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Synthesis of Pentacyclic 13-Aza-dibenzo[*a,de*]anthracenes via Anionic Cascade Ring Closure

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Table of content:

S2:	Synthesis of 1a , 1b and 1c
S3:	Synthesis of 3a-c from 1a-c .
S4:	Synthesis of 7 and 4a .
S5:	Synthesis of 4b and 4c .
S6:	General procedure for the synthesis of 5a-c from 4a-c .

General. All reactions were performed in flame-dried glassware under N₂ using syringe-septum cap techniques. Flash column chromatography (FC) was performed using silica gel with heptane/EtOAc as eluent. Melting points are uncorrected. All NMR spectra were recorded on at 300/75 MHz using CDCl₃ or DMSO-*d*₆ as solvent. The multiplicities of ¹³C-NMR signals were assigned from APT-spectra. All reagents were used as received. THF was distilled from Na/benzophenone under nitrogen, DMF and DMSO were sequentially dried and stored over 3Å molecular sieves.

2-(2-Bromophenoxy)-benzonitrile (1a). 2-Bromophenol (2.11 mL, 20.0 mmol), 2-fluorobenzonitrile (2.17 mL, 20.0 mmol) and freshly ground K_2CO_3 (4.14 g, 30.0 mmol) were stirred in DMF (15 mL) at 100 °C under N_2 for 48 hours. At rt sat. NH_4Cl (50 mL) was added. Extraction with Et_2O (5x50 mL) and the combined organic phases were washed with brine (50 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (Heptane/ $EtOAc$) yielding 5.20 g (95 %) of **1a** as colorless crystals, mp 77-78 °C (Heptane/ $EtOAc$), R_f (Heptane/ $EtOAc$ 4:1) 0.38. 1H -NMR (300 MHz, $CDCl_3$): 6.67 (dd, 1H, J = 8.5, 0.5 Hz), 7.11-7.19 (m, 3H), 7.37 (td, 1H, J = 7.8, 1.6 Hz), 7.46 (ddd, 1H, J = 8.5, 7.5, 1.7 Hz), 7.65-7.71 (m, 2H). ^{13}C -NMR (75 MHz, $CDCl_3$): 103.1 (s), 115.7 (d), 115.8 (s), 115.9 (s), 122.5 (d), 122.8 (d), 126.9 (d), 129.0 (d), 134.0 (d), 134.20 (d), 134.23 (d), 151.4 (s), 159.1 (s). Anal. Calcd. for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 56.94; H, 2.86; N, 4.93.

2-(2-Bromophenylsulfanyl)-benzonitrile (1b). 2-Bromothiophenol (1.20 mL, 10.0 mmol), 2-fluorobenzonitrile (1.20 mL, 11.0 mmol) and freshly ground K_2CO_3 (2.1 g, 15 mmol) were stirred in DMF (9 mL) at 100 °C under N_2 for 24 hours. At rt sat. NH_4Cl (25 mL) was added. Extraction with Et_2O (5x25 mL) and the combined organic phases were washed with brine (25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptane/ $EtOAc$) yielding 2.95 g (99 %) of **1b** as colorless crystals, mp 92-93 °C (heptane/ $EtOAc$), R_f (heptane/ $EtOAc$ 4:1) 0.47. 1H -NMR (300 MHz, $CDCl_3$): 7.18-7.24 (m, 2H), 7.27-7.30 (m, 2H), 7.36 (td, 1H, J = 7.6, 1.2 Hz), 7.49 (td, 1H, J = 7.6, 1.6 Hz), 7.64-7.73 (m, 2H). ^{13}C -NMR (75 MHz, $CDCl_3$): 114.3 (s), 116.7 (s), 126.9 (s), 127.4 (d), 128.3 (d), 129.7 (d), 131.5 (d), 133.2 (d), 133.6 (d), 133.7 (d), 134.0 (d), 134.2 (s), 139.6 (s). Anal. Calcd. for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.83. Found: C, 54.06; H, 2.82; N, 4.64.

2-[(2-Bromophenyl)-methylamino]-benzonitrile (1c). Potassium *tert*-butoxide (1.06 g, 9.41 mmol) was dissolved in DMSO (8 mL) under N_2 at rt. 2-Bromoaniline (784 mg, 4.56 mmol) was added neat via syringe giving a dark yellow-brown solution.¹ After 10 min at rt the flask was cooled to ~10 °C before 2-fluorobenzonitrile (590 μ L, 5.47 mmol) was added over 2 min. The mixture was subsequently stirred 1 hour at rt before MeI (850 μ L, 13.7 mmol) was added. After 30 min, the mixture was quenched with sat. NH_4Cl (20 mL) and extracted with Et_2O (4x25 mL). The combined organic phases were washed with brine (20 mL), dried (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptane/ $EtOAc$) yielding 1.17 g (89%) of **1c** as slightly yellow crystals. Recrystallisation from heptane/ $EtOAc$ gave

colorless crystals, mp 87-89 °C, R_f (heptane/EtOAc 4:1) 0.44. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.36 (s, 3H), 6.86-6.94 (m, 2H), 7.12-7.21 (m, 2H), 7.35 (td, 1H, $J = 7.7, 1.4$ Hz), 7.41-7.49 (m, 2H), 7.67 (dd, 1H, $J = 8.1, 1.5$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 41.1 (q), 101.4 (s), 117.5 (d), 117.7 (s), 119.8 (d), 123.3 (s), 128.0 (d), 128.5 (d), 128.8 (d), 133.5 (d), 134.2 (d), 135.4 (d), 146.9 (s), 151.7 (s). Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{BrN}_2$: C, 58.56; H, 3.86; N, 9.76. Found: C, 58.50; H, 3.87, N, 9.50.

General procedure for the ring closure of 1a and 1b to 3a and 3b. *Tert*-butyllithium (1.7 M in pentane, 1.70 mmol) was added to THF (4 mL) at -78 °C. 5 min later, the substrate (0.8 mmol) dissolved in THF (1 mL) was added drop wise, causing an instant coloring of the solution (deep red). Stirring was continued at -78 °C for 5 min before the cooling bath was removed. At rt, 4N HCl (10 mL) was added, causing precipitation. The mixture was heated to gentle reflux (oilbath at 70 °C) for 12 hours before being cooled to rt. Sat. NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3x25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptanes/EtOAc).

Xanthone (3a). 224 mg 1a gave 137 mg (82%) of xanthone (3a) which was identical to an authentic sample as judged by TLC, $^1\text{H-NMR}^2$ and GC-MS.

Thioxanthone (3b). 240 mg 1b gave 131 mg (75%) of thioxanthone (3b) which was identical to an authentic sample as judged by TLC, $^1\text{H-NMR}^3$ and GC-MS.

(10-Methyl-acridin-9-ylidene)-carbamic acid ethyl ester (3c). *Tert*-butyllithium (1.7 M in pentane, 1.64 mmol) was added to THF (4 mL) at -78 °C. 5 min later 1c (224 mg, 0.78 mmol) dissolved in THF (1 mL) was added drop wise, causing an instant coloring of the solution (deep red). Stirring was continued at -78 °C for 5 min before the cooling bath was removed. At rt, ethyl chloroformate (0.15 mL, 1.56 mmol) was added and stirring was continued at rt for 30 min before NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3x25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptanes/EtOAc 1:1) giving 184 mg (84%) of 3c as bright yellow crystals. Mp 154 °C (Heptane/EtOAc), reported⁴ 158-160 °C ($\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$). R_f (heptane/EtOAc 1:1) 0.31. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 1.37 (t, 3H, $J = 7.1$ Hz), 3.81 (s, 3H), 4.36 (q, 2H, $J = 7.1$ Hz), 7.20 (ddd, 2H, $J = 8.1, 7.2, 0.9$ Hz), 7.41 (d,

2H, $J = 9.0$ Hz), 7.63 (ddd, 2H, $J = 8.7, 6.9, 1.5$ Hz), 8.22 (dd, 2H, $J = 8.4, 1.5$ Hz). ^{13}C -NMR (75 MHz, CDCl_3): 14.5 (q), 34.3 (q), 61.8 (t), 114.4 (d), 119.4 (s), 121.2 (d), 127.4 (d), 132.7 (d), 141.3 (s), 155.6 (s), 163.8 (s).

2-Fluoro-6-(2-fluorophenyl)benzonitrile (7). 2-Chloro-6-fluorobenzonitrile (2.57 g, 16.5 mmol), 2-(2-fluorophenyl)-5,5-dimethyl-[1,3,2]dioxaborinane⁵ (3.78 g, 18.2 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (380 mg, 0.33 mmol) were dissolved in 2M K_2CO_3 (20 mL), EtOH (20 mL) and toluene (100 mL) under N_2 . The mixture was heated to 80 °C for 63 hours. At rt the mixture was diluted with brine (100 mL) and water was added until two clear phases appeared, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (4x50 mL) and the combined organic phases were washed once with brine (100 mL). The solvent was removed under reduced pressure, and the crude product was evaporated onto silica (~2g). The crude product was filtrated through silica (~50 g), using first heptane (200 mL, discarded) and then heptane/EtOAc 3:1 (500 mL) which contained the product. The solvent was evaporated and the residue was recrystallized from heptane giving 2.60 g (73%) of **6** as colorless crystals. A second crystalisation yielded 0.17 g (5%) of **7** bringing the total yield of **7** to 2.77 g (78%). Mp 73-74 °C (heptane), R_f (heptane/EtOAc 3:1) 0.48. ^1H -NMR (300 MHz, CDCl_3): 7.20-7.34 (m, 4H), 7.39-7.51 (m, 2H), 7.65 (ddd, 1H, $J = 8.5, 7.9, 5.8$ Hz). ^{13}C -NMR (75 MHz, CDCl_3): 102.2 (s(d), $J_{\text{C-F}} = 15.7$ Hz), 113.0 (s), 115.3 (d(d), $J_{\text{C-F}} = 19.9$ Hz), 116.2 (d(d), $J_{\text{C-F}} = 21.9$ Hz), 124.5 (d(d), $J_{\text{C-F}} = 3.9$ Hz), 124.7 (s(dd), $J_{\text{C-F}} = 14.8, 2.3$ Hz), 126.6 (d(dd), $J_{\text{C-F}} = 3.4, 1.9$ Hz), 131.1 (d(d), $J_{\text{C-F}} = 2.5$ Hz), 131.3 (d(d), $J_{\text{C-F}} = 8.3$ Hz), 134.2 (d(d), $J_{\text{C-F}} = 9.1$ Hz), 141.4 (s), 159.3 (s(d), $J_{\text{C-F}} = 250$ Hz), 163.8 (s(d), $J_{\text{C-F}} = 260$ Hz). Anal. Calcd. for $\text{C}_{13}\text{H}_7\text{F}_2\text{N}$: C, 72.56; H, 3.28; N, 6.51. Found: C, 72.41; H, 3.52, N, 6.36.

2-(2-Bromophenoxy)-6-(2-fluorophenyl)benzonitrile (4a). 2-Bromophenol (0.16 mL, 1.5 mmol), 2-fluoro-6-(2-fluorophenyl)benzonitrile (**7**) (217 mg, 1.01 mmol) and freshly ground K_2CO_3 (276 mg, 2.0 mmol) were stirred in DMF (1 mL) at 100 °C under N_2 for 24 hours. At rt sat. NH_4Cl (20 mL) was added. Extraction with Et_2O (5x20 mL) and the combined organic phases were washed once with brine (20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptane/EtOAc) yielding 343 mg (92%) of **4a** as colorless crystals, mp 94-96 °C (heptane/EtOAc), R_f (heptane/EtOAc 4:1) 0.37. ^1H -NMR (300 MHz, CDCl_3): 6.68 (dd, 1H, $J = 8.5, 0.9$ Hz), 7.14-7.32 (m, 5H), 7.35-7.53 (m, 4H), 7.69 (dd, 1H, $J = 7.8, 1.5$ Hz). ^{13}C -NMR (75 MHz, CDCl_3): 103.7 (s), 114.6 (d), 114.7 (s), 115.99 (s), 116.02 (d), 116.3 (d), 122.5 (d), 124.3 (d(d), $J_{\text{C-F}} = 4.0$ Hz), 124.8 (d(d), $J_{\text{C-F}} = 1.9$ Hz), 125.4 (s(d), $J_{\text{C-F}} = 14.6$ Hz),

127.0 (d), 129.0 (d), 131.0 (d(d), $J_{\text{C-F}} = 8.0$ Hz), 131.2 (d(d), $J_{\text{C-F}} = 2.3$ Hz), 133.4 (d), 134.2 (d), 141.5 (s), 151.5 (s), 159.4 (s(d), $J_{\text{C-F}} = 249$ Hz), 159.8 (s). Anal. Calcd. for $\text{C}_{19}\text{H}_{11}\text{BrFNO}$: C, 61.98; H, 3.01; N, 3.80. Found: C, 61.87; H, 2.78, N, 3.77.

2-(2-Bromophenylsulfanyl)-6-(2-fluorophenyl)benzonitrile (4b). 2-Bromothiophenol (0.140 mL, 1.17 mmol), 2-fluoro-6-(2-fluorophenyl)benzonitrile (**7**) (240 mg, 1.12 mmol) and freshly ground K_2CO_3 (310 mg, 2.23 mmol) were stirred in DMF (2 mL) at 80 °C under N_2 for 15 hours. At rt sat. NH_4Cl (20 mL) was added. Extraction with Et_2O (5x20 mL) and the combined organic phase was washed once with brine (20 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptane/ EtOAc) yielding 336 mg (78%) of **4b** as colorless crystals, mp 130-132 °C (heptane/ EtOAc), R_f (heptane/ EtOAc 4:1) 0.37. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 7.15 (dd, 1H, $J = 8.0, 1.1$ Hz), 7.19-7.54 (m, 9H), 7.71 (dd, 1H, $J = 7.9, 1.4$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 113.8 (s), 115.6 (s), 116.0 (d), 116.2 (d), 124.3 (d(d), $J_{\text{C-F}} = 3.7$ Hz), 125.5 (s(d), $J_{\text{C-F}} = 15.1$ Hz), 127.5 (s), 128.4 (d), 129.0 (d(d), $J_{\text{C-F}} = 1.3$ Hz), 129.9 (d), 131.0 (d(d), $J_{\text{C-F}} = 8.0$ Hz), 131.1 (d(d), $J_{\text{C-F}} = 2.5$ Hz), 132.4 (d), 133.7 (s), 133.8 (d), 134.2 (d), 141.0 (s), 141.3 (s), 159.3 (s(d), $J_{\text{C-F}} = 249$ Hz). Anal. Calcd. for $\text{C}_{19}\text{H}_{11}\text{BrFNS}$: C, 59.33; H, 2.89; N, 3.65. Found: C, 59.53; H, 2.67, N, 3.60.

2-[(2-Bromophenyl)-methylamino]-6-(2-fluorophenyl)benzonitrile (4c). Potassium *tert*-butoxide (256 mg, 2.28 mmol) was dissolved in DMSO (4 mL) under N_2 at rt. 2-Bromoaniline (392 mg, 2.28 mmol) was added neat via syringe giving a dark yellow-brown solution.¹ After 10 min at rt the flask was cooled to ~10 °C before 2-fluoro-6-(2-fluorophenyl)benzonitrile (**7**) (377 mg, 1.75 mmol) dissolved in DMSO (1 mL) was added. The mixture was subsequently stirred 1 hour at rt before MeI (425 μL , 6.84 mmol) was added. After 30 min, the mixture was quenched with sat. NH_4Cl (20 mL) and extracted with Et_2O (4x25 mL). The combined organic phase was washed with brine (20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was purified by FC (heptane/ EtOAc) yielding 556 mg (83%) of **4c** as a very viscous, slightly yellow oil. Crystallisation from heptane/ EtOAc gave 359 mg colorless crystals, mp 118-119 °C, R_f (heptane/ EtOAc 3:1) 0.35. $^1\text{H-NMR}$ (300 MHz, CDCl_3): 3.42 (s, 3H), 6.93-6.98 (m, 2H), 7.07-7.24 (m, 4H), 7.31-7.41 (m, 3H), 7.47 (dd, 1H, $J = 8.3, 7.8$ Hz), 7.65 (dd, 1H, $J = 8.0, 1.5$ Hz). $^{13}\text{C-NMR}$ (75 MHz, CDCl_3): 41.7 (q), 103.9 (s), 115.9 (d(d), $J_{\text{C-F}} = 22.0$ Hz), 116.3 (s), 118.1 (d), 122.6 (d(d), $J_{\text{C-F}} = 1.4$ Hz), 122.7 (s), 124.0 (d(d), $J_{\text{C-F}} = 3.7$ Hz), 126.5 (s(d), $J_{\text{C-F}} = 14.9$ Hz), 127.4 (d), 127.5 (d), 128.7 (d), 130.4 (d(d), $J_{\text{C-F}} = 8.0$ Hz), 131.3 (d(d), $J_{\text{C-F}} = 2.9$ Hz), 132.7 (d),

134.3 (d), 142.1 (s), 147.3 (s), 153.2 (s), 159.4 (s(d), $J_{C-F} = 14.6$ Hz), $J_{C-F} = 248$ Hz). Anal. Calcd. for $C_{20}H_{14}BrFN_2$: C, 63.01; H, 3.70; N, 7.35. Found: C, 62.79; H, 3.55, N, 7.28.

General procedure for the anionic ring closures of 4a-c to 5a-c. *Tert*-butyllithium (1.7 M in pentane, 2.1 eq) was added to THF (4 mL) at -78 °C. 5 min later the substrate (1.0 eq) dissolved in THF (1 mL) was added drop wise, causing an instant coloring of the solution (deep red). After 5 min at -78 °C the cooling bath was removed, and stirring was continued at rt for 30 min before sat. NH_4Cl (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3x25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave the crude product which was purified by FC (heptanes/EtOAc).

8-Oxa-13-aza-dibenzo[*a,de*]anthracene (5a). Run 1: 111 mg **4a** gave 65 mg (81%) **5a**, Run 2: 88 mg **4a** gave 62 mg (96%) **5a**. Average yield: 89%. Mp 190-191 °C (heptane/EtOAc), reported⁶ 189-191 °C (EtOAc). 1H - and ^{13}C -data ($CDCl_3$) are in full agreement with literature values.⁶

8-Thia-13-aza-dibenzo[*a,de*]anthracene (5b). Run 1: 78 mg **4b** gave 54 mg (94%) **5b**, Run 2: 127 mg **4b** gave 83 mg (88%) **5b**. Average yield: 91 %. Mp 175-176 °C (heptane/EtOAc), reported⁶ 173-175 °C (EtOAc/hexanes). 1H - and ^{13}C -data ($CDCl_3$) are in full agreement with literature values.⁶

8-Methyl-8H-8,13-diaza-dibenzo[*a,de*]anthracene (5c). Run 1: 170 mg **4c** gave 96 mg (76%) **5c**, Run 2: 140 mg **4c** gave 74 mg (72%) **5c**. Average yield: 74 %. Mp 199-200 °C (heptane/EtOAc), reported⁷ 204-6 °C (EtOAc/Ethanol 1:1). 1H - and ^{13}C -data ($DMSO-d_6$) are in full agreement with literature values.⁷

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