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The Witkop–Winterfeldt oxidation converts tetrahydropyridoindoles into pyrroloquinolones and cinnolines by an unprecedented scaffold rearrangement

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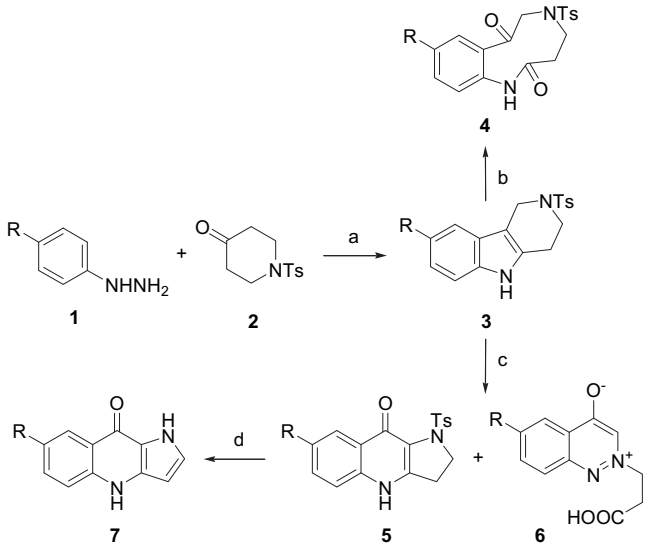
ABSTRACT

The Fischer indole reaction between phenylhydrazines and tosyl-4-piperidone furnishes tetrahydropyrido[4,3-*b*]indoles. In a Witkop–Winterfeldt-oxidation using ozone such indole derivatives are converted into medium-sized dicarbonyl ring systems, which cyclize to pyrroloquinolones. A detailed study of the reaction intermediates and the characterization of a cinnoline betaine side product formed by an unprecedented ring closure mechanism are reported.

1. Introduction

The indole scaffold is present in many natural products and is regarded as a privileged scaffold for medicinal chemistry. Consequently, numerous synthetic strategies have been developed to give access to different varieties of this compound class.[1] Furthermore, the ring system is distinguished by an amazingly rich choice of follow up reactions offering the opportunity for derivatization reactions. Most notably, the indole ring can be converted into other ring systems, leading to further privileged structures. Among others, the oxospiroindole rearrangement,[2] the Witkop–Winterfeldt-oxidation to quinolones,[3] and a recently published Pd-catalyzed ring expansion[4] to quinolines should be mentioned in this context, offering considerable synthetic potential following the idea of scaffold-diversifying reactions as a means to increase the structural diversity of compound libraries.[5] We have recently reported about the solid phase synthesis of tetrahydropyridoindoles (tetrahydro-γ-carbolines), which delivered upon cleavage pyrrolo[3,2-*b*]quinolones a previously unknown ring system.[6] Having already addressed the scope of this reaction on solid phase, we will now report about a scalable solution phase synthesis for some of these heterocycles and discuss the synthetic opportunities presented by several intermediates lying along this reaction sequence (Scheme 1).



Scheme 1. Synthesis of pyrrolo[3,2-*b*]quinolones by Witkop–Winterfeldt-oxidation of tetrahydro-γ-carbolines: (a) Fischer indole synthesis; (b) Witkop-oxidation; (c) Witkop–Winterfeldt-oxidation; (d) Detosylation.

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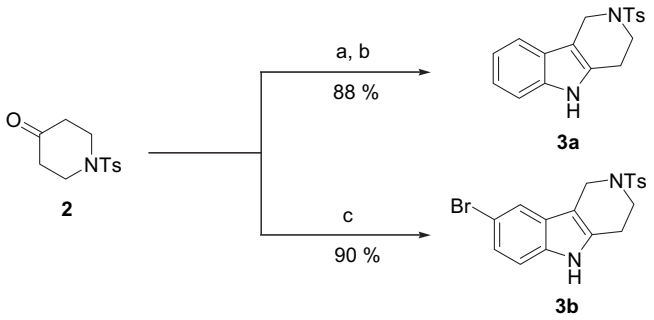
2. Results and discussion

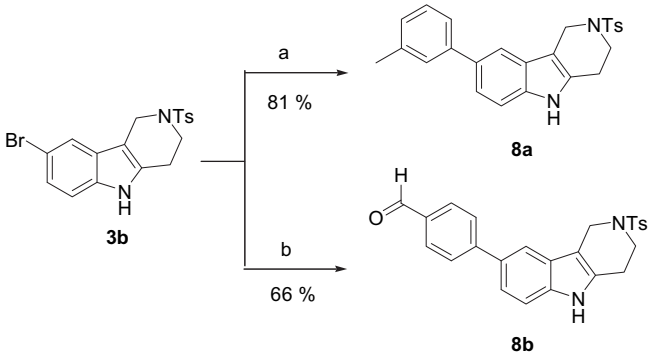
2.1. Synthesis of tetrahydro-1*H*-pyrido-[4,3-*b*]indoles

By classic Fischer indole synthesis *N*-toysl-4-piperidone (**2**) was converted into the corresponding tetrahydro-γ-carbolines **3a**,**b** (Scheme 2). This initial step proved most challenging in the analogous solid phase synthesis,[6] where it required water- and oxygen-free conditions and was carried out under $ZnCl_2$ catalysis for a broad range of phenylhydrazine substrates. Here, acetic acid effected the transformation in case of *p*-bromophenylhydrazine hydrochloride within a few hours in very good yield without the need for chromatographic purification when working under oxygen-free conditions. Similarly, unsubstituted phenylhydrazine afforded mainly the corresponding intermediate phenylhydrazone and required additional treatment with trifluoroacetic acid to quantitatively effect the [3,3]-sigmatropic rearrangement leading to the formation of the indole nucleus.



Scheme 2. Synthesis of tetrahydro-1*H*-pyrido-[4,3-*b*]indoles: (a) Phenylhydrazine, AcOH, 70 °C, 3.5 h; (b) 1,2-Dichloroethane, 3% trifluoroacetic acid, 70 °C, 19 h; (c) 4-Bromophenylhydrazine hydrochloride, AcOH, 70 °C, 3.5 h.

The availability of bromine substituted indole derivatives provides the opportunity to introduce various substituents via Pd-catalyzed transformations in order to create diversity. The structural class of biphenyls, another example of a privileged structure,[7] can be accessed via Suzuki cross-coupling of indole **3b** with arylboronic acids under conditions reported by Buchwald et al.[8] Again, optimization of the reaction conditions in solution was less cumbersome, when compared to solid phase, and involved an aqueous solvent system and extended reaction times in case of poorly soluble, electron-deficient 4-formylphenylboronic acid. Biphenyl derivatives **8a**,**b** could be isolated in good yields after flash column chromatography (Scheme 3).

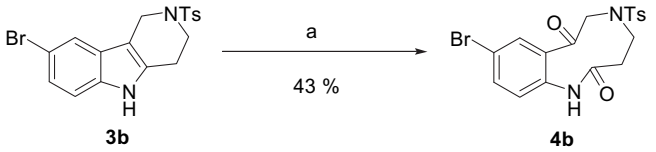


Scheme 3. Suzuki cross-coupling with bromoindole **3b**: (a) 1 mol % $Pd(OAc)_2$, 2 mol % SPhos, K_3PO_4, *m*-tolylboronic acid, toluene, 100 °C, 24 h; (b) 1 mol % $Pd(OAc)_2$, 2 mol % SPhos, K_3PO_4, 4-formylphenylboronic acid, toluene/THF/H_2O 5:6:1, 90 °C, 45 h.

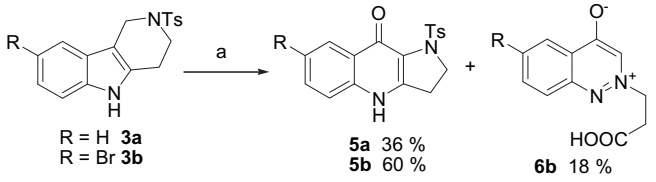
2.2. Witkop–Winterfeldt-oxidation of tetrahydro-1*H*-pyrido-[4,3-b]indoles

The powerful Witkop–Winterfeldt oxidation conveniently rearranges indoles into the corresponding quinolones.[3] In the first step, oxidation of γ-carboline **3b** yields keto-lactam **4b** (Scheme 4). The intrinsic instability of this intermediate due to facile formation of the Camps cyclization product (via intramolecular condensation) required careful handling and its purification by trituration at 0 °C.

Thus, a one-pot reaction was considered as most efficient to transform tosylated γ-carbolines **3a**,**b** directly into the corresponding dihydropyrrolo[3,2-*b*]quinolones **5a**,**b**. Similarly as in our solid phase reaction, ozone was well suited to achieve the oxidation reaction,[3,6] while pyridine acted as a reducing agent for the assumed intermediate ozonide, because the resulting pyridine *N*-oxide could be easily removed in an aqueous workup. Addition of triethylamine led to smooth cyclization and aqueous washing procedures effectively provided the desired compounds. The low to moderate yields of isolated dihydropyrrolo[3,2-*b*]quinolones **5** could be attributed to the formation of a by-product, which in one case was isolated and unambiguously identified as cinnoline betaine **6b** by NMR and X-ray analysis (Scheme 5) (Fig 1).[9,10]



Scheme 4. Ozonolysis of γ-carboline leading to nine-membered keto-lactam: (a) O_3, CH_2Cl_2, −78 °C, 5 min, then pyridine, −78 °C to rt (1 h).



Scheme 5. Witkop–Winterfeldt-oxidation under conditions affording cyclised quinolone products: (a) O_3, CH_2Cl_2, −78 °C, 15 min, then pyridine, −78 °C to rt (2 h), then Et_3N, rt, o. n.

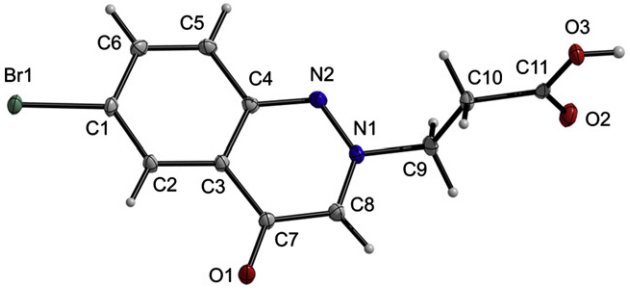
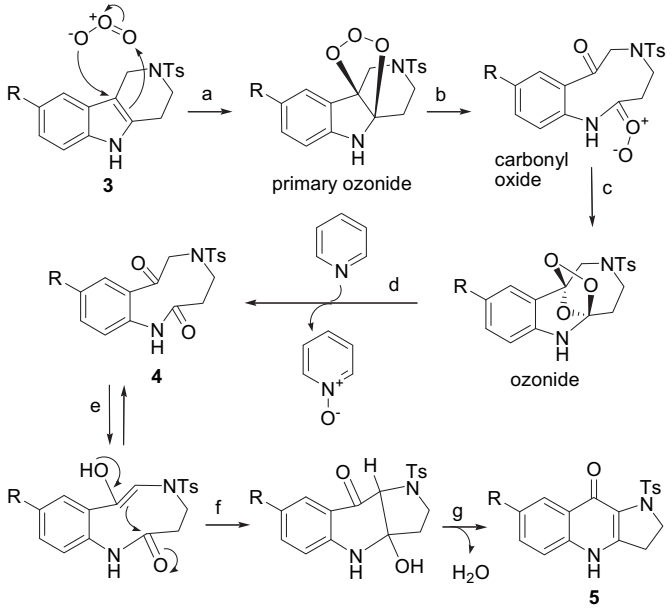


Fig. 1. X-ray crystal structure of cinnoline betaine **6b**.

2.2.1. Mechanism of cyclization. During the optimization of the Witkop–Winterfeldt oxidation on solid phase we had not noticed any by-product formation, but rather accepted the relatively low yielding sequence, a fact that could have well been attributed to several other peculiarities of the polymer-bound reaction process. The solution phase synthesis, however, soon revealed the presence of another compound, which was separated from dihydropyrrolo [3,2-*b*]quinolones **5** upon aqueous basic washing. Acidification of the aqueous phase yielded a precipitate, which showed typical

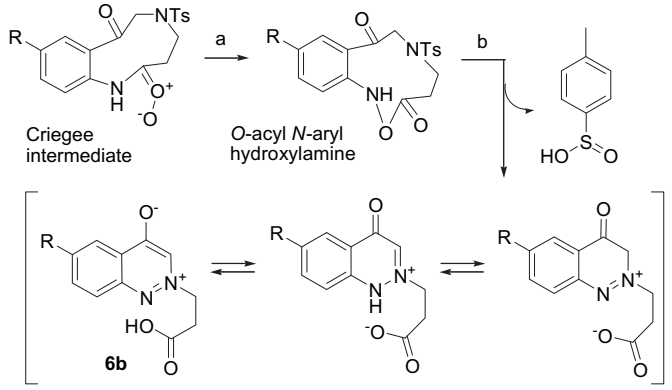
characteristics of a carboxylic acid. Its actual structure could only be determined when the compound eventually crystallized from a DMSO solution and was subjected to X-ray analysis.

Taking into consideration the three-step mechanism of ozonolysis as described by Criegee (Scheme 6),[11] γ-carbolines **3** will add a molecule of ozone on their C2–C3 π-bond and their cyclization products will decompose into carbonyl and carbonyl oxide. In another cycloaddition reaction ozonides will be formed, which undergo reduction by pyridine to the observed keto-lactams **4**. Those are cyclised under elimination of water to dihydropyrrolo [3,2-*b*]quinolones **5**.



Scheme 6. Proposed mechanism for the formation of dihydropyrrolo[3,2-*b*]quinolones: (a) Formation of the primary ozonide via 1,3-dipolar cycloaddition; (b) Decomposition into carbonyl carbonyl oxide; (c) 1,3-Dipolar cycloaddition; (d) Reduction; (e) Keto-enol tautomerism; (f) 6-*Enolendo-exo-trig* cyclization; (g) Water elimination.

The formation of cinnoline betaines of type **6b** from γ-carbolines **3** is unprecedented, but could involve the formation of an *O*-acyl *N*-arylhydroxylamine in analogy to the rearrangement of carbonyloxides into esters, lactones or acid anhydrides as postulated by Criegee (Scheme 7).[11]

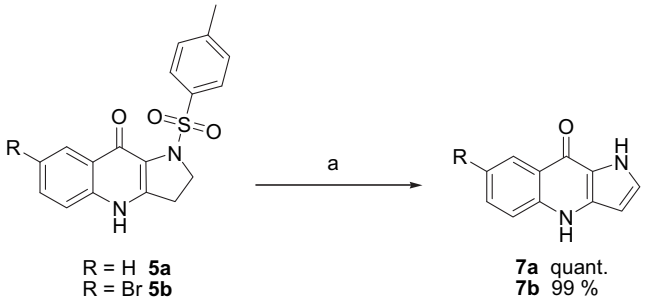


Scheme 7. Mechanistic proposal for the formation of cinnoline betaines: (a) Rearrangement; (b) Sulfinic acid elimination and ring closure.

Such *O*-acyl *N*-arylhydroxylamines and their reactivity with nucleophilic amines have been investigated by Boche as active metabolites and the cause of carcinogenicity of aromatic amines.[12] Generally, nucleophilic substitution at an electrophilic nitrogen centre is best represented by the Raschig hydrazine synthesis.[13] However, examples of this type of reaction involving electron-deficient nitrogen nucleophiles are rare, and have not been reported for tertiary sulfonamides but only for secondary sulfonamides in alkaline solution.[14] Thus, we cannot entirely rule out preceding β-elimination of sulfinate under basic conditions, which would lead to a much more reactive imine nitrogen nucleophile. Eventually, ring closure would yield a mesomerism-stabilized hydrazinium derivative, best represented as cinnoline betaine **6b** (Scheme 7).

2.3. Detosylation of pyrrolo[3,2-*b*]quinolones

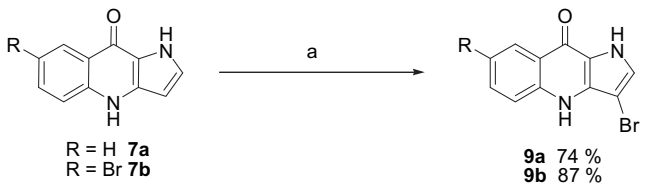
Sulfonamides can be regarded as one of the most stable nitrogen protecting groups usually requiring reductive conditions for their cleavage.[15] However, in the present case, facile basic deprotection was achieved favoured by the formation of an aromatic 14 π-electron system. The use of DMF as co-solvent to ensure complete solubility of the tosyl protected compounds turned out to be central to the success of the desired transformation. Under these conditions, the reaction proceeds with slower kinetics even at rt (Scheme 8).



Scheme 8. Detosylation of dihydropyrrolo[3,2-*b*]quinolones under basic conditions: (a) DMF/Et_3N 1:1, 80 °C, 20 h.

2.4. Bromination of pyrrolo[3,2-*b*]quinolones

The pyrrolo[3,2-*b*]quinolone itself might serve as a building block for library syntheses. Considering its electronic properties, pyrroloquinolone **7** seems to be perfectly suited to undergo selective electrophilic substitution reactions. The highest electron density is likely to be found in the pyrrole moiety. ^{1}H NMR data suggest the C-3 position as the by far most nucleophilic centre. This predicted selectivity was explored by using bromination as a representative electrophilic aromatic substitution reaction. Bromination with *N*-bromosuccinimide readily occurred at rt furnishing **9a**,**b** in good yields. Similar to the detosylation procedure, the reaction proceeded without formation of by-products and succinimide and bromine were removed in an aqueous workup (Scheme 9).



Scheme 9. Selective bromination of pyrrolo[3,2-*b*]quinolones: (a) *N*-bromosuccinimide, AcOH, rt, 1 h.

3. Conclusion

We could demonstrate that tetrahydro-1*H*-pyrido-[4,3-*b*]-indoles can be subjected to Witkop–Winterfeldt-oxidation. Treatment with

ozone leads to a nine-membered keto-lactam, which can either be isolated or in situ cyclised to dihydropyrrolo[3,2-*b*]quinolones. As side products in the ozonolysis reaction alkyl cinnoline betaines are formed, which most likely might be formed via a Criegee intermediate. The unique electronic properties of the generated pyrrolo[3,2-*b*]quinolones enable their derivatisation, e. g., via electrophilic aromatic substitution, selectively on the pyrrole moiety. In addition to the substitution pattern introducible in the Fischer indole reaction by employing various phenylhydrazine derivatives,[6] access to a privileged structure building block is granted.

4. Experimental

4.1. General

Chemicals were purchased commercially and used without purification unless otherwise stated. Phenylhydrazine was purified by distillation and stored at 4 °C under Ar atmosphere. Dichloromethane (DCM) and MeOH were dried over CaH_2 and distilled under Ar atmosphere before use. Toluene and pyridine were dried by storing over molecular sieve (MS) 4 Å. Tetrahydrofuran (THF) was dried by heating at reflux temperature under Ar atmosphere over Na, until benzophenone indicated dryness by a deep blue colour. Dry THF was usually prepared directly prior to its use. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 2000, Varian Mercury plus 300 and 400 and Bruker DRX 400 spectrometers and chemical shifts are referenced to residual protonated solvent signals as internal standard. Mass spectra were obtained with a Bruker Daltonics 7 T APEX II FT-ICR-MS (ESI, high resolution), a Jeol SX 102 A (FAB, high resolution, matrix: *m*-nitrobenzylalcohol) and a Bruker Esquire3000 plus (ESI, low resolution). The X-ray single-crystal data of compound **6b** were collected on a Bruker-AXS Kappa APEX II CCD diffractometer at 100(2) K. HPLC was performed on a Knauer Smartline instrument with Autosampler 3800, Manager 5000 Low Pressure Gradient, Pump 1000, UV Diode Array Detector 2600 and Fraction Collector Isco Foxy Junior FC100. For analytical measurements a Macherey–Nagel EC 125/4 Nucleodur 100-3 C18 ec column with a CC 8/4 Nucleodur 100-5 C18 ec pre-column was used. A general acetonitrile/water gradient with 0.05% (v/v) TFA at a flow rate of 0.5 mL/min was applied (0.0–6.0 min: 10% MeCN const., 6.0–26.0 min: 100% MeCN lin. gradient, 26.0–32.0 min: 100% MeCN const., 32.0–32.5 min: 10% MeCN lin., 32.5–40.0 min: 10% MeCN lin.). The elution time and the local maxima in the absorption spectrum between 200 and 500 nm are given. Semi-preparative HPLC was carried out on the same instrument utilizing a VP 125/21 Nucleodur 100-5 C18 ec column with VP 50/21 Nucleodur 100-5 C18 ec pre-column at a flow rate of 20 mL/min. As a general rule for HPLC purifications, the gradient was adjusted for each semi-preparative run according to the observed peak elution time/percentage of MeCN in the analytical chromatogram, usually starting at a MeCN value 30% lower than that detected for elution of the compound in the analytical run. Silica gel chromatography was performed with Merck silica gel 60 (230–400 mesh). Analytical thin layer chromatography (TLC) was performed using Merck silica gel 60-F_{254} and spots were visualized using a UV lamp (λ=254, 366 nm) or by treatment with cerium ammonium molybdate solution (CAM; 2 g Ce $(SO_4)_2$, 50 g $(NH_4)_2MoO_4$, 50 mL concentrated H_2SO_4 in 400 mL water) followed by heating. Ozonizations were carried out on a Fischer Ozongenerator 500. Melting points were determined with a Boetius melting-point apparatus and are uncorrected.

4.2. Synthesis of tetrahydro-γ-carbolines (3) general procedure

A 1 L three-neck round-bottom flask equipped with a reflux condenser and gas inlet was charged consecutively with 15.0 g (59.2 mmol, 1.0 equiv) 1-tosylpiperidin-4-one (**2**),[16] 500 mL AcOH and 1.1 equiv phenylhydrazine derivative (**1**). The suspension was degassed by vacuum/N_2 cycles and slowly warmed to 70 °C. If a black mixture is obtained at this stage, this might be an indication for residual oxygen, usually leading to decomposition and very low yields of isolated compound after flash chromatography. After stirring at 70 °C for 3.5 h the solution was cooled to 0 °C and 300 mL degassed, cold (0 °C) satd aq KOH was carefully added under N_2 atmosphere. The resulting suspension was poured on ice in a 2 L round-bottom flask and additional solid KOH was added under cooling until pH 8 was reached. It is important that the temperature of the reaction mixture is maintained below 25 °C during the whole process by providing sufficient external cooling with an ice-water bath. After extraction with EtOAc (3×400 mL) the combined organic layers were dried over $MgSO_4$, filtrated, and concentrated in vacuo [In case of incomplete conversion as detected by analytical HPLC, the solid residue is taken up in 140 mL DCE and degassed by bubbling Ar through it while immersing in an ultrasonic bath. Then 4 mL TFA are added and the mixture heated under Ar atmosphere at 70 °C until HPLC analysis indicates complete conversion (19 h). The solvent is evaporated under reduced pressure and TFA is co-evaporated with toluene (3×20 mL)]. The solid residue was suspended in 150 mL pre-cooled (−18 °C) $CHCl_3$ and the mixture was homogenized by immersing the flask in an ultrasonic bath. A solid was collected by filtration through a sintered glass funnel and washed with cold $CHCl_3$ before dried under high vacuum.

Phenylhydrazine (**1a**) (7.04 g, 65.1 mmol) yield after TFA treatment 17.0 g (52 mmol, 88%) 2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**3a**)[17] as slightly orange-white solid. Mp 188–190 °C; ^{1}H NMR (400 MHz, DMSOd_6): δ=10.95 (s, 1H, NH), 7.74 (d, ^3J=8.3 Hz, 2H, Ar–H), 7.42 (d, ^3J=8.1 Hz, 2H, Ar–H), 7.39 (d, ^3J=7.6 Hz, 1H, Ar–H), 7.27 (d, ^3J=8.0 Hz, 1H, Ar–H), 7.03 (ddd, ^3J=8.2, 7.2 Hz, ^4J=1.1 Hz, 1H, Ar–H), 6.95 (ddd, ^3J=7.9, 7.2 Hz, ^4J=1.0 Hz, 1H, Ar–H), 4.25 (s, 2H, CH_2N), 3.41 (t, ^3J=5.8 Hz, 2H, CH_2N), 2.83 (t, ^3J=5.6 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=143.5 (C_q, C_{Ar}), 135.8 (C_q, C_{Ar}), 133.7 (C_q, C_{Ar}), 131.7 (C_q, C_{Ar}), 129.8 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 124.9 (C_q, C_{Ar}), 120.8 (CH, C_{Ar}), 118.6 (CH, C_{Ar}), 117.2 (CH, C_{Ar}), 111.0 (CH, C_{Ar}), 104.1 (C_q, C_{Ar}), 43.5 (CH_2, CH_2N), 43.0 (CH_2, CH_2N), 23.1 (CH_2), 21.0 (CH_3); HRMS (FAB): *m*/*z*: calcd for $C_{18}H_{19}N_2O_2S^+$ $[M+H]^+$: 327.1162, found 327.1172; HPLC: t_R=26.9 min, λ_{max}=224, 273 nm.

4-Bromophenylhydrazine hydrochloride (**1b**) (14.6 g, 65.1 mmol) yield 21.0 g (53 mmol, 90%) 8-bromo-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**3b**) as a brownish-white-grey solid. Mp 170–171 °C; ^{1}H NMR (400 MHz, DMSOd_6): δ=11.12 (s, 1H, NH), 7.74 (d, ^3J=8.2 Hz, 2H, Ar–H), 7.64 (d, ^4J=1.7 Hz, 1H, Ar–H), 7.40 (d, ^3J=8.2 Hz, 2H, Ar–H), 7.24 (d, ^3J=8.6 Hz, 1H, Ar–H), 7.13 (dd, ^3J=8.6 Hz, ^4J=1.9 Hz, 1H, Ar–H), 4.25 (s, 2H, CH_2N), 3.41 (t, ^3J=5.7 Hz, 2H, CH_2N), 2.84 (t, ^3J=5.3 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=143.4 (C_q, C_{Ar}), 134.5 (C_q, C_{Ar}), 133.6 (C_q, C_{Ar}), 133.5 (C_q, C_{Ar}), 129.7 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 126.7 (C_q, C_{Ar}), 123.1 (CH, C_{Ar}), 119.7 (CH, C_{Ar}), 112.8 (CH, C_{Ar}), 111.2 (C_q, C_{Ar}), 104.1 (C_q, C_{Ar}), 43.3 (CH_2, CH_2N), 42.8 (CH_2, CH_2N), 23.1 (CH_2), 21.0 (CH_3); HRMS (MeOH, ESI$^+$): *m*/*z*: calcd for $C_{18}H_{17}BrN_2NaO_2S^+$ $[M+Na]^+$: 427.0086; found 427.0090; HPLC: t_R=31.3 min, λ_{max}=229, 287 nm.

*4.2.1. 8-m-Tolyl-2-tosyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indole (**8a**).* A 10 mL Schlenk tube was dried under vacuum, filled with Ar and charged consecutively with 2.2 mg (0.010 mmol, 1.0 mol %) Pd $(OAc)_2$, 8.2 mg (0.020 mmol, 2.0 mol %) *S*-PHOS,[8] 0.204 g (1.50 mmol, 1.5 equiv) *m*-tolylboronic acid, 0.425 g (2.00 mmol, 2.0 equiv) mortar-powdered, anhydrous K_3PO_4, 0.405 g (1.00 mmol, 1.0 equiv) 8-bromo-2-tosyl-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole (**3b**), and 3 mL toluene. The mixture was degassed by vacuum/Ar cycles. A yellow-brown suspension formed and the mixture was heated at 100 °C in a sealed tube for 24 h. After cooling to rt 1 mL

Et_2O was added, the mixture filtrated through a pad of silica in a sintered glass funnel, eluted with EtOAc (1×50 mL) and EtOAc/MeOH (1:1, 1×50 mL) and concentrated to dryness. 0.43 g yellow-brown residue were obtained and subjected to flash column chromatography [EtOAc/cyclohexane 1:9 to EtOAc/cyclohexane 7:3; R_f=0.41 (EtOAc/cyclohexane 2:3, CAM)] to obtain a cloudy-yellow oil that upon trituration with DCM and evaporation crystallized to furnish 0.338 g (0.811 mmol, 81%) of the title compound as a yellowish-white solid. Mp 180–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.90 (s, 1H, NH), 7.77 (d, ^3J=8.3 Hz, 2H, Ar–H), 7.58 (d, ^4J=1.1 Hz, Ar–H), 7.46–7.41 (m, 2H, Ar–H), 7.39 (dd, ^3J=8.4 Hz, ^4J=1.7 Hz, 1H, Ar–H), 7.35–7.29 (m, 4H, Ar–H), 7.14 (d, ^3J=7.5 Hz, 1H, Ar–H), 4.41 (s, 2H, CH_2N), 3.52 (t, ^3J=5.7 Hz, 2H, CH_2N), 2.87 (t, ^3J=5.7 Hz, 2H, Ar–H), 2.44 (s, 3H, CH_3), 2.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, APT): δ=143.7 (C_q, C_{Ar}), 142.4 (C_q, C_{Ar}), 138.3 (C_q, C_{Ar}), 135.5 (C_q, C_{Ar}), 134.1 (C_q, C_{Ar}), 133.5 (C_q, C_{Ar}), 131.7 (C_q, C_{Ar}), 129.9 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 128.2 (CH, C_{Ar}), 127.7 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 126.0 (C_q, C_{Ar}), 124.5 (CH, C_{Ar}), 121.7 (CH, C_{Ar}), 116.1 (CH, C_{Ar}), 111.1 (CH, C_{Ar}), 106.5 (C_q, C_{Ar}), 43.6 (CH_2, CH_2N), 43.2 (CH_2, CH_2N), 23.9 (CH_2, CH_2), 21.7 (CH_3), 21.7 (CH_3); HRMS (FAB): *m/z*: calcd for $C_{25}H_{24}N_2O_2S^+$ $[M]^+$: 416.1553; found 416.1538; HPLC: t_R=31.3 min, λ_{max}=254 nm.

*4.2.2. 4-(2-Tosyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-8-yl) benzaldehyde (**8b**).* A 10 mL Schlenk tube was dried under vacuum, filled with Ar and charged consecutively with 0.010 g (0.025 mmol, 1.0 equiv) **3b**, 0.006 g (0.037 mmol, 1.5 equiv) 4-formylphenylboronic acid, 0.011 g (0.049 mmol, 2.0 equiv) mortar-powdered, anhydrous K_3PO_4, 1 mL toluene/THF (1:1), 0.2 mg (0.49 μmol, 2.0 mol %) SPhos and 0.2 mL (0.25 μmol, 1.0 mol %) of a 1.2 mg/mL (THF/H_2O 1:1) $Pd(OAc)_2$ solution. The clear colourless suspension was degassed by vacuum/N_2 cycles. Stirring was performed at 90 °C until HPLC analysis indicated complete conversion (45 h). The mixture was cooled to rt and 3 mL EtOAc were added. After filtration through a pad of silica and elution with 50 mL EtOAc, the filtrate was concentrated to dryness.Yellow oil (0.020 g) was obtained and subjected to semi-preparative HPLC. Title compound (7 mg, 0.016 mmol, 66%) was isolated as a yellow amorphous solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ=10.06 (s, 1H, CHO), 7.95 (d, ^3J=8.2 Hz, 2H, Ar–H), 7.91 (s, 1H, NH), 7.80 (d, ^3J=6.6 Hz, 2H, Ar–H), 7.77 (d, ^3J=6.6 Hz, 2H, Ar–H), 7.67 (s, 1H, Ar–H), 7.46 (dd, ^3J=8.5 Hz, ^4J=1.6 Hz, 1H, Ar–H), 7.38 (d, ^3J=8.5 Hz, 1H, Ar–H), 7.32 (d, ^3J=8.1 Hz, 1H, Ar–H), 4.43 (s, 2H, CH_2N), 3.56 (t, ^3J=5.7 Hz, 2H, CH_2N), 2.93 (t, ^3J=5.6 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3) ppm; ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=192.6 (CH, CHO), 147.6 (C_q, C_{Ar}), 143.5 (C_q, C_{Ar}), 136.1 (C_q, C_{Ar}), 134.1 (C_q, C_{Ar}), 133.6 (C_q, C_{Ar}), 133.0 (C_q, C_{Ar}), 130.1 (CH, C_{Ar}), 129.8 (CH, C_{Ar}), 129.4 (C_q, C_{Ar}), 127.3 (CH, C_{Ar}), 126.9 (CH, C_{Ar}), 125.7 (C_q, C_{Ar}), 120.2 (CH, C_{Ar}), 116.4 (CH, C_{Ar}), 111.5 (CH, C_{Ar}), 105.1 (C_q, C_{Ar}), 43.4 (CH_2, CH_2N), 43.0 (CH_2, CH_2N), 23.2 (CH_2, CH_2), 21.0 (CH_3) ppm; HPLC: t_R=26.9 min, λ_{max}=229, 281, 325 nm.

*4.2.3. 9-Bromo-5-tosyl-3,4,5,6-tetrahydro-1H-1,5-benzodiazonine-2,7-dione (**4b**).* A Schlenk tube was filled with N_2 and charged with 2.00 g (4.93 mmol, 1.0 equiv) **3b** and 240 mL DCM. The solution was cooled to −78 °C before a stream of O_3 was passed through the solution until a blue colour developed (5 min). The O_3 stream was continued for 5 min. Then, surplus O_3 was removed by passing a stream of N_2 through the solution for 5 min. 0.52 mL (6.41 mmol, 1.3 equiv) pyridine were added and the solution was allowed to warm to rt (1 h). The orange solution was washed with H_2O (2×), dried over $MgSO_4$, filtrated, and concentrated in vacuo. The residue was suspended in 120 mL H_2O/MeOH (1:1) and homogenized by immersing in an ultrasonic bath. The mixture was kept at 0 °C overnight before a brown solid was collected by filtration. After washing with H_2O and drying under high vacuum 0.919 g (2.10 mmol, 43%) of the title compound was obtained. Mp 222–225 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.72 (d, ^4J=2.3 Hz, 1H, 8-H), 7.66 (dd, ^3J=8.4 Hz, ^4J=2.3 Hz, 1H, 10-H), 7.60 (d, ^3J=8.3 Hz, 2H, 2′-H, 6′-H), 7.32 (d, ^3J=8.2 Hz, 2H, 3′-H, 5′-H), 7.11 (d, ^3J=8.2 Hz, 1H, 11-H), 4.03 (s, 2H, 6-H), 3.48 (br t, ^3J=6.4 Hz, 2H, 4-H), 2.54 (br s, 2H, 3-H), 2.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, APT): δ=201.5 (C_q, C-7), 174.4 (C_q, C-2), 144.6 (C_q, C-4′), 141.9 (C_q, C-11a), 135.2 (CH, C-10), 134.9 (C_q, C-1′), 134.1 (CH, C-8), 131.3 (C_q, C-7a), 130.7 (CH, C-11), 130.3 (CH, C-3′, C-5′), 127.2 (CH, C-2′, C-6′), 123.9 (C_q, C-9), 59.9 (CH_2, C-6), 49.0 (CH_2, C-4), 36.0 (CH_2, C-3), 21.7 (CH_3). The structural assignment was confirmed by 2-D NMR (HH-COSY, HSQC, HMBC). HRMS (MeOH, ESI+): *m/z*: calcd for $C_{18}H_{17}BrN_2NaO_4S^+$ $[M+Na]^+$: 458.9985; found 458.9990; HPLC: t_R=23.3 min, λ_{max}=216 nm.

4.3. Synthesis of tosyl dihydropyrrolo[3,2-*b*]quinolones (5) general procedure

A 250 mL Schlenk tube was charged with 1.0 equiv tosyl γ-carboline **3** and 150 mL DCM. The yellow-brown suspension was homogenized by immersing the tube in an ultrasonic bath and cooled to −78 °C. Then a stream of O_3 was passed through the solution until a blue colour developed (15 min). The O_3 stream was continued for 5 min. Then surplus O_3 was removed by passing a stream of N_2 through the solution for 10 min and the blue colour completely vanished. Afterwards 1.55 mL (1.52 g, 19.3 mmol, 1.3 equiv) pyridine was added to the cold (−78 °C) mixture. The mixture was allowed to warm to rt (2 h) before 5.34 mL (3.89 g, 38.4 mmol, 2.6 equiv) Et_3N were added. After stirring at rt overnight the brown suspension was concentrated under reduced pressure to dryness. The residue was suspended in 100 mL 10% aq $KHSO_4$ and homogenized by immersing in an ultrasonic bath for 30 min. A light-brown solid was collected by filtration through a sintered glass funnel and washed with H_2O (4×30 mL). The solid was suspended in 100 mL 10% aq $NaHCO_3$ and homogenized by immersing in an ultrasonic bath for 60 min. The solid was collected by filtration through a sintered glass funnel and washed with water (5×30 mL). The filter cake was dried by sucking air through the funnel on a Büchner flask under membrane pump vacuum overnight.

Compound **3a** (4.82 g, 14.8 mmol) yield 1.80 g (5.29 mmol, 36%) 1-tosyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**5a**) as a slightly brownish-white solid. Mp 207–209 °C; ^{1}H NMR (200 MHz, DMSOd_6): δ=12.06 (s, 1H, NH), 8.15 (dd, ^3J=8.1 Hz, ^4J=1.3 Hz, 1H, Ar–H), 7.65 (d, ^3J=8.3 Hz, 1H, Ar–H), 7.61 (overlaid ddd, ^3J=8.4, 7.1 Hz, ^4J=1.2 Hz, 1H, Ar–H), 7.46 (d, ^3J=8.2 Hz, 1H, Ar–H), 7.34 (d, ^3J=8.0 Hz, 2H, Ar–H), 7.36–7.30 (overlaid m, 1H, Ar–H), 3.99 (t, ^3J=7.6 Hz, 2H, CH_2N), 2.53–2.47 (overlaid m, CH_2CH_2N), 2.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=168.0 (C_q, C=O), 149.4 (C_q, C_{Ar}), 143.5 (C_q, C_{Ar}), 138.8 (C_q, C_{Ar}), 134.9 (C_q, C_{Ar}), 131.1 (CH, C_{Ar}), 129.5 (CH, C_{Ar}), 127.6 (CH, C_{Ar}), 126.6 (C_q, C_{Ar}), 125.5 (CH, C_{Ar}), 123.1 (CH, C_{Ar}), 121.6 (C_q, C_{Ar}), 118.0 (CH, C_{Ar}), 50.1 (CH_2, CH_2N), 28.4 (CH_2, CH_2CH_2N), 21.0 (CH_3); HRMS (MeOH, ESI+): *m/z*: calcd for $C_{18}H_{16}N_2NaO_3S^+$ $[M+Na]^+$: 363.0774; found 363.0773; HPLC: t_R=21.3 min, λ_{max}=219, 326 nm.

Compound **3b** (6.00 g, 14.8 mmol) yield 3.71 g (8.85 mmol, 60%) 7-bromo-1-tosyl-2,3-dihydro-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**5b**) as a brownish-white solid. Mp 230–231 °C; ^{1}H NMR (400 MHz, DMSOd_6): δ=12.31 (s, NH), 8.23 (d, ^4J=2.2 Hz, 1H, 8-H), 7.76 (dd, ^3J=8.9 Hz, ^4J=2.2 Hz, 1H, 6-H), 7.65 (d, ^3J=8.1 Hz, 2H, 1′-H, 6′-H), 7.44 (d, ^3J=8.8 Hz, 1H, 5-H), 7.34 (d, ^3J=8.1 Hz, 2H, 2′-H, 5′-H), 4.00 (t, ^3J=7.5 Hz, 2H, 2-H), 2.52 (overlaid t, ^3J=7.7 Hz, 2H, 3-H), 2.36 (s, 3H, CH_3); ^{13}C NMR (75 MHz, DMSOd_6, APT): δ=166.6 (C_q, C-9), 150.1 (C_q, C-9a), 143.7 (C_q, C-4′), 137.7 (C_q, C-4a), 134.8 (C_q, C-1′), 133.9 (CH, C-6), 129.6 (CH, C-2′, C-5′), 128.2 (C_q, C-8a), 127.7 (overlaid CH, C-8), 127.6 (CH, C-1′, C-6′), 122.0 (C_q, C-3a), 120.7 (CH, C-5), 116.0 (C_q, C-7), 50.2 (CH_2, C-2), 28.5 (CH_2, C-3), 21.1 (CH_3). The

structural assignment was confirmed by 2-D NMR (HH-COSY, HSQC, HMBC). HRMS (MeOH, ESI+): *m*/*z*: calcd for $C_{18}H_{16}BrN_2O_3S^+$ $[M+H]^+$: 419.0060; found 419.0060; HPLC: t_R=21.3 min, λ_{max}=221, 263, 333 nm.

A by-product was collected from the $NaHCO_3$ wash phase upon acidification with concentrated HCl and filtration of the precipitate. 0.776 g (2.61 mmol, 18%) 6-bromo-2-(2-carboxyethyl)cinnolin-2-ium-4-olate (**6b**) were obtained as a brownish-white solid. ^{1}H NMR (300 MHz, DMSOd_6): δ=12.55 (br s, NH), 8.39 (s, 1H), 8.18 (d, ^4J=2.3 Hz, 1H, Ar–H), 7.90 (dd, ^3J=9.0 Hz, ^4J=2.3 Hz, 1H, Ar–H), 7.77 (d, ^3J=9.0 Hz, 1H, Ar–H), 4.70 (t, ^3J=6.8 Hz, 2H, CH_2N), 3.06 (t, ^3J=6.8 Hz, 2H, CH_2CH_2N) ppm.; ^{13}C NMR (75 MHz, DMSOd_6, APT): δ=171.6 (C_q, C=O), 168.6 (C_q, C=O), 147.5 (C_q, C_{Ar}), 135.7 (CH, C_{Ar}), 134.2 (CH, C_{Ar}), 128.7 (CH, C_{Ar}), 126.7 (C_q, C_{Ar}), 125.1 (CH, C_{Ar}), 120.9 (C_q, C_{Ar}), 59.8 (CH_2, CH_2N), 33.3 (CH_2, CH_2CH_2N) ppm. 2D-NMR analytical (HH-COSY, HSQC, HMBC) and X-ray data is given in the Supplementary data. HRMS: (MeCN/DMSO, ESI+): *m*/*z*: calcd for $C_{11}H_{10}BrN_2O_3^+$ $[M+H]^+$: 296.9869; found 296.9871; HPLC: t_R=18.7 min, λ_{max}=215, 260, 358, 375 nm.

4.4. Detosylation of tosyl dihydropyrrolo[3,2-*b*]quinolones (5) general procedure

A 250 mL round-bottom flask was charged with tosyl dihydropyrrolo[3,2-*b*]quinolone **5** and 50 mL DMF. The suspension was homogenized by immersing the flask in an ultrasonic bath for 60 min before 50 mL Et_3N were added. The mixture was heated at 80 °C until HPLC analysis indicated complete conversion (20 h). The solvents were evaporated under reduced pressure and the residue was suspended in 70 mL 10% aq $NaHCO_3$ and homogenized by immersing in an ultrasonic bath for 10 min. A solid was collected by filtration and washed with H_2O until neutral reaction of the filtrate before drying under high vacuum.

Compound **5a** (1.70 g, 5.0 mmol) yield 1.06 g (5.8 mmol, quant.) 1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**7a**)[6] as a light-brown solid. Mp 126–130 °C; HPLC: t_R=16.2 min, λ_{max}=239, 304, 349, 362 nm.

Compound **5b** (1.66 g, 3.96 mmol) yield 1.03 g (3.92 mmol, 99%) 7-bromo-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**7b**)[6] as a light-brown solid. Mp 231–233 °C; HPLC: t_R=19.2 min, λ_{max}=244, 309, 356, 372 nm.

4.5. Bromination of pyrrolo[3,2-*b*]quinolones general procedure

A 25 mL round-bottom flask was charged consecutively with 1.0 equiv **7**, 15 mL AcOH and 1.1 equiv *N*-bromosuccinimide. The suspension was homogenized by immersing in an ultrasonic bath under Ar atmosphere for 1 h. The solvent was evaporated in vacuo and the residue suspended in 20 mL 5% aq Na_2SO_3 and homogenized by immersing in an ultrasonic bath for 1 min. A solid was collected by filtration through a sintered glass funnel and washed with H_2O until neutral reaction of the filtrate before dried under high vacuum.

Compound **7a** (0.184 g, 1.00 mmol) yield 0.195 g (0.741 mmol, 74%) 3-bromo-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**9a**) as a light-brown solid. Mp 227–232 °C; ^{1}H NMR (400 MHz, DMSOd_6): δ=12.27 (s, 1H, NH), 11.51 (s, 1H, NH), 8.25 (dd, ^3J=8.1 Hz, ^4J=1.1 Hz, 1H, 8-H), 7.77 (d, ^3J=8.3 Hz, 1H, 5-H), 7.61 (overlaid ddd, ^3J=8.4, 7.0 Hz, ^4J=1.5 Hz, 1H, 6-H), 7.58 (overlaid d, ^3J=3.2 Hz, 1H, 2-H), 7.21 (ddd, ^3J=7.9, 7.0 Hz, ^4J=1.0 Hz, 1H, 7-H), 6.21 (dd, ^3J=2.4 Hz, ^4J=2.4 Hz, 1H, 3-H); ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=166.2 (C_q, C=O), 139.9 (C_q, C_{Ar}), 133.4 (C_q, C_{Ar}), 130.8 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 125.3 (CH, C_{Ar}), 121.9 (C_q, C_{Ar}), 120.2 (CH, C_{Ar}), 119.8 (C_q, C_{Ar}), 117.6 (CH, C_{Ar}), 80.5 (C_q, C-3); HRMS (MeOH, ESI+): *m*/*z*: calcd for $C_{11}H_7BrN_2NaO^+$ $[M+Na]^+$: 284.9634; found 284.9635; HPLC: t_R=20.2 min, λ_{max}=243, 303, 351, 364 nm.

Compound **7b** (0.300 g, 1.14 mmol) yield 0.340 g (0.994 mmol, 87%) 3,7-dibromo-1*H*-pyrrolo[3,2-*b*]quinolin-9(4*H*)-one (**9b**) as a brown solid. Mp 292–294 °C; ^{1}H NMR (400 MHz, DMSOd_6): δ=12.38 (s, 1H, NH), 11.81 (s, 1H, NH), 8.33 (s, 1H, 8-H), 7.76–7.73 (m, 2H, 6-H, 5-H), 7.66 (d, ^3J=3.0 Hz, 1H, 2-H); ^{13}C NMR (100 MHz, DMSOd_6, APT): δ=164.6 (C_q, C=O), 138.6 (C_q, C_{Ar}), 133.8 (C_q, C_{Ar}), 133.5 (CH, C_{Ar}), 128.3 (CH, C_{Ar}), 127.3 (CH, C_{Ar}), 123.2 (C_q, C_{Ar}), 120.3 (CH, C_{Ar}), 119.7 (C_q, C_{Ar}), 112.7 (C_q, C_{Ar}), 80.9 (C_q, C-3); HRMS (MeOH, ESI+): *m*/*z*: calcd for $C_{11}H_7Br_2N_2O^+$ $[M+H]^+$: 340.8920; found 340.8919; HPLC: t_R=23.0 min, λ_{max}=247, 258, 308, 357, 372 nm.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.11.110. These data include MOL files and InChIKeys of the most important compounds described in this article.

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