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Straightforward Access to Hexahydropyrrolo[2,3-*b*]indole Core by a Regioselective C3-Azo Coupling Reaction of Arenediazonium Compounds with Tryptamines

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Abstract

A base-mediated regioselective electrophilic addition of arenediazonium salts at the C3-position of tryptamines followed by cyclization provides an efficient entry to C3-nitrogenated hexahydropyrrolo[2,3-*b*]indoles (HPIs) that can subsequently be transformed into 3-arylhexahydropyrrolo[2,3-*b*]indoles and other HPI derivatives. The reaction is the first example of a 1,2-diamination that utilizes easily accessible arenediazonium salts as nitrogenous electrophiles.

Keywords

Diazonium compounds; Electrophilic addition; Hydrazines; Pyrroloindolines; Synthetic methods

Introduction

Hexahydropyrrolo[2,3-*b*]indole (HPI) framework is widely represented among natural products. Over 1000 alkaloids and peptides containing this structural motif have been isolated to date. The HPI natural products exhibit a range of interesting biological activities, e.g. as cytotoxic and neuroprotective agents, and cholinesterase inhibitors (Figure 1).

These interesting properties combined with unusual structural features have rendered these natural products attractive synthetic targets.¹ In particular, hexahydropyrrolo[2,3-*b*]indoles bearing a C3–N bond have presented a notable synthetic challenge, due to the difficulties associated with the introduction of the nitrogenous substituents in the C3-position of indoles.

Electrophilic addition followed by cyclization is a general and efficient method of synthesis of pyrroloindolines. Toward this end, a number of electrophilic reagents have recently been utilized for the construction of this tricyclic core from tryptophanes and tryptamines. Thus, Quing described a trifluoromethylsulfanilation-cyclization cascade mediated by CF₃SNHPh.² Selenofunctionalization of tryptamines has also been extensively documented and employed in total synthesis.³ Fluoro-⁴ chloro-⁵ bromocyclizations⁶ en route to hexahydropyrrolo[2,3-

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b]indoles have been reported as well. In addition, installation of 3-hydroxy group has been achieved by oxidatively-induced cyclizations of tryptamines with hypervalent iodine reagents,⁷ singlet oxygen,⁸ DMDO,⁹ and photochemically with heterocyclic *N*-oxides.¹⁰ Some of the recent methods that have been used to introduce a nitrogen substituent in the C3-position of hexahydropyrrolo[2,3-*b*]indoles include reactions of tryptamines with *N*-iodosuccinimide and primary or secondary amine,¹¹ iodine/*tert*-butyl hydrogen peroxide/amine,¹² azodicarboxylates,¹³ sequential bromocyclization/base-mediated nucleophilic substitution,¹⁴ rhodium-catalyzed amidation,¹⁵ condensation with *N*-oxyindoles,¹⁶ and iodine azide-mediated cyclization¹⁷ (Figure 1).

Arenediazonium compounds have recently emerged as versatile reagents for a variety of C–C-bond-forming reactions. Some examples include Heck-Matsuda reaction¹⁸ palladium-catalyzed C–H-arylation,¹⁹ as well as²⁰ Meerwein and Sandmeyer-type reactions.²¹ On the other hand, examples of use of arenediazonium compounds for the formation of C–N-bonds are relatively rare. Thus, Knochel described an efficient indazole synthesis from functionalized organozinc reagents.²² Aggarwal employed arenediazonium compounds for stereospecific amination of alkylboronates.²³ In addition, azo-coupling reaction with arenes has been used for the synthesis of new dyes²⁴ and as a vehicle for the tyrosine-specific bioconjugation.²⁵ Although arenediazonium salts have previously been used as electrophiles in reactions with electron-rich alkenes and silyl enol ethers,²⁶ they have not been employed as electrophiles for a 1,2-diamination. Herein, we describe an azo-coupling/cyclization cascade as a straightforward method of synthesis of pyrrolidinoindolines bearing the C3–N-linkage, and their use for preparation of further HPI compounds.

Results and Discussion

Initial experiments with *N*-acetyltryptamine (**1**) and benzenediazonium tetrafluoroborate (**2**) have shown that the desired HPI product **3** can be formed, albeit in a low yield at room temperature in CH₂Cl₂ and with NaHCO₃ as a base (Table 1, entry 1). Acetonitrile proved to be a better medium than dichloromethane and methanol, and a moderate improvement was observed at –78 °C (entries 2–4). Subsequent base screen demonstrated that cesium carbonate was superior to other basic alkali metal salts (entries 5–9). Finally, the optimal yield of **3** was obtained at –20 °C with a reduced amount of diazonium salt **2** (entry 11) and cesium carbonate as a base. Interestingly, *tert*-butyldimethylsilyl-protected indole **4** also proved to be a viable substrate and afforded product **3** as a result of concomitant desilylation. Generally, the effects of solvent, base and temperature (entries 12–19) on the performance of substrate **4** were similar to those of unprotected indole **1**, although a higher yield of coupling product **3** was obtained under optimized conditions (entry 20).

We then proceeded with the study of the scope of the reaction. Since synthetically useful yields were obtained for both unprotected indole **1** and *N*-silylindole **4**, the unprotected tryptamines were used as substrates. Under the optimized conditions a variety of diazonium compounds have reacted readily with substituted tryptamines. In general, reactions with arenediazonium salts bearing electron-withdrawing substituents proceeded more cleanly and afforded higher yields than their less electrophilic counterparts (Figure 2). Thus, 3,5-

bis(trifluoromethyl)benzenediazonium tetrafluoroborate proved to be a particularly efficient reagent.

ortho-Substituted diazonium salts were somewhat less reactive, requiring longer reaction times to give synthetically useful yields of pyrroloindolines (e.g. compounds **13**, **16** and **19**).

The azo-cyclization reaction also appears to exhibit a broad scope with respect to the tryptamine counterparts. The general requirement for the nucleophilic *N*-terminus was a presence of an electron-withdrawing group on the C3-side chain nitrogen, as no azocyclization products were observed with tryptamines bearing *N*-alkyl groups or with unprotected tryptamine. On the other hand, carbamides, sulfonamides and carbamates gave the desired products (e.g. **6**, **7**, **9**, and **12**) in good yields. In addition to 3-amidoalkyl side chains, substrates with *O*-termini in the C3-side chain also proved to give rise to diazenes. Thus, both tryptophol and 3-indoleacetic acid afforded products **8** and **18** in excellent yields. Substrates that were expected to give rise to products with a six-membered C-ring did not afford diazenes in isolable quantities. Finally, Boc-protected methyl ester of tryptophan reacted with diazonium compounds to give the corresponding pyrroloindolines (**19–21**) in good yields.

Photoinduced extrusion of nitrogen from unsymmetrical azo compounds was recently exploited by Movassaghi as a general and powerful strategy to heterodimeric hexahydropyrroloindoles.²⁷ A sequence of the arenediazonium/tryptamine cascade and the photochemical nitrogen extrusion can provide a transition metal-free two-step shortcut to 3-aryl-substituted hexahydropyrroloindoles.

The HPI subunit²⁸ bearing a C3-aryl group is present in a number of natural products e.g. asperazine²⁹ (Figure 1), naseaeazines A and B,³⁰ and pestalazine A³¹

Indeed, irradiation of tryptophol-derived compound **8** in *tert*-butanol afforded nitrogen extrusion product **22** in 42% yield (Table 2). Similarly, tryptophan-derived diazene **21** produced 3-phenyl-substituted product **23** in a 41 % yield. Attempts to use diazenes bearing substituents in the aromatic ring (e.g. **7**, **15**, and **19**), as well as phenyl-substituted diazenes **11** and **12** with *N*-tosyl and endocyclic amido groups led to scission of the C-ring, and only precursors **5** were isolated, highlighting the intricate balance of electronic effects during the solvent-caged photochemical process.

Substituted hydrazines are important molecular scaffolds in drug discovery. A number of hydrazines are currently used or investigated for the treatment of psychiatric disorders,³² tuberculosis,³³ and cancer.³⁴ We have, therefore, studied the reduction of 3-arylazopyrroloindolines to the corresponding substituted hydrazine derivatives (Table 3). It was found that unsymmetrical hydrazines **24–28** can be formed efficiently from the corresponding diazenes **3**, **9**, **10**, **12**, and **13** in high yields using hydrazine hydrate as a reducing agent.³⁵ On the other hand, attempts to induce reductive cleavage of the N–N-bond to 3-amino-hexahydropyrroloindoles led to exclusive formation of ring-scission products **5** with zinc and indium metals as reducing agents under acidic conditions (acetic acid in THF and HCl in CH₃OH).

In order to gain insights into the mechanism of the reaction the influence of the electronic factors on the reaction of tryptamine **5a** with arenediazonium compounds was studied (Figure 3). The Hammett plot of the reaction afforded a ρ -value of 0.59. This ρ -value is substantially lower than Hammett reaction constants observed for the reactions of indole, as well as 2- and 3-methylindole ($\rho = 3-3.3$).³⁶ The large ρ -values for these substrates were explained by the formation of the Wheland intermediate in the rate-limiting step.

On the other hand, studies by Jackson and Lynch point to the second step (proton abstraction) as the rate-limiting step.³⁷ Based on the relatively small Hammett reaction constant observed for the azocyclization of **5a**, the mechanism appears to be better described by the Jackson-Lynch model. This is in line with the recent mechanistic observation on the reversibility of the initial phenylselenation step in the phenylselenation/cyclization cascade reaction of tryptamines.³⁸

Conclusions

In summary, we have developed an arenediazonium-induced cyclization cascade of tryptamines, tryptophan derivatives and related 3-substituted indoles. The reaction affords 3-arylazoexahydropyrrolo[2,3-*b*]indoles in good to excellent yields, and, in combination with photoinduced nitrogen extrusion provides a simple transition metal-free two-step entry to arylhexahydropyrrolo[2,3-*b*]indoles related to asperazine and other secondary metabolites with the pyrroloindoline framework. The unsymmetrical diazenes can also be reduced to the corresponding hydrazo compounds in high yields.

Experimental Section

General Methods

Anhydrous dichloromethane were collected under argon from an LC Technologies solvent purification system. Acetonitrile was dried over 4 Å molecular sieves. 3 Å Molecular sieves were freshly dried at 100 °C and allowed to cool to room temperature under positive argon pressure before use. All chemicals were used as commercially available (Sigma-Aldrich, Acros, Alfa Aesar, Combi-Blocks, Strem). Arenediazonium salts have been prepared according to the literature procedure.³⁹ All reactions were conducted with continuous magnetic stirring under an atmosphere of argon in oven-dried glassware. Low-temperature experiments were conducted using a Neslab Cryotrol CB-80 cryostat. Reactions were monitored by TLC until deemed complete using silica gel-coated glass plates (Merck Kieselgel 60 F254) and neutral alumina plates. Plates were visualized under ultraviolet light (254 nm). Column chromatography was performed using CombiFlash Rf-200 (Teledyne-Isco) automated flash chromatography system. ¹H, ¹³C, ¹⁹F NMR spectra were recorded at 300 and 500 (¹H), and 75.5 and 125 MHz (¹³C), 282 MHz (¹⁹F) in CDCl₃ solutions if not otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) from the residual solvent peak and coupling constants (*J*) in Hz. Infrared measurements were carried out neat on a Bruker Vector 22 FT-IR spectrometer fitted with a Specac diamond attenuated total reflectance (ATR) module. Specific optical rotations were measured on a Rudolph Research Analytical Autopol IV digital polarimeter using a 1 dm cell.

General Procedure 1 (GP1) for the synthesis of pyrroloindolines 3, 6–21

To a solution of indole derivative **4**, **5a–f** (100 mg, 0.352 mmol, 1 equiv.), 3 Å molecular sieves (50 mg), and cesium carbonate (572 mg, 1.76 mmol, 5 equiv.) in the appropriate solvent [CH₃CN, CH₂Cl₂, or CH₃CN/CH₂Cl₂ (1:1)] (4 mL) at –20, 0 or 23 °C was added diazonium salt (230 mg, 0.704 mmol, 2 equiv.). The reaction was allowed to stir for 12 h then filtered through Celite and the solids were washed with dichloromethane (3 x 5 mL). After concentrating under reduced pressure, the crude product was purified by column chromatography [hexanes/EtOAc, on neutral alumina] to yield the desired product.

1-((3a*R*,8a*S*)-3a-(Phenyldiazenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-1(2*H*)-yl)ethanone (3)

According to GP1, *N*-[2-(1-(*tert*-Butyldimethylsilyl)-1*H*-indol-3-yl)ethyl]acetamide (**4**) (500 mg, 2.47 mmol), 3 Å molecular sieves (600 mg), and cesium carbonate (4.0 g, 12.37 mmol, 5 equiv.) in acetonitrile (25 mL) were reacted with benzenediazonium tetrafluoroborate (948 mg, 4.94 mmol, 2 equiv.) at –20 °C for 12 h. The crude product was purified by column chromatography to yield **3** (701 mg, 93 %) as red oil. – ¹H NMR (500 MHz): 2.08 (3 H, s), 3.44–3.50 (2 H, m), 3.69–3.77 (2 H, m), 6.19 (1 H, s), 6.67 (1 H, d, *J* = 7.5 Hz), 6.80 (1 H, dt, *J* = 1, 7.5 Hz), 7.17 (1 H, dt, *J* = 1, 8 Hz), 7.30 (1 H, dd, *J* = 1, 7.5 Hz), 7.41–7.50 (3 H, m), 7.70–7.73 (2 H, m) ppm. – ¹³C NMR (125 MHz): 22.4, 34.5, 46.9, 77.9, 88.4, 109.8, 119.0, 122.6, 124.9, 126.5, 128.3, 129.0, 130.1, 131.0, 150.1, 151.7, 170.8 ppm. – IR: 1128, 1282, 1361, 1415, 2893, 3026 cm^{–1}. – MS ESI: 307.2, calcd: 307.1553, HRMS found: 307.1554 [M + H⁺].

(3a*R*,8a*S*)-1-Benzyl-3a-[(3,5-bis(trifluoromethyl)phenyl)diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (6)

According to GP1, *N*-benzyl-2-(1*H*-indol-3-yl)acetamide (**5b**) (100 mg, 0.364 mmol), 3 Å molecular sieves (50 mg), cesium carbonate (572 mg, 1.76 mmol, 5 equiv.) in acetonitrile (4 mL) was reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (238 mg, 0.728 mmol, 2 equiv.) at –20 °C. The crude product was purified to yield HPI **6** (127 mg, 69 %) as red oil. – ¹H NMR (500 MHz): 3.31 (1 H, d, *J* = 17.5 Hz), 3.46 (1 H, d, *J* = 17.5 Hz), 4.41–4.50 (1 H, m), 4.97 (1 H, d, *J* = 15 Hz), 5.88 (1 H, s), 6.77 (1 H, d, *J* = 9 Hz), 7.03–7.48 (8 H, m), 7.79–8.04 (2 H, m), 8.16 (1 H, s), 8.31 (1 H, s) ppm. – ¹³C NMR (125 MHz): 40.4, 44.4, 78.6, 83.0, 110.5, 120.0, 122.6, 123.0, 127.4, 128.1, 129.1, 132.7, 135.6, 146.8, 151.3, 152.6, 153.1, 170.4 ppm. – ¹⁹F NMR (282 MHz): –62.9 ppm. – IR: 1043, 1146, 1252, 1381, 1498, 2871, 2964 cm^{–1}. – MS ESI: 503.1, calcd: 503.1312, HRMS found: 503.1311 [M + H⁺].

1-((3a*R*,8a*S*)-3a-((3,5-Bis(trifluoromethyl)phenyl)diazenyl)-5-methoxy-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-1(2*H*)-yl)ethanone (7)

According to GP1, melatonin (200 mg, 0.862 mmol), cesium carbonate (1.4 g, 4.31 mmol, 5 equiv.), and 3 Å molecular sieves (200 mg) in acetonitrile (8.6 mL) were reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (565 mg, 1.72 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield HPI **7** (215 mg, 55%) as red oil. – ¹H NMR (500 MHz): 1.68 (1 H, s), 2.11 (3 H, s), 2.67–2.70 (1 H, m),

3.52 (1 H, quart., $J = 2.5$ Hz), 3.78 (3 H, s), 5.17 (1 H, s), 6.16 (1 H, s), 6.64 (1 H, d, $J = 8.5$ Hz), 6.80 (1 H, dd, $J = 2.5, 8.5$ Hz), 6.87 (1 H, d, $J = 2.5$ Hz), 7.97 (1 H, s), 8.18 (2 H, s) ppm. – ^{13}C NMR (75 MHz): 22.4, 34.2, 46.8, 56.0, 78.5, 89.5, 111.0 (d, $J = 22.5$ Hz), 115.8, 122.4 (d, $J = 3$ Hz), 124.3 (d, $J = 3$ Hz), 126.7, 132.6 (quart., $J = 34.5$ Hz), 144.2, 151.8, 153.7, 170.4 ppm. – ^{19}F NMR (282 MHz): –62.9 ppm. – IR: 1025, 1133, 1345, 1465, 2988, 3026 cm^{-1} . – MS ESI: 471.1, calcd: 471.1261, HRMS found: 471.1263 $[\text{M}^-]$.

(3aR,8aS)-3a-(Phenyldiazenyl)-3,3a,8,8a-tetrahydro-2H-furo[2,3-*b*]indole (8)

According to GP1, tryptophol (300 mg, 1.86 mmol), 3 Å molecular sieves (250 mg), cesium carbonate (3 g, 9.31 mmol, 5 equiv.) in acetonitrile (18 mL) were reacted with benzenediazonium tetrafluoroborate (714 mg, 3.72 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield HPI **8** (470 mg, 96%) as red oil. – ^1H NMR (300 MHz): 2.57 (1 H, dd, $J = 4, 12.5$ Hz), 2.76–2.86 (1 H, m), 3.90–3.99 (1 H, m), 4.24 (1 H, t, $J = 7$ Hz), 5.07 (1 H, d, $J = 2$ Hz), 6.35 (1 H, d, $J = 3$ Hz), 6.73 (1 H, d, $J = 8$ Hz), 6.88 (1 H, t, $J = 7$ Hz), 7.19–7.54 (5 H, m), 7.81–7.85 (2 H, m) ppm. – ^{13}C NMR (75 MHz): 38.6, 67.3, 91.5, 96.3, 109.3, 119.3, 122.6, 125.5, 128.5, 129.1, 129.9, 131.0, 150.5, 152.0 ppm. – IR: 1123, 1325, 1413, 2998, 3036 cm^{-1} . – MS ESI: 266.1, calcd: 266.1288, HRMS found: 266.1285 $[\text{M} + \text{H}^+]$.

(3aR,8aS)-Benzyl 3a-((3,5-bis(trifluoromethyl)phenyl)diazenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2H)-carboxylate (9)

According to GP1, benzyl [2-(1*H*-indol-3-yl)ethyl]carbamate **5d** (300 mg, 1.02 mmol), cesium carbonate (1.66 g, 5.01 mmol, 5 equiv.), 3 Å molecular sieves (250 mg) in acetonitrile (10 mL) were reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (669 mg, 2.04 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield HPI **9** (340 mg, 88 %) as orange oil. – ^1H NMR (500 MHz, rotamers): 2.60–2.69 (2 H, m), 3.37–3.42 (1 H, m), 3.88–3.99 (1 H, m), 4.85 (0.5 H, br s), 5.16–5.32 (2 H, m), 6.10 (0.5 H, s), 6.14 (0.5 H, s), 6.79 (2 H, dd, $J = 7.5, 29$ Hz), 6.84 (1 H, t, $J = 7.5$ Hz), 7.19–7.48 (6 H, m), 7.97 (1 H, s), 8.19 (2 H, s) ppm. – ^{13}C NMR (125 MHz, rotamers): 34.0, 34.7, 45.3, 45.6, 67.1, 67.4, 77.5, 78.1, 89.9, 91.0, 109.9, 110.1, 119.3, 119.6, 121.8, 122.5, 122.9, 124.0, 124.2, 125.0, 125.5, 125.6, 128.0, 128.0, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.6, 128.7, 130.5, 130.6, 132.5, 132.8, 136.3, 149.8, 150.1, 151.9, 154.1, 155.0 ppm. – ^{19}F NMR (282 MHz): –62.9 ppm. – IR: 1144, 1183, 1280, 1369, 1422, 1699, 2896, 3024 cm^{-1} . – MS ESI: 533.1, calcd: 533.1418, HRMS found: 533.1951 $[\text{M}^-]$.

(3aR,8aS)-*tert*-Butyl 3a-[(2,4,5-trifluorophenyl)diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2H)-carboxylate (10)

According to GP1, *tert*-butyl [2-(1*H*-indol-3-yl)ethyl]carbamate (**5a**) (200 mg, 0.769 mmol), cesium carbonate (1.25 g, 3.84 mmol, 5 equiv.), and 3 Å molecular sieves (200 mg) in acetonitrile (7.7 mL) were reacted with 2,4,5-trifluorobenzenediazonium tetrafluoroborate (378 mg, 1.54 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **10** (198 mg, 62 %) as red oil. – ^1H NMR (500 MHz): 1.56 (4.5 H, s), 1.63 (4.5 H, s), 3.31–3.66 (2 H, m), 3.76–3.90 (2 H, m), 4.88 (0.5 H, br s), 5.31 (0.5 H, br

s), 6.02–6.10 (2 H, m), 6.74–7.31 (6 H, m) ppm. – ^{13}C NMR (125 MHz): 14.2, 21.0, 28.5, 28.5, 28.7, 34.0, 34.3, 36.7, 45.3, 45.7, 60.5, 78.5, 78.6, 80.2, 80.5, 81.4, 89.2, 90.2, 101.7, 102.0, 103.9, 104.1, 104.2, 106.0, 106.2, 106.3, 106.4, 106.6, 109.8, 109.9, 111.1, 111.1, 111.1, 119.1, 119.5, 125.0, 125.1, 126.9, 126.9, 128.2, 128.3, 128.3, 128.6, 128.6, 128.9, 130.1, 130.2, 130.2, 132.0, 135.6, 135.7, 145.7, 145.8, 147.4, 147.5, 147.6, 147.7, 147.8, 149.4, 150.0, 150.00, 150.4, 150.4, 153.8, 154.8, 156.4, 158.4, 171.2 ppm. – ^{19}F NMR (282 MHz): –126.1, –127.6, –137.6, –138.2, –139.8 ppm. – IR: 1159, 1207, 1286, 1411, 1527, 1631, 2999, 3053 cm^{-1} . – MS ESI: 417.2, calcd: 417.2446, HRMS found: 417.1544 [M^-].

(3aR,8aS)-1-Benzyl-3a-(phenyldiazenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-2(1*H*)-one (11)

According to GP1, *N*-benzyl-2-(1*H*-indol-3-yl)acetamide (**5b**) (1.0 g, 3.64 mmol), 3 Å molecular sieves (300 mg), cesium carbonate (5.95 g, 18.20 mmol, 5 equiv.) in acetonitrile (36 mL) were reacted with benzenediazonium tetrafluoroborate (1.40 g, 7.28 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **11** (1.18 g, 88 %) as a red oil. – ^1H NMR (500 MHz): 3.23 (1 H, d, $J = 17.5$ Hz), 3.47 (1 H, d, $J = 17.5$ Hz), 4.38 (1 H, d, $J = 15$ Hz), 5.10 (1 H, d, $J = 15$ Hz), 5.81 (1 H, d, $J = 4$ Hz), 6.78 (1 H, d, $J = 8$ Hz), 6.95 (1 H, t, $J = 8.5$ Hz), 7.25 (1 H, t, $J = 7.5$ Hz), 7.34–7.50 (9 H, m), 7.72–7.75 (2 H, m) ppm. – ^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$): 39.4, 41.8, 76.7, 81.7, 109.8, 118.2, 120.2, 121.2, 123.8, 126.2, 127.3, 127.7, 128.9, 130.0, 135.1, 148.5, 149.9, 169.4 ppm. – IR: 1057, 1162, 1306, 1440, 2899, 3025 cm^{-1} . – MS ESI: 369.1, calcd: 369.1710, HRMS found: 369.1712 [$\text{M} + \text{H}^+$].

(3aR,8aS)-3a-(Phenyldiazenyl)-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (12)

According to GP1, *N*-[2-(1*H*-indol-3-yl)ethyl]-4-methylbenzenesulfonamide (**5c**) (100 mg, 0.318 mmol), 3 Å molecular sieves (50 mg), cesium carbonate (516 mg, 1.59 mmol, 5 equiv.) in acetonitrile (3 mL) were reacted with benzenediazonium tetrafluoroborate (122 mg, 0.636 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **12** (84 mg, 64 %) as orange oil. – ^1H NMR (300 MHz): 2.41 (3 H, s), 2.43–2.56 (1 H, m), 3.17–3.23 (1 H, m), 3.40–3.54 (1 H, m), 4.29–4.35 (1 H, m), 5.06 (1 H, br s), 6.14 (1 H, s), 6.73 (1 H, d, $J = 8$ Hz), 6.83 (1 H, t, $J = 7.5$ Hz), 7.07–7.51 (9 H, m), 7.57–7.72 (2 H, m), 7.82–7.89 (2 H, m) ppm. – ^{13}C NMR (75 MHz): 21.5, 35.5, 47.2, 80.4, 90.5, 110.1, 119.4, 122.2, 124.7, 127.4, 128.4, 129.0, 129.8, 130.2, 131.2, 135.6, 143.7, 149.5, 151.4 ppm. – IR: 1046, 1161, 1305, 1401, 1439, 1598, 1610, 1702, 2973, 3063 cm^{-1} . – MS ESI: 417.0, calcd: 417.1391, HRMS found: 417.1429 [M^-].

(3aR,8aS)-*tert*-Butyl 3a-[-(2-bromophenyl)diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (13)

According to GP1, *tert*-butyl [2-(1*H*-indol-3-yl)ethyl]carbamate (**5a**) (100 mg, 0.384 mmol), cesium carbonate (630 mg, 1.92 mmol, 5 equiv.), and 3 Å molecular sieves (100 mg) in acetonitrile (4 mL) were reacted with 2-bromobenzenediazonium tetrafluoroborate (207 mg, 0.768 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **13** (160 mg, 95 %) as orange oil. – ^1H NMR (500 MHz, rotamers): 1.52 (4.5 H, s), 1.59 (4.5 H, s), 2.55–2.68 (2 H, m), 3.30–3.37 (2 H, m), 3.75 (1 H, dt, $J = 1$,

8.5 Hz), 3.88 (1 H, dt, $J = 1$, 8.5 Hz), 4.84 (1 H, br s), 5.28 (1 H, br s), 6.08 (1 H, s), 6.13 (1 H, s), 6.71 (1 H, d, $J = 7.5$ Hz), 6.82 (1 H, quart, $J = 8$ Hz), 7.19–7.44 (4 H, m), 7.70–7.72 (2 H, m) ppm. – ^{13}C NMR (125 MHz, rotamers): 28.5, 28.7, 34.1, 34.3, 45.2, 45.7, 78.5, 78.7, 80.1, 80.5, 89.9, 91.0, 109.7, 109.9, 118.0, 118.1, 119.0, 119.4, 124.4, 125.2, 125.2, 126.3, 126.4, 127.9, 127.9, 128.6, 130.1, 130.2, 131.8, 131.8, 133.5, 133.5, 149.1, 149.9, 150.2, 153.7, 154.7 ppm. – IR: 1028, 1071, 1208, 1308, 1366, 1468, 1553, 1683, 2883, 2977, 3055 cm^{-1} . – MS ESI: 441.0, calcd: 441.0932, HRMS found: 440.0997 $[\text{M}^-]$.

(3a*R*,8a*S*)-*tert*-Butyl 3a-(phenyldiazenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (14)

According to GP1, *tert*-butyl [2-(1*H*-indol-3-yl)ethyl]carbamate (**5a**) (200 mg, 0.769 mmol), cesium carbonate (1.25 g, 3.84 mmol, 5 equiv.), and 3 Å molecular sieves (200 mg) in acetonitrile (7.7 mL) was reacted with benzenediazonium tetrafluoroborate (295 mg, 1.54 mmol, 2 equiv.) at $-20\text{ }^{\circ}\text{C}$. The crude product was purified by column chromatography to yield **14** (207 mg, 74 %) as red oil. – ^1H NMR (300 MHz, rotamers): 1.45–1.60 (9 H, m), 2.56–2.69 (3 H, m), 3.25–3.37 (1 H, m), 3.70–3.90 (1 H, m), 5.99 (1 H, br s), 6.10 (1 H, s), 6.71 (1 H, d, $J = 8.5$ Hz), 6.76–6.83 (1 H, m), 7.14–7.51 (5 H, m), 7.68 (1 H, m), 7.91 (1 H, d, $J = 8$ Hz) ppm. – ^{13}C NMR (125 MHz, rotamers): 27.4, 28.5, 28.5, 28.7, 34.0, 34.4, 45.2, 45.6, 78.1, 80.1, 80.5, 88.5, 89.1, 90.1, 109.0, 109.8, 109.8, 109.9, 111.3, 119.3, 122.0, 122.1, 122.5, 122.6, 122.6, 122.7, 122.7, 122.8, 125.0, 125.0, 128.2, 128.9, 128.9, 129.0, 129.0, 129.1, 129.8, 130.0, 130.9, 131.2, 151.6, 151.7, 151.8, 153.7, 154.7 ppm. – IR: 1121, 1164, 1252, 1307, 1393, 1456, 1515, 1604, 1695, 2890, 2978, 3061 cm^{-1} . – MS ESI: 363.1, calcd: 363.1826, HRMS found: 363.1710 $[\text{M}^-]$.

(3a*R*,8a*S*)-*tert*-Butyl 3a-[(3,5-bis(trifluoromethyl)phenyl)diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (15)

According to GP1, *tert*-butyl [2-(1*H*-indol-3-yl)ethyl]carbamate (**5a**) (200 mg, 0.769 mmol), cesium carbonate (1.25 g, 3.84 mmol, 5 equiv.), 3 Å molecular sieves (200 mg) in acetonitrile (8 mL) were reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (500 mg, 1.53 mmol, 2 equiv.) at $-20\text{ }^{\circ}\text{C}$. The crude product was purified by column chromatography to yield **15** (373 mg, 97 %) as an orange oil. – ^1H NMR (500 MHz): 1.52–1.62 (18 H, m), 2.61–2.67 (1 H, m), 2.72–2.75 (2 H, m), 3.22–3.41 (2 H, m), 3.78–4.00 (3 H, m), 5.87 (1 H, br s), 6.11 (1 H, s), 6.20 (1 H, s), 7.73–7.98 (4 H, m), 8.10–8.31 (3 H, m) ppm. – ^{13}C NMR (125 MHz, rotamers): 28.3, 28.6, 34.2, 34.7, 45.0, 45.4, 77.9, 78.1, 80.9, 81.2, 82.3, 90.3, 108.9, 110.0, 118.0, 119.2, 119.5, 120.0, 121.4, 121.4, 121.8, 122.1, 122.4, 122.9, 123.0, 124.0, 124.0, 124.3, 124.4, 125.0, 125.1, 125.3, 125.7, 125.8, 126.1, 126.5, 126.9, 127.0, 129.8, 129.9, 130.4, 130.5, 130.6, 131.7, 133.5, 145.9, 146.1, 150.0, 150.3, 151.3, 151.6, 151.8, 152.0, 153.3, 153.3, 154.1, 154.5 ppm. – ^{19}F NMR (282 MHz): -62.9 ppm. – IR: 1058, 1107, 1177, 1279, 1368, 1481, 1610, 2938, 3031 cm^{-1} . – MS ESI: 499.1 $[\text{M}^-]$, calcd: 522.1466, HRMS found: 522.1474 $[\text{M}+\text{Na}^+]$.

(3a*R*,8a*S*)-tert-Butyl 3a-[(4-methoxy-2-nitrophenyl)diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (16)

According to GP1, *tert*-butyl [2-(1*H*-indol-3-yl)ethyl]carbamate (**5a**) (50 mg, 0.192 mmol), cesium carbonate (315 mg, 0.960 mmol, 5 equiv.), and 3 Å molecular sieves (100 mg) in acetonitrile (2 mL) were reacted with 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (102 mg, 0.384 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield HPI **16** (53 mg, 63 %) as purple oil. – ¹H NMR (500 MHz, rotamers): 1.49 (4.5 H, s), 1.57 (4.5 H, s), 2.45–2.64 (2 H, m), 3.23–3.32 (1 H, m), 3.71–3.89 (2 H, m), 3.91 (3 H, s), 4.72–4.85 (1 H, br s), 5.22–5.26 (1 H, br s), 5.30 (1 H, d, *J* = 1.5 Hz), 5.95 (1 H, s), 6.01 (1 H, s), 6.69 (1 H, d, *J* = 7.5 Hz), 6.78 (1 H, quart., *J* = 8 Hz), 7.08 (1 H, d, *J* = 9 Hz), 7.15–7.40 (4 H, m) ppm. – ¹³C NMR (125 MHz, rotamers): 14.1, 22.7, 28.4, 28.6, 33.6, 45.2, 45.2, 45.8, 56.2, 78.3, 78.8, 80.2, 80.5, 89.7, 90.8, 108.3, 109.7, 109.8, 119.0, 119.1, 119.4, 119.8, 119.8, 125.1, 126.0, 128.3, 130.2, 130.2, 138.3, 138.4, 148.4, 149.9, 150.3, 153.6, 154.6, 161.2, 161.2 ppm – IR: 1120, 1254, 1356, 1440, 2983, 3044 cm^{–1}. – MS ESI: 438.0, calcd: 438.1783, HRMS found: 438.1678 [M[–]].

((3a*R*,8a*S*)-3a-(3,5-Bis(trifluoromethyl)phenyl)diazenyl)-5-chloro-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-1(2*H*)-yl)(phenyl)methanone (17)

According to GP1, *N*-(2-(5-Chloro-1*H*-indol-3-yl)ethyl)benzamide (**5e**) (30 mg, 0.105 mmol), cesium carbonate (171 mg, 0.528 mmol, 5 equiv.), and 3 Å molecular sieves (50 mg) in acetonitrile (1 mL) were reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (68 mg, 0.210 mmol, 2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **17** (38 mg, 88 %) as yellow oil. – ¹H NMR (500 MHz): 1.27 (1 H, s), 1.65–1.70 (1 H, br s), 2.63 (1 H, quart., *J* = 5 Hz), 3.61 (1 H, quart. *J* = 10 Hz), 3.82 (1 H, quart., *J* = 5 Hz), 5.45 (1 H, s), 6.48 (1 H, s), 6.66 (1 H, d, *J* = 8 Hz), 7.19 (1 H, d, *J* = 8 Hz), 7.27 (1 H, s), 7.40–7.54 (5 H, m), 7.99 (1 H, s), 8.21 (1 H, s) ppm. – ¹³C NMR (125 MHz): 35.0, 48.6, 78.2, 89.0, 110.8, 121.8, 123.0 (d, *J* = 3 Hz), 123.9 (d, *J* = 25 Hz), 124.4, 125.3, 126.9, 127.1, 128.3, 128.4, 130.6, 132.8 (quart., *J* = 34 Hz), 135.4, 149.0, 151.7, 170.2 ppm. – ¹⁹F NMR (282 MHz): –62.9 ppm. – IR: 1088, 1107, 1177, 1369, 1448, 1577, 1624, 2924, 2995, 30888, 3326 cm^{–1}. – MS ESI: 527.1, calcd: 537.0922, HRMS found: 537.0901 [M[–]].

(3a*R*,8a*S*)-3a-[(3,5-Bis(trifluoromethyl)phenyl)diazenyl]-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indol-2-one (18)

Indole-3-acetic acid (200 mg, 1.14 mmol), cesium carbonate (1.85 g, 5.70 mmol, 5 equiv.), and 3 Å molecular sieves (200 mg) in acetonitrile (11 mL) and dichloromethane (11 mL) were reacted with 3,5-bis(trifluoromethyl)benzenediazonium tetrafluoroborate (747 mg, 2.28 mmol, 2 equiv.) at 23 °C. The crude product was purified by column chromatography to yield **18** (380 mg, 84 %) as orange oil. – ¹H NMR (500 MHz): 3.38 (1 H, d, *J* = 19 Hz), 3.72 (1 H, d, *J* = 19 Hz), 7.41–7.58 (2 H, m), 7.74–8.24 (4 H, m), 8.46 (2 H, s) ppm. – ¹³C NMR (75 MHz): 29.7, 37.6, 83.1, 117.6, 119.2, 120.9, 121.0, 121.4, 121.9, 123.1, 123.6, 124.5, 125.3, 125.8, 127.2–132.0, 132.3, 132.8, 133.3, 133.8, 149.9, 151.0, 152.1, 171.6 ppm. – ¹⁹F NMR (282 MHz): –63.1 ppm. – IR: 1092, 1135, 1263, 1369, 1442, 1516, 2801, 2963, 3033 cm^{–1}. – MS ESI: 546.9, calcd: 546.9732, HRMS found: 546.9678 [M+Cs⁺].

(2S,3R,8S)-1-tert-Butyl 2-methyl 3a-(naphthalen-1-yl diazenyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (19)

According to GP1, (S)-Boc-Trp-OMe (**5f**) (75 mg, 0.235 mmol), cesium carbonate (381 mg, 1.17 mmol, 5 equiv.), 3 Å molecular sieves (100 mg), in acetonitrile (2.5 mL) was reacted with naphthalene-1-diazonium tetrafluoroborate (227 mg, 0.940 mmol, 4 equiv.) at 23 °C. The crude product was purified by column chromatography to yield **19** (83 mg, 75 %) as a red oil. – $[\alpha]_D^{23} +111$ (c 1.35, CHCl₃). – ¹H NMR (500 MHz, rotamers): 1.46 (9 H, s), 1.59 (3 H, s), 2.80–3.36 (4 H, m), 3.63 (3 H, s), 5.51 (1 H, s), 6.36 (1 H, s), 6.74–6.81 (2 H, m), 7.13–7.96 (8 H, m), 8.66–8.69 (1 H, m) ppm. – ¹³C NMR (125 MHz, rotamers): 28.2, 28.6, 29.7, 37.5, 38.0, 52.2, 52.4, 59.6, 59.6, 80.3, 81.2, 88.5, 109.7, 110.2, 112.4, 119.2, 120.8, 123.1, 124.6, 125.5, 125.8, 126.3, 126.5, 126.9, 127.0, 127.9, 128.3, 128.5, 130.2, 131.4, 134.1, 146.6, 149.6, 154.1, 172.7 ppm. – IR: 1144, 1165, 1257, 1317, 1456, 1506, 1694, 2950, 2974, 3050 cm^{–1}. – MS ESI: 473.9 [M+H⁺], calcd: 471.2038, HRMS found: 471.1363 [M[–]].

(2S,3R,8S)-1-tert-Butyl 2-methyl 3a-[(4-iodophenyl) diazenyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (20)

According to GP1, (S)-Boc-Trp-OMe (**5f**) (75 mg, 0.235 mmol), 3 Å molecular sieves (100 mg), and cesium carbonate (381 mg, 1.17 mmol, 5 equiv.) in acetonitrile (2.5 mL) were reacted with 4-iodobenzenediazonium tetrafluoroborate (297 mg, 0.940 mmol, 4 equiv.) at 23 °C. The crude product was purified by column chromatography to yield **20** (68 mg, 53 %) as orange oil. – $[\alpha]_D^{23} +35$ (c 0.6, CHCl₃). – ¹H NMR (500 MHz, rotamers): 1.43–1.58 (9 H, m), 2.76–3.02 (2 H, m), 3.67 (3 H, s), 4.31–4.38 (1 H, m), 5.45 (1 H, br s), 6.22 (1 H, s), 6.71–6.80 (1 H, m), 7.08–7.45 (3 H, m), 7.70 (2 H, dd, *J* = 3, 9 Hz), 7.80 (2 H, dd, *J* = 3, 9 Hz) ppm. – ¹³C NMR (125 MHz, rotamers): 28.2, 37.4, 37.8, 52.1, 59.3, 80.1, 81.2, 87.8, 97.9, 110.0, 110.2, 119.2, 119.8, 124.2, 124.3, 124.3, 124.5, 124.5, 126.7, 128.4, 128.5, 128.5, 130.2, 138.3, 138.3, 139.3, 149.5, 150.8, 154.1, 172.7 ppm. – IR: 1212, 1299, 1448, 1515, 2931, 2999, 3042 cm^{–1}. – MS ESI: 546.0, calcd: 547.0848, HRMS found: 547.3660 [M[–]].

(2S,3aR,8aS)-1-tert-Butyl 2-methyl 3a-phenyldiazenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indole-1,2(2H)-dicarboxylate (21)

According to GP1, (S)-Boc-Trp-OMe (**5f**) (1.28 g, 3.14 mmol), 3 Å molecular sieves (1.2 g), and cesium carbonate (5.10 g, 15.7 mmol, 5 equiv.) in acetonitrile (31 mL) was reacted with benzenediazonium tetrafluoroborate (1.93 g, 10.0 mmol, 3.2 equiv.) at –20 °C. The crude product was purified by column chromatography to yield **21** (1.28 g, 96 %) as red oil. – ¹H NMR (300 MHz, rotamers): 1.42 (9 H, s), 1.56 (3 H, s), 2.74–3.05 (2 H, m), 4.30–4.40 (1 H, m), 5.45 (1 H, br s), 6.23 (1 H, s), 6.70–6.79 (2 H, m), 7.11–7.70 (4 H, m) ppm. – ¹³C NMR (125 MHz): 28.3, 37.9, 52.2, 59.4, 78.9, 80.2, 81.1, 87.7, 110.2, 119.2, 122.6, 122.6, 124.6, 127.0, 128.4, 129.0, 130.2, 131.1, 149.6, 151.6, 154.1, 172.7 ppm. – IR: 1013, 1146, 1215, 1345, 2890, 2993, 3026 cm^{–1}. – MS ESI: 421.2, calcd: 421.1881, HRMS found: 421.1880 [M[–]].

(3*R*,8*S*)-3a-Phenyl-3,3a,8,8a-tetrahydro-2*H*-furo[2,3-*b*]indole⁴⁰ (22)

Diazene **8** (80 mg, 0.300 mmol) in *tert*-butanol (5 mL) was irradiated with UV light using low-pressure Hg lamp in a quartz photoreactor for 12 h. The crude product was purified by column chromatography to yield **22** (30 mg, 42 %) as an orange oil. – ¹H NMR (500 MHz): 2.57 (1 H, dd, *J* = 4.5, 12 Hz), 2.80 (1 H, dd, *J* = 7.5, 11 Hz), 3.73 (1 H, dd, *J* = 7.5, 11 Hz), 4.17–4.33 (1 H, m), 4.68 (1 H, br s), 5.67 (1 H, s), 6.71 (1 H, d, *J* = 7.5 Hz), 6.80 (1 H, d, *J* = 7 Hz), 7.07 (1 H, d, *J* = 7 Hz), 7.14 (1 H, t, *J* = 8 Hz), 7.30–7.40 (5 H, m) ppm. – ¹³C NMR (125 MHz): 40.5, 62.3, 68.3, 100.5, 108.7, 119.3, 124.6, 126.1, 126.7, 128.4, 128.7, 132.7, 144.0, 149.4 ppm. – IR: 1033, 1282, 1384, 2845, 2975, 3051 cm^{–1}.

(2*S*,3*R*,8*S*)-1-*tert*-Butyl 2-methyl 3a-phenyl-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1,2(2*H*)-dicarboxylate (23)

Diazene **21** (118 mg, 0.279 mmol) in *tert*-butanol (5 mL) was irradiated with UV light using low-pressure Hg lamp in a quartz photoreactor for 12 h. The crude product was purified by column chromatography [hexanes/EtOAc/silica gel] to yield **23** (45 mg, 41 %) as brown oil. – ¹H NMR (500 MHz): 1.41–1.47 (9 H, m), 1.54–1.60 (3 H, m), 2.71–3.05 (4 H, m), 3.21 (1 H, s), 3.75 (3 H, s), 5.53 (1 H, br s), 5.65 (1 H, s), 6.68–6.83 (2 H, m), 6.99–7.79 (7 H, m) ppm. – ¹³C NMR (125 MHz, rotamers): 33.5, 33.6, 45.1, 45.5, 67.1, 67.3, 76.6, 78.0, 110.1, 110.2, 112.2, 119.4, 119.5, 123.6, 123.9, 126.7, 127.8, 128.0, 128.1, 128.3, 128.3, 128.3, 128.5, 128.7, 130.4, 132.2, 136.2, 149.9, 150.1, 150.7, 150.9, 154.1, 155.1 ppm. – IR: 1156, 1228, 1369, 1480, 1695, 2726, 2877, 2983, 3050 cm^{–1}. – MS ESI: 395.8 [M+H⁺], calcd: 393.1820, HRMS found: 393.1660 [M[–]].

General Procedure 2 (GP2) for the synthesis of hydrazines 24–28

To a solution of diazene in ethanol was added hydrazine hydrate and the reaction mixture was heated at 50 °C for 3–12 h. The solution was then concentrated under reduced pressure and purified by column chromatography [hexanes/EtOAc/silica gel] to yield the desired product.

1-((3*aR*,8*aS*)-3a-(2-Phenylhydrazinyl)-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indol-1(2*H*)-yl)ethanone (24)

According to GP2, **3** (200 mg, 0.653 mmol) and hydrazine hydrate (1 mL) in ethanol (5 mL) were heated to 50 °C. The product was isolated after 12 h by concentrating under reduced pressure to yield **24** (199 mg, 99 %) as a yellow oil. – ¹H NMR (500 MHz, rotamers): 2.35 (3 H, s), 3.28–3.45 (4 H, m), 3.75 (1 H, br s), 4.93 (1 H, br s), 5.31 (1 H, s), 5.71 (1 H, br s), 6.72 (1 H, d, *J* = 8 Hz), 6.88 (1 H, d, *J* = 7.5 Hz), 7.12–7.83 (7 H, m) ppm. – ¹³C NMR (125 MHz, rotamers): 21.5, 34.6, 47.1, 78.3, 80.1, 106.7, 110.4, 119.4, 119.4, 119.4, 122.2, 123.5, 124.9, 125.7, 126.4, 126.8, 127.2, 127.3, 127.4, 128.3, 128.7, 129.7, 129.8, 130.3, 134.0, 135.1, 143.5, 144.0, 150.0 ppm. – IR: 1014, 1174, 1315, 1396, 1555, 2875, 3053 cm^{–1}. – MS ESI: 305.1, calcd: 305.1408, HRMS found: 305.1372 [M[–]].

(3a*R*,8a*S*)-Benzyl 3a-[2-(3,5-bis(trifluoromethyl)phenyl)hydrazinyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (25)

According to GP2, diazene **9** (63 mg, 0.117 mmol) was reacted with hydrazine hydrate (37 μ L, 1.17 mmol, 10 equiv.) in ethanol (1 mL) at 50 °C. After 8 h, the solvent was removed under reduced pressure to yield **25** (63 mg, 99%) as a yellow oil. – ^1H NMR (500 MHz): 2.31–2.38 (2 H, m), 3.17–3.22 (1 H, m), 3.75–3.84 (1 H, m), 4.02 (1 H, s), 5.08–5.30 (2 H, m), 5.37 (1 H, s), 5.56 (1 H, br s), 5.77 (1 H, s), 6.58–6.65 (2 H, m), 6.80–6.83 (1 H, m), 7.16–7.37 (9 H, m) ppm. – ^{13}C NMR (125 MHz): 33.4, 44.6, 45.1, 45.5, 67.1, 67.3, 76.6, 77.6, 78.0, 110.1, 110.2, 112.0, 112.0, 112.0, 112.0, 112.2, 119.4, 119.5, 122.4, 123.6, 123.9, 124.6, 126.4, 126.7, 127.8, 128.0, 128.1, 128.3, 128.3, 128.4, 128.5, 128.7, 130.4, 131.9, 132.2, 136.2, 136.3, 149.9, 150.1, 150.7, 150.9, 154.1, 155.1 ppm. – ^{19}F NMR (282 MHz): –62.7 ppm. – IR: 1047, 1130, 1266, 1278, 1357, 1457, 1621, 2889, 3038 cm^{-1} . – MS ESI: 535.1, calcd: 535.1574, HRMS found: 535.1205 [M^-].

(3a*R*,8a*S*)-*tert*-Butyl 3a-[2-(2,4,5-trifluorophenyl)hydrazinyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (26)

According to GP2, **10** (90 mg, 0.217 mmol) and hydrazine hydrate (500 μ L) in ethanol (3 mL) was heated to 50 °C. The product was isolated after 12 h by concentrating under reduced pressure to yield **26** (89 mg, 98 %) as yellow oil. – ^1H NMR (500 MHz, rotamers): 1.41–2.26 (9 H, m), 3.05–3.26 (4 H, m), 3.58–3.79 (4 H, m), 3.94 (1 H, br s), 4.00 (1 H, br s), 4.71 (1 H, br s), 5.21–5.51 (2 H, m), 6.53–7.41 (5 H, m) ppm. – ^{13}C NMR (125 MHz, rotamers): 17.8, 25.0, 28.4, 33.3, 45.3, 78.0, 80.1, 80.5, 102.8 – 105.4, 110.0, 110.1, 110.4 (d, $J = 6$ Hz), 110.5 (d, $J = 6$ Hz), 111.2 (d, $J = 3$ Hz), 111.4 (d, $J = 3$ Hz), 113.7, 116.0 – 116.3 (m), 117.9 – 118.2 (m), 119.0, 119.3, 123.8 (d, $J = 16$ Hz), 126.2, 127.1 (d, $J = 16$ Hz), 128.3, 130.2, 135.6 – 135.9 (m), 144.6, 145.7 – 148.0, 149.9, 150.3, 153.6, 154.7, 159.7 ppm. – ^{19}F NMR (282 MHz): –147.2, –141.9, –139.3, –138.4, –136.3, –130.0 ppm. – IR: 1094, 1159, 1216, 1305, 1325, 1458, 1529, 2875, 3041 cm^{-1} . – MS ESI: calcd: 420.1773, HRMS found: 420.1558 [M^-].

(3a*R*,8a*S*)-3a-(2-Phenylhydrazinyl)-1-tosyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole (27)

According to GP2, **12** (110 mg, 0.263 mmol) was reacted with hydrazine hydrate (500 μ L) in ethanol (5 mL) at 50 °C for 12 h. The crude product was purified by column chromatography to yield **27** (84 mg, 76 %) as a yellow oil. – ^1H NMR (500 MHz): 2.07–2.22 (2 H, m), 2.44 (3 H, s), 2.94 (1 H, t, $J = 6.5$ Hz), 3.26–3.49 (3 H, m), 3.84 (1 H, br s), 4.91 (1 H, br s), 5.24 (1 H, s), 5.26 (1 H, br s), 5.39 (1 H, s), 5.24 (1 H, s), 5.26 (1 H, br s), 5.39 (1 H, s), 6.70–7.09 (7 H, m), 7.19–7.34 (4 H, m) ppm. – ^{13}C NMR (125 MHz): 21.5, 25.5, 29.7, 34.8, 43.0, 47.1, 78.1, 80.4, 102.7, 103.0, 103.5, 103.7, 105.2, 105.4, 105.6, 109.2, 110.1, 110.3, 111.3, 111.6, 118.5, 119.5, 122.3, 122.6, 123.3, 126.6, 127.0, 127.2, 128.3, 129.6, 129.9, 130.5, 135.2, 144.0, 149.9 ppm. – IR: 1094, 1159, 1216, 1305, 1325, 1458, 1529, 2875, 3041 cm^{-1} .

(3a*R*,8a*S*)-tert-Butyl 3a-[2-(2-bromophenyl)hydrazinyl]-3,3a,8,8a-tetrahydropyrrolo[2,3-*b*]indole-1(2*H*)-carboxylate (28)

According to GP2, diazene **13** (100 mg, 0.226 mmol) was reacted with hydrazine hydrate (500 μ L) in ethanol (5 mL) at 50 °C for 4 h. The product was azeotroped to yield hydrazine **28** (99 mg, 99 %) as a yellow oil. – ^1H NMR (500 MHz, rotamers): 1.46–1.51 (9 H, m), 2.18–2.44 (4 H, m), 3.08–3.17 (2 H, m), 3.62 (1 H, dt, $J = 2$, 8.5 Hz), 3.75 (1 H, dt, $J = 2$, 8.5 Hz), 3.89 (1 H, br s), 3.94 (1 H, br s), 4.66 (1 H, s), 5.18 (br s), 5.23 (1 H, s), 5.30 (1 H, s), 5.72 (1 H, s), 5.76 (1 H, s), 6.64 (2 H, dt, $J = 1$, 8 Hz), 6.67 (1 H, s), 6.69 (1 H, s), 6.81–6.86 (2 H, m), 7.12 (3 H, quart, $J = 7.5$ Hz), 7.30–7.37 (5 H, m) ppm. – ^{13}C NMR (125 MHz, rotamers): 14.8, 17.9, 25.1, 25.1, 28.4, 28.6, 33.0, 33.4, 45.1, 45.4, 76.5, 77.6, 78.2, 80.0, 80.4, 107.2, 110.1, 110.2, 114.4, 114.5, 119.0, 119.3, 119.6, 119.6, 123.5, 123.8, 127.4, 127.6, 128.2, 128.3, 130.1, 132.1, 146.3, 146.4, 149.9, 150.2, 153.7, 154.7, 159.7 ppm. – IR: 1166, 1237, 1322, 1408, 1646, 2863, 2927, 3045, 3293 cm^{-1} . – MS ESI: 441.1, calcd: 443.1088, HRMS found: 441.1171 [M^-].

General Procedure 3 for kinetic experiments (GP3)

To a solution of **5a** (50 mg, 0.192 mmol, 1 equiv.), cesium carbonate (312 mg, 0.961 mmol, 5 equiv.), and 3 Å molecular sieves in acetonitrile (2 mL) at 23 °C was added arenediazonium salt (0.192 mmol, 1 equiv.) in one portion. An aliquot was drawn at 2 min., concentrated under reduced pressure, and conversion of **5a** was determined by ^1H NMR. Each experiment was repeated in quadruple, and the average was used for the Hammett plot.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative hexahydropyrrolo[2,3-*b*]indole natural products.

Figure 2.

Synthetic scope of the reaction of arenediazonium compounds with tryptamines, substituted tryptophan derivatives and related 3-substituted indoles. Reaction conditions: [a] ArN_2BF_4 (2 equiv.), 3 Å molecular sieves, CH_3CN , $-20\text{ }^\circ\text{C}$, 12 h. [b] **4**, ArN_2BF_4 (2 equiv.), 3 Å molecular sieves, CH_2Cl_2 , $0\text{ }^\circ\text{C}$, 12 h. [c] ArN_2BF_4 (2 equiv.), 3 Å molecular sieves, CH_3CN , $23\text{ }^\circ\text{C}$, 12 h. [d] ArN_2BF_4 (2 equiv.), 3 Å molecular sieves, $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$ (1:1), $23\text{ }^\circ\text{C}$, 12 h.

Figure 3. Hammett plot for the reaction of tryptamine **5a** with arenediazonium compounds.

Scheme 1.

Construction of the pyrrolidinoindoline framework bearing the C3–N-linkage.

Table 1

Diazonium-mediated pyrroloindoline synthesis.^[a]

Entry	Substrate	2(equiv.)	Base	Solvent(Temp., °C)	Yield, <i>b</i> %
1	1	5	NaHCO ₃	CH ₂ Cl ₂ (23)	10
2	1	5	NaHCO ₃	CH ₃ CN (23)	40
3	1	5	NaHCO ₃	CH ₃ OH (23)	0
4	1	5	NaHCO ₃	CH ₂ Cl ₂ (-78)	26
5	1	5	Na ₂ CO ₃	CH ₂ Cl ₂ (-78)	27
6	1	5	K ₂ CO ₃	CH ₂ Cl ₂ (-78)	24
7	1	5	K ₃ PO ₄	CH ₂ Cl ₂ (-78)	24
8	1	5	Li ₂ CO ₃	CH ₂ Cl ₂ (-78)	17
9	1	5	Cs ₂ CO ₃	CH ₂ Cl ₂ (-78)	37
10	1	2	Cs ₂ CO ₃	CH ₂ Cl ₂ (0)	20
11	1	2	Cs ₂ CO ₃	CH ₂ Cl ₂ (-20)	62
12	4	2	NaHCO ₃	CH ₃ CN (23)	23
13	4	2	NaHCO ₃	CH ₂ Cl ₂ (23)	9
14	4	2	NaHCO ₃	CH ₃ OH (23)	0
15	4	2	NaHCO ₃	CH ₂ Cl ₂ (-78)	27
16	4	2	Cs ₂ CO ₃	CH ₂ Cl ₂ (-50)	42
17	4	2	NaHCO ₃	CH ₂ Cl ₂ (-50)	28
18	4	2	Cs ₂ CO ₃	CH ₃ CN (-20)	58
19	4	2	Cs ₂ CO ₃	CH ₂ Cl ₂ (-20)	83
20	4	2	Cs ₂ CO ₃	CH ₂ Cl ₂ (0)	96

[a] Reaction conditions: **1** or **4** (0.25 mmol), base (5 equiv.), 3 Å molecular sieves (150 mg), solvent (2.5 mL).

[b] Determined by ^1H NMR spectroscopy.

Table 2

Photoinduced nitrogen extrusion from 3-phenylazopyrrolo-indolines **8** and **21**.^[a]

Substrate	X	R ¹	Product	Yield, % ^[b]
8	O	H	22	42
21	NHBoc	CO ₂ CH ₃	23	41

^[a] Reaction conditions: low-pressure Hg lamp (254 nm), 0.06M (**8**) or 0.05M (**21**) solution in *tert*-butanol, 23°C, 12 h.

^[b] Isolated yield after column chromatography.

Table 3Hydrazine-mediated reduction of 3-arylazopyrroloindolines.^[a]

Substrate	R ¹	R ²	Product	Yield, % ^[b]
3	C(O)CH ₃	Ph	24	99
9	C(O)OBn	3,5-bis(trifluoromethyl)phenyl	25	99
10	C(O)OtBu	2,4,5-trifluorophenyl	26	98
12	SO ₂ Tol	Ph	27	76
13	C(O)OtBu	2-bromophenyl	28	99

^[a]Reaction conditions: N₂H₄·H₂O, ethanol (0.05–0.1M), 50 °C, 3–12 h.^[b]Isolated yield.