloride (855 mg, 4.49 mmol), and benzyltriethylammonium chloride (60 mg, 0.26 mmol) were dissolved in toluene (20 mL) and added water (10 mL) and NaOH (28%) (10 mL). The mixture was stirred vigorously for 45 min at room temperature. The mixture was then diluted with EtOAc (100 mL) and poured into water (100 mL). The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, pre-adsorbed on Celite® (545 coarse) in vacuo, and purified by flash chromatography (FM) to yield 1.62 g (86%) of clear oil/white foam. LC–MS: UV=99.4% (t_R=1.36 min), ELS=100% (t_R=1.41 min), *m*/*z*=484.3 (79%), 428.2 (40%), 384.4 (100%) (t_R=1.43 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 1.48 (9H, s), 2.38 (3H, s), 2.99 (4H, br s), 3.0–4.5 (4H, vbr s), 7.01 (1H, d, *J*=8 Hz), 7.26–7.35 (3H, m), 7.75 (1H, d, *J*=9 Hz), 7.84 (2H, d, *J*=8 Hz), 8.31 (1H, s), 10.61 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 21.8, 28.5, 43.5, 44.3, 52.6, 80.1, 109.8, 114.7, 122.1, 122.2, 126.3, 127.4, 130.37, 130.44, 134.4, 136.4, 146.2, 147.7, 154.8, 187.9. HRMS: ($M+H^+$: $C_{25}H_{29}N_3O_5S$) calculated: 484.1901, found: 484.1896, deviation: 1.04 ppm. TLC: R_f=0.37 (EtOAc/heptane, 1:1).

*4.4.9. Benzyl 4-(toluene-4-sulfonyl)-4,6,6a,7,9,10-hexahydro-4,8,10a-triaza-acephenanthrylene-8-carboxylate (**18**).* Compound **16** (540 mg, 1.04 mmol) and *p*-tosylhydrazide (200 mg, 1.07 mmol) were suspended in toluene (15 mL). The mixture was subjected to sonication for 3 h at room temperature. To the reaction mixture was added $MgSO_4$ and after 15 min filtered. The resulting solution was transferred to a microwave vial and toluene added to a total volume of 20 mL. NaH (60%) (44 mg, 1.10 mmol) was then added carefully and the mixture purged with argon for 30 min until gas formation had ceased. The vial was sealed and heated using microwave irradiation for 12 min at 130 °C. The resulting thick suspension was transferred to a separation funnel with EtOAc (100 mL) and satd $NaHCO_3$ (100 mL). The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, pre-adsorbed on Celite® (545 coarse) in vacuo and purified by flash chromatography (FM) to yield 285 mg (54%) of white foam. LC–MS: UV=100% (t_R=1.84 min), ELS=100% (t_R=1.90 min), *m*/*z*=502.5 (100%) (t_R=1.88 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.33 (3H, s), 2.6–3.2 (6H, br m), 3.73 (1H, br m), 4.15–4.35 (2H, br m), 5.15 (2H, s), 6.47 (1H, m), 7.06 (1H, br s), 7.19 (3H, m), 7.3–7.4 (6H, m), 7.74 (2H, d, *J*=9 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 22.0, 27.0, 43.7, 46.4, 49.5, 55.6, 67.8, 104.3, 105.4, 115.5, 117.5, 120.3, 127.2, 128.4, 128.6, 129.0, 130.2, 134.5, 136.0, 136.9, 142.2, 145.1, 155.3. HRMS: ($M+H^+$: $C_{28}H_{28}N_3O_4S$) calculated: 502.1795, found: 502.1772, deviation: 4.6 ppm; ($M+Na^+$: $C_{28}H_{27}N_3NaO_4S$) calculated: 524.1615, found: 524.1610, deviation: 1.0 ppm. TLC: R_f=0.40 (EtOAc/heptane, 1:1).

*4.4.10. tert-Butyl 4-tosyl-6a,7,9,10-tetrahydro-4H-pyrazino[1,2-a]pyrrolo[4,3,2-de]quinoline-8(6H)-carboxylate (**19**).* Compound **17** (498 mg, 1.03 mmol) and *p*-tosylhydrazide (200 mg, 1.07 mmol) were suspended in toluene (15 mL). The reaction mixture was subjected to sonication for 3 h at room temperature. To the reaction mixture was added $MgSO_4$ and after 15 min filtered. The resulting solution was transferred to a microwave vial and toluene added to a total volume of 20 mL. NaH (60%) (45 mg, 1.13 mmol) was then added carefully and the mixture purged with argon for 30 min until gas formation had ceased. The vial was sealed and heated using microwave irradiation for 12 min at 130 °C. The resulting thick suspension was transferred to a separation funnel with EtOAc

(100 mL) and satd $NaHCO_3$ (100 mL) The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, pre-adsorbed on Celite® (545 coarse) in vacuo, and purified by flash chromatography (FM) to yield 246 mg (51%) of white foam. LC–MS: UV=97.5% (t_R=1.81 min), ELS=100% (t_R=1.87 min), m/z=467.2 (5%), 412.4 (29%), 368.4 (100%) (t_R=1.87 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 1.47 (9H, s), 2.31 (3H, s), 2.65 (1H, ddd, J=16, 11, 2 Hz), 2.72 (1H, dt, J=12, 3 Hz), 2.65–2.88 (1H, m), 2.88–3.18 (3H, m), 3.70 (1H, dm, J=12 Hz), 4.00–4.38 (2H, br s), 6.47 (1H, d, J=8 Hz), 7.05 (1H, d, J=1 Hz), 7.15–7.21 (3H, m), 7.36 (1H, d, J=9 Hz), 7.74 (2H, d, J=9 Hz). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 21.6, 26.7, 28.5, 42.7, 43.7, 46.1, 48.7, 49.5, 55.3, 80.3, 103.9, 105.0, 115.4, 117.1, 120.0, 126.8, 129.8, 134.2, 135.6, 142.1, 144.7, 154.4. HRMS: ($M+H^+$: $C_{25}H_{29}N_3O_4S$) calculated: 468.1952, found: 468.1939, deviation: 2.63 ppm. TLC: R_f=0.41 (EtOAc/heptane, 1:1).

*4.4.11. Benzyl 4-(5-formyl-1H-indol-4-yl)-piperazine-1-carboxylate (**20**).* Prepared using *method A*. Slight greenish oil/foam (1.34 g, 3.69 mmol, 13%). LC–MS: UV=97.6% (t_R=1.29), ELS=100% (t_R=1.35), m/z=364.8 (100%) (t_R=1.34 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 3.39 (4H, br s), 3.72 (4H, br s), 5.20 (2H, s), 6.75 (1H, m), 7.19 (1H, d, J=9 Hz), 7.21 (1H, t, J=3 Hz), 7.31–7.42 (5H, m), 7.71 (1H, d, J=9 Hz), 9.11 (1H, br s), 10.53 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 44.7, 53.6, 67.5, 103.6, 108.6, 122.7, 122.8, 123.3, 124.9, 128.0, 128.2, 128.6, 136.6, 141.3, 150.6, 155.5, 191.9. HRMS: ($M+H^+$: $C_{21}H_{22}N_3O_3$) calculated: 364.1656, found: 364.1646, deviation: 2.7 ppm. ($M+Na^+$: $C_{21}H_{21}N_3NaO_3$) calculated: 386.1475, found: 386.1466, deviation: 2.3 ppm. TLC: R_f=0.26 (EtOAc/heptane, 1:1).

*4.4.12. Benzyl 4-(5-formyl-1-tosyl-1H-indol-4-yl)piperazine-1-carboxylate (**21**).* Compound **20** (1.34 g, 3.68 mmol), *p*-tosyl chloride (813 mg, 4.26 mmol), and benzyltriethylammonium chloride (60 mg, 0.26 mmol) were dissolved in toluene (20 mL) and water (10 mL) and NaOH (28%) (10 mL) added. The mixture was stirred vigorously for 45 min at room temperature. The mixture was then diluted with EtOAc (100 mL) and poured into water (100 mL). The organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, pre-adsorbed on Celite® (545 coarse) in vacuo, and purified by flash chromatography (FM) to yield 1.70 g (89%) of yellow foam. LC–MS: UV=95% (t_R=1.78 min), ELS=100% (t_R=1.83 min), m/z=518.5 (100%) (t_R=1.82 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.37 (3H, s), 3.30(4H, br s), 3.69 (4H, br s), 5.18 (2H, s), 6.86 (2H, d, J=4 Hz), 7.25–7.29 (2H, m), 7.31–7.41 (5H, m), 7.61 (1H, d, J=4 Hz), 7.76–7.83 (4H, m), 10.46 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 44.5, 53.5, 67.4, 108.2, 110.0, 125.8, 126.0, 126.2, 126.4, 127.1, 128.1, 128.2, 128.6, 130.2, 134.8, 136.6, 139.4, 145.7, 149.3, 155.3, 191.1. HRMS: ($M+H^+$: $C_{28}H_{28}N_3O_5S$) calculated: 518.1744, found: 518.1723, deviation: 4.1 ppm. ($M-Na^+$: $C_{28}H_{27}N_3NaO_5S$) calculated: 540.1564, found: 540.1546, deviation: 3.3 ppm. TLC: R_f=0.38 (EtOAc/heptane, 1:1).

*4.4.13. 3,6,6a,7,9,10-Hexahydro-3,8,10a-triaza-cyclopenta[c]fluorene-8-carboxylic acid benzyl ester (**22**).* Prepared as described for compound **18**. HRMS: ($M+H^+$: $C_{28}H_{28}N_3O_4S$) calculated: 502.1795, found: 502.1774, deviation: 4.2 ppm. ($M+Na^+$: $C_{28}H_{27}N_3NaO_4S$) calculated: 524.1615, found: 524.1609, deviation: 1.1 ppm.

*4.4.14. 6,6a,7,8,9,10-Hexahydro-3H-3,8,10a-triaza-cyclopenta[c]fluorine (**23**).* Prepared as described for compound **7**. HRMS: ($M+H^+$: $C_{13}H_{16}N_3$) calculated: 214.1339, found: 214.1344, deviation: 2.3 ppm. Unstable compound that could not be characterized.

*4.4.15. Benzyl 6a,7,9,10-tetrahydro-4H-pyrazino[1,2-a]pyrrolo[4,3,2-de]quinoline-8(6H)-carboxylate (**24**).* Prepared using *method C*. Clear, colorless oil (78%) LC–MS: UV=93.6% (t_R=1.20 min), ELS=100% (t_R=1.25 min), m/z=348.2 (100%) (t_R=1.24 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.64 (1H, m), 2.94–3.08 (2H, m), 3.08–3.22 (2H, m), 3.44 (1H, m), 4.05–4.35 (3H, m), 5.17 (2H, s), 6.48 (1H, br s), 6.73 (1H, d, J=8 Hz), 6.95 (1H, d, J=8 Hz), 7.02 (1H, t, J=3 Hz), 7.28–7.38 (5H, m), 8.23 (1H, br s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 33.2, 43.8, 44.0, 46.8, 48.1, 48.3, 63.9, 67.8, 99.1, 101.7, 113.5, 117.2, 119.7, 123.7, 128.4, 128.6, 129.0, 137.1, 138.3, 143.1, 155.9. HRMS: ($M+H^+$: $C_{21}H_{21}N_3O_2$) calculated: 348.1707, found: 348.1698, deviation: 2.37 ppm. TLC: R_f=0.37 (EtOAc/heptane, 1:1).

*4.4.16. tert-Butyl 6a,7,9,10-tetrahydro-4H-pyrazino[1,2-a]pyrrolo[4,3,2-de]quinoline-8(6H)-carboxy-late (**25**).* Prepared using *method C*. Clear, colorless oil (76%). LC–MS: UV=97.9% (t_R=1.32 min), ELS=100% (t_R=1.37 min), m/z=314.3 (10%), 258.5 (31%), 214.2 (100%) (t_R=1.39 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 1.53 (9H, s), 2.77–2.99 (3H, m), 3.00–3.27 (3H, m), 3.82 (1H, dm, J=12 Hz), 4.03–4.45 (2H, br m), 6.37 (1H, d, J=8 Hz), 6.71 (1H, s), 6.82 (1H, d, J=8 Hz), 7.11 (1H, t, J=8 Hz), 8.10 (1H, br s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 27.1, 28.5, 42.8, 43.9, 46.3, 48.9, 49.9, 56.1, 80.1, 99.3, 102.5, 108.6, 115.4, 118.0, 124.0, 134.4, 141.8, 154.7. HRMS: ($M+H^+$: $C_{18}H_{23}N_3O_2$) calculated: 314.1863, found: 314.1855, deviation: 2.67 ppm. TLC: R_f=0.48 (EtOAc/heptane, 1:1).

*4.4.17. 3-(Toluene-4-sulfonyl)-3,6,6a,7,9,10-hexahydro-3,8,10a-triaza-cyclopenta[c]fluorene-8-carboxylic acid benzyl ester (**26**).* Prepared using *method C*. Clear, colorless oil (73%). LC–MS: UV=94% (t_R=1.20 min), ELS=100% (t_R=1.24 min), m/z=348.2 (100%), 304.3 (24%), 257.7 (31%), 214.2 (57%) (t_R=1.24 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 2.64 (1H, m), 2.93–3.22 (4H, m), 3.44 (1H, m), 4.02–4.35 (3H, m), 5.17 (2H, s), 6.48 (1H, m), 6.73 (1H, d, J=8 Hz), 6.95 (1H, d, J=8 Hz), 7.02 (1H, dd, J=3 Hz, 3 Hz), 7.28–7.39 (5H, m). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 33.2, 43.8, 44.0, 46.8, 48.1, 48.3, 63.9, 67.8, 99.1, 101.7, 113.5, 117.2, 119.7, 123.7, 128.4, 128.6, 129.0, 137.1, 138.3, 143.1, 155.9. HRMS: ($M+H^+$: $C_{21}H_{21}N_3O_2$) calculated: 348.1707, found: 348.1723, deviation: 4.79 ppm. TLC: R_f=0.37 (EtOAc/heptane, 1:2).

*4.4.18. 8-Propyl-6,6a,7,8,9,10-hexahydro-4H-pyrazino[1,2-a]pyrrolo[4,3,2-de]quinoline (**27**).* Compound **7** (120 mg, 0.56 mmol) was dissolved in THF (3 mL) and DMSO (3 mL). To the solution was added *i*-Pr_2NEt (120 μL, 0.69 mmol) and *n*-propylbromide (65 μL, 0.72 mmol). The reaction mixture was heated to 60 °C and stirred for 18 h. The mixture was transferred to a separation funnel containing EtOAc (75 mL) and satd $NaHCO_3$ (50 mL). The phases were separated and the organic phase was washed with brine (50 mL), dried over $MgSO_4$, concentrated in vacuo, and purified using flash chromatography (FM) to yield 69 mg of a pale white, glassy oil (48%). The enantiomers were separated using an SFC system. LC–MS: UV=99.4% (t_R=0.35 min), ELS=100% (t_R=0.37 min), m/z=255.9 (100%) (t_R=0.40 min, APPI, ($M+H^+$)). ^1H NMR: (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J=7 Hz), 1.49 (2H, se, J=8 Hz), 1.94 (1H, t, J=11 Hz), 2.15 (1H, dt, J=12, 3 Hz), 2.29 (2H, t, J=7 Hz), 2.67 (2H, m), 2.9–3.1 (4H, m), 3.70 (1H, dm, J=12 Hz), 6.19 (1H, d, J=8 Hz), 6.69 (1H, d, J=9 Hz), 6.78 (1H, m), 6.88 (1H, t, J=8 Hz), 10.50 (1H, s). ^{13}C NMR: (125 MHz, $CDCl_3$) δ: 11.8, 19.5, 27.1, 45.9, 52.5, 56.1, 59.7, 59.8, 98.0, 102.0, 107.7, 115.5, 117.8, 122.9, 134.0, 142.0. HRMS: ($M+H^+$: $C_{16}H_{22}N_3$) calculated: 256.1808, found: 256.1812, deviation: ppm. TLC: R_f=0.28 (EtOAc/heptane: TEA, 12:8:1). X-ray crystallography: crystal data: $C_{16}H_{21}N_3$, M_r=255.36, orthorhombic, space group $P2_12_12_1$ (No. 19), a=6.5007(3) Å, b=11.8492(12) Å, c=17.645(2) Å, V=1359.1(2) $Å^3$, Z=4, D_c=1.248 Mg m^{-3}, $F(000)$=552, μ(Mo Kα)=0.075 mm^{-1}, T=122 (1) K, crystal dimensions=0.65×0.32×0.18 mm.

Data collection and processing: Diffraction data were collected on an Enraf-Nonius KappaCCD diffractometer using graphite monochromated Mo Kα radiation (λ=0.71073 Å).[14] The reflections

were measured in the range $-8\leq h\leq 8$, $-15\leq k\leq 15$, $-22\leq l\leq 22$, ($2.88^\circ<\theta<27.58^\circ$). Data were reduced using the program EvalCCD.[15,16] A total of 19,804 reflections were averaged according to the point group symmetry 222 resulting in 3142 unique reflections (R_{int}=0.052 on F_o^2). Absorption correction was applied using the program NUMABS (T_{min}=0.930; T_{max}=0.973) as part of the program maXus.[17,18]

Structure solution and refinement. The structure was solved by the direct method using the programme SHELXS97[18–20] and refined using the programme SHELXL97.[21] Full matrix least-squares refinement on F^2 was performed, minimizing $\sum w(F_o^2-F_c^2)^2$, with anisotropic displacement parameters for the non-hydrogen atoms. The positions of all hydrogen atoms were located on intermediate difference electron density maps and they were refined with fixed isotropic displacement parameters. The refinement (235 parameters, 3142 reflections) converged at R_F=0.0292, wR_{F2}=0. 0730 for 2972 reflections with $F_o>4\sigma(F_o)$; $w=1/[\sigma^2(F_o^2)+(0.0372P)^2+0.2330P]$, where $P=(F_o^2+2F_c^2)/3$; S=1.080. In the final difference Fourier map maximum and minimum electron densities were 0.214 and −0.143 e Å^{-3}, respectively. Absolute configuration could not be identified based on the structure determination (Flack parameter=0.2(16)).[22] Complex atomic scattering factors for neutral atoms were as incorporated in SHELXL97.[21,23] CCDC 783989.

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Supplementary data

Full spectroscopic data for all new and stable compounds and crystallographic data for compound **27**. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.09.023.

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