Supporting Information

Synthesis of new pentacyclic chromophores through a highly regio-
and diastereoselective cascade process

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Table of Contents

A. Experimental Procedures ............................................ 2
   General Information .............................................. 2
   Synthesis of 4d, 4e, 5d and spectral data ...................... 2
   General procedure for the preparation of pentacycles 3 and spectral data ...................... 4
   General procedure for the preparation of aldehydes 6 and spectral data ...................... 8
   Synthesis of 8 and spectral data .................................. 8
B. Copies of 1H and 13C NMR spectra ............................... 11
C. X-Ray diffraction of compounds 3a, 3c and 3f .................. 26
D. Theoretical calculations ........................................... 29
E. References .......................................................... 36
A. Experimental Procedures

**General Information.** Melting points were measured on a Totoli apparatus. Proton and carbon NMR spectra were recorded on Bruker AMX-400, AC-200 or AC-250 Fourier transform spectrometers using an internal deuterium lock. Chemical shifts are quoted in parts per million (ppm) downfield of tetramethylsilane. Coupling constants $J$ are quoted in Hz. Mass spectra with electronic impact (MS-EI) were recorded from a Shimadzu QP 2010 apparatus. High resolution masse spectra were recorded from a Brucker micrOTOFQ. THF was distilled from sodium/benzophenone and stored on sodium wire before use. Toluene and methanol were used as received. All reagents were used as received. TLC was performed on silica gel plates and visualized with a UV lamp (254 nm). Chromatography was performed on silica gel (70-230 mesh).

![Structural formula of 4d](image)

**5-Bromo-2-chloro-4,6-dimethylpyridine (4d).** To a solution of 2-amino-5-bromo-4,6-dimethylpyridine$^1$ (0.7 g, 3.46 mmol) in HCl conc. (5.5 mL) at -5°C was added a solution of NaNO$_2$ (0.62 g, 9 mmol) in H$_2$O (5.5 mL) and the mixture was stirred for 10 min. CuCl (0.43 g, 4.3 mmol) was then added slowly by portions of 50 mg. After 5 min, the cooling bath was removed and the mixture was stirred at room temperature for 4h. NaOH 2M was added until pH7 and the product was extracted with ether (3 X 30 mL). The organic phase was washed with brine (50 mL) and dried over MgSO$_4$ and concentrated. The crude was purified by chromatography on silica gel (Hexane / EtOAc 95 / 5) to give 4d as a white solid (383 mg, 50% yield). m.p. 49°C; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ = 7.05 (s, 1H, Pyr), 2.65 (s, 3H, 6-CH$_3$), 2.39 (s, 3H, 4-CH$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$ = 150.4, 141.4, 134.2, 123.4, 122.7, 25.4, 23.2 ppm; MS (70 eV): m/z (%): 221 (100) [MH$^+$], 183 (15), 140 (15), 104 (60), 77 (45), 51 (25); HRMS m/z calcd for C$_7$H$_7$BrClN: 220.9501, found: 221.9524 ([MH$^+$]).

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5-Bromo-2-chloro-4-phenylpyridine (4e). To a degassed toluene solution (4 mL) containing Pd(PPh₃)₄ (29 mg, 0.025 mmol) and 5-bromo-2-chloro-4-iodopyridine² (333 mg, 1.05 mmol), degassed solutions of phenylboronic acid (122 mg, 1 mmol) in methanol (2 mL) and Na₂CO₃ (212 mg, 2 mmol) in water (2 mL) were successively added. After heating for 12h at 100°C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and dried over MgSO₄. After concentration, the residue was purified by chromatography on silica gel (hexane/ethyl acetate: 98/2) to give 4e as a white solid (230 mg, 86% yield). m.p. 68°C; H NMR (CDCl₃, 250 MHz): δ = 8.59 (s, 1H, Hₐ), 7.50 – 7.40 (m, 5H, Hₐ,d,e), 7.32 (s, 1H, H₉); C NMR (CDCl₃, 50 MHz): δ = 151.9, 150.4, 137.1, 129.3, 128.7, 128.5, 125.9, 119.4 ppm; MS (70 eV): m/z (%): 269 (100) [M⁺], 153 (58), 126 (40), 63 (20), 50 (12); HRMS m/z calcd for C₁₁H₇BrClN: 268.9501, found: 269.9521 ([MH⁺]).

4-(Dimethyl)amino-2-formylbenzenzeneboronic acid (5d): To a solution of 2-bromo-5-dimethylaminobenzaldehyde³ (1g, 4.39 mmol) in toluene (40 mL) were added ethylene glycol (8 mL) and p-toluenesulfonic acid (83 mg, 0.44 mmol). The reactor was equipped with a Dean-Stark apparatus and the mixture was heated at 130°C for 15h. After cooling to room temperature, solid Na₂CO₃ (100 mg) was added and the mixture was washed with water and separated, dried over MgSO₄ and concentrated. Filtration on a pad of silica gel (hexanes/EtOAc 1/1) afforded the desired acetal (1g, 85%). H NMR (CDCl₃, 200 MHz): δ = 7.34 (d, J = 8.8 Hz, 1H, Hₐ), 6.95 (d, J = 2.8 Hz,
1H, Hc), 6.58 (dd, J = 2.8, 8.8 Hz, 1H, Hb), 6.03 (s, 1H, OCH), 4.12 (m, 2H, OCH₂), 2.94 ppm (s, 6H, CH₃).

To a n-BuLi solution (2.5 in hexanes, 1.65 mL, 4.1 mmol) in Et₂O (10 mL) at -65°C was slowly added a solution of the previously prepared acetal (1 g, 3.73 mmol) in THF (5 mL) then the mixture was stirred for 15 min at -78°C. B(Oi-Pr)₃ (4.1 mmol, 1 mL) was then slowly added and stirring was continued for 30 min at -78°C before raising to room temperature. HCl 2M (10 mL) was added and the mixture was refluxed for 1h. After being cooled to room temperature the mixture was made basic by adding NaOH 2M (15 mL) and extracted with Et₂O. The aqueous phase was then treated with HCl 2M until pH7. The precipitated yellow solid was filtered, washed with water and Et₂O and dried in vacuo (500 mg, 71%). 

**¹H NMR (CD₃COCD₃, 200 MHz):** δ = 9.30 (s, 1H, CHO), 7.14 (d, J = 8.4 Hz, 1H, Hₐ), 6.99 (s, 2H, B(OH)₂), 6.54 (s, 1H, Hc), 6.14 (d, J = 8.4 Hz, 1H, Hb), 2.22 ppm (s, 6H, CH₃); 

**¹³C NMR (CD₃COCD₃, 50 MHz):** δ = 183.2, 140.5, 128.3, 120.4, 117.7, 114.7, 108.3, 41.0 ppm.

**General procedure for the preparation of pentacycles 3.** Synthesis of 3b: To a degassed toluene solution (10 mL) containing Pd(PPh₃)₄ (116 mg, 0.01 mmol) and 4b (192 mg, 1 mmol), degassed solutions of 5a (375 mg, 2.5 mmol) in methanol (5 mL) and Na₂CO₃ (530 mg, 5 mmol) in water (5 mL) were successively added. After heating for 12h at 100°C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and dried over MgSO₄. After concentration, the residue was purified by chromatography on silica gel (hexane/ethyl acetate: 9/1).

Yellow-green solid, m.p. 175°C; 

**¹H NMR (CDCl₃, 400 MHz):** δ = 7.87 (d, J = 7.5 Hz, 1H, H₅), 7.69 (d, J = 7.5 Hz, 1H, H₈), 7.61 (d, J = 7.5 Hz, 1H, H₁), 7.59 (t, J = 7.5 Hz, 1H, H₇), 7.51 (d, J = 7.5 Hz, 7.49 (d, J = 7.5 Hz, 1H, H₄).
1H, H₆), 7.50 (t, J = 7.5 Hz, 1H, H₅), 7.39 (t, J = 7.5 Hz, 1H, H₂), 7.35 (t, J = 7.5 Hz, 1H, H₃), 6.52 (dd, J = 2.8, 6.0 Hz, 1H, H₇), 6.29 (d, J = 6.0 Hz, 1H, H₄), 5.72 (s, 1H, OH), 5.45 (d, J = 5.6 Hz, 1H, H₈), 4.68 ppm (dd, J = 2.8, 5.6 Hz, 1H, H₉); ¹³C NMR (CDCl₃, 50 MHz): δ = 169.4, 143.0, 136.7, 135.8, 134.7, 133.8, 131.8, 129.7, 129.0, 128.6, 127.7, 125.0, 123.1, 120.9, 120.1, 112.7, 103.5, 78.2, 65.8 ppm; MS (70 eV): m/z (%): 287 (100) [M⁺], 269 (35), 258 (30), 182 (40); HRMS m/z calcd for C₁₉H₁₃NO₂: 287.0866, found: 310.0866 ([M+Na]⁺).

Yellow-green solid, m.p. 193°C; ¹H NMR (CDCl₃, 400 MHz): δ = 7.82 (d, J = 7.6 Hz, 1H, H₅), 7.67 (d, J = 7.6 Hz, 1H, H₆), 7.64 – 7.50 (m, 3H, H₁,4,7), 7.49 (t, J = 7.6 Hz, 1H, H₇), 7.36 (m, 2H, H₂,3), 6.12 (s, 1H, H₈), 5.92 (s, 1H, OH), 5.40 (d, J = 6.4 Hz, 1H, H₉), 4.63 (m, 1H, H₄), 2.24 ppm (d, J = 2.4 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz): δ = 169.4, 143.4, 136.4, 134.6, 133.5, 131.9, 130.1, 129.2, 128.8, 128.4, 128.0, 124.9, 123.8, 123.5, 123.3, 120.2, 109.1, 77.9, 66.4, 18.2 ppm; HRMS m/z calcd for C₂₀H₁₅NO₂: 301.1098, found: 324.0967 ([M+Na]⁺).

Yellow solid, m.p. 200°C; ¹H NMR (CDCl₃, 400 MHz): δ = 7.85 (d, J = 7.6 Hz, 1H, H₅), 7.69 (d, J = 7.6 Hz, 1H, H₆), 7.62 (d, J = 7.5 Hz, 1H, H₁), 7.57 (d, J = 7.6 Hz, 1H, H₇), 7.50 (d, J = 7.5 Hz, 1H, H₄), 7.49 (t, J = 7.6 Hz, 1H, H₆), 7.39 (t, J = 7.5 Hz, 1H, H₂), 7.36 (t, J = 7.5 Hz, 1H, H₃), 6.53 (d, J = 6.4 Hz, 1H, H₈), 6.31 (d, J = 6.4 Hz, 1H, H₉), 5.57 (broad s, 1H, OH), 5.24 (d, JHb-OH = 2.0 Hz, 1H, H₉), 1.25 ppm (s, 3H, CH₃); ¹³C NMR (CDCl₃, 50 MHz): δ = 168.8, 143.3, 142.7, 135.7, 133.6, 132.0, 129.6, 129.2, 128.6, 128.2, 125.1, 123.3, 121.8, 121.3, 120.3, 112.3, 103.6, 79.9, 67.6, 17.4
ppm; MS (70 eV): m/z (%): 301 (30) [M\(^+\)], 286 (100); HRMS m/z calcd for C\(_{20}\)H\(_{15}\)NO\(_2\): 301.1098, found: 324.1025 ([M+Na\(^+\)].

Green solid, m.p. 210°C; \(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta = 7.88\) (d, \(J = 7.5\) Hz, 1H, H\(_5\)), 7.73 (d, \(J = 7.5\) Hz, 1H, H\(_8\)), 7.66 (d, \(J = 7.5\) Hz, 1H, H\(_1\)), 7.62 (t, \(J = 7.5\) Hz, 1H, H\(_7\)), 7.61 (d, \(J = 7.0\) Hz, 1H, H\(_4\)), 7.53 (t, \(J = 7.5\) Hz, 1H, H\(_6\)), 7.38 (m, 2H, H\(_{2,3}\)), 6.19 (s, 1H, H\(_d\)), 5.57 (s, 1H, H\(_b\)), 5.46 (s, 1H, OH), 2.30 (s, 3H, CH\(_3\)), 1.24 ppm (s, 3H, CH\(_3\)); \(^{13}\)C NMR (CDCl\(_3\), 150 MHz): \(\delta = 169.6, 143.8, 136.4, 136.1, 135.2, 133.1, 132.0, 129.3, 128.6, 128.4, 128.3, 124.9, 124.2, 123.4, 123.2, 120.3, 109.1, 79.6, 68.3, 18.4, 17.5 ppm; MS (70 eV): m/z (%): 315 (35) [M\(^+\)], 300 (100), 285 (16); HRMS m/z calcd for C\(_{21}\)H\(_{17}\)NO\(_2\): 315.1273, found: 338.1173 ([M+Na\(^+\)].

Green solid, m.p. 214°C; \(^1\)H NMR (CDCl\(_3\), 250 MHz): \(\delta = 7.93\) (d, \(J = 7.5\) Hz, 1H, H\(_5\)), 7.69 (d, \(J = 7.5\) Hz, 1H, H\(_8\)), 7.75 – 7.40 (m, 8H, Ph and H\(_{4,6,7}\)), 7.33 (t, \(J = 7.5\) Hz, 1H, H\(_1\)), 7.07 (t, \(J = 7.5\) Hz, 1H, H\(_3\)), 6.82 (d, \(J = 7.5\) Hz, 1H, H\(_1\)), 6.29 (s, 1H, H\(_d\)), 5.93 (s, 1H, OH), 5.57 (d, \(J = 6.0\) Hz, 1H, H\(_b\)), 4.77 ppm (d, \(J = 6.0\) Hz, 1H, H\(_a\)); \(^{13}\)C NMR (CDCl\(_3\), 75 MHz): \(\delta = 169.8, 144.2, 138.9, 135.7, 134.0, 132.4, 131.6, 129.8, 129.75, 129.4, 129.3, 128.6, 128.5, 128.4, 125.2, 123.9, 123.8, 120.7, 108.4, 67.0 ppm; MS (70 eV): m/z (%): 294 (100) ([M-H\(_2\)O-C\(_4\)H\(_4\)]\(^+\)), 266 (55), 258 (70), 228 (50), 202 (45), 101 (32), 76 (25), 51 (15); HRMS m/z calcd for C\(_{25}\)H\(_{17}\)NO\(_2\): 363.1273, found: 386.1169 ([M+Na\(^+\)].
Green solid, m.p. 170°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 7.50$ (d, $J = 8.5$ Hz, 1H, $H_8$), 7.34 (d, $J = 8.5$ Hz, 1H, $H_1$), 7.25 (d, $J = 2.5$ Hz, 1H, $H_3$), 7.09 (d, $J = 2.0$ Hz, 1H, $H_4$), 7.07 (dd, $J = 2.5$, 8.5 Hz, 1H, $H_7$), 6.86 (dd, $J = 2.0$, 8.5 Hz, 1H, $H_2$), 6.28 (dd, $J = 2.5$, 6.5 Hz, 1H, $H_c$), 6.09 (d, $J = 6.5$ Hz, 1H, $H_d$), 5.80 (s, 1H, OH), 5.31 (d, $J = 5.5$ Hz, 1H, $H_b$), 4.57 (dd, $J = 2.5$, 5.5 Hz, 1H, $H_a$), 3.84 (s, 3H, OCH$_3$), 3.83 ppm (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta = 169.5$, 161.5, 160.8, 145.2, 135.9, 132.8, 129.4, 128.8, 128.0, 122.2, 121.5, 120.6, 116.9, 110.7, 108.5, 105.6, 103.0, 78.2, 66.2, 55.7, 55.6 ppm; HRMS $m/z$ calcd for C$_{21}$H$_{17}$NO$_4$: 347.1153, found: 370.1024 ([M+Na]$^+$).

Green solid, m.p. 130°C; $^1$H NMR (CDCl$_3$, 400 MHz): $\delta = 7.76$ (d, $J = 8.4$ Hz, 1H, $H_3$), 7.52 (d, $J = 9.2$ Hz, 1H, $H_4$), 7.11 (d, $J = 2.0$ Hz, 1H, $H_8$), 7.02 (dd, $J = 2.0$, 8.4 Hz, 1H, $H_6$), 6.97 (m, 2H, $H_{1,3}$), 6.46 (dd, $J = 2.8$, 6.0 Hz, 1H, $H_c$), 6.23 (d, $J = 6.0$ Hz, 1H, $H_d$), 5.64 (s, 1H, OH), 5.38 (d, $J = 5.6$ Hz, 1H, $H_b$), 4.62 (dd, $J = 2.8$, 5.6 Hz, 1H, $H_a$), 3.90 (s, 3H, OCH$_3$), 3.84 ppm (s, 3H, OCH$_3$); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta = 169.5$, 163.2, 160.4, 137.2, 137.1, 136.8, 135.7, 134.3, 126.3, 126.0, 124.7, 117.0; 116.5, 112.6, 104.9, 104.2, 103.2, 77.9, 66.2, 55.6, 55.4 ppm; HRMS $m/z$ calcd for C$_{21}$H$_{17}$NO$_4$: 347.1153, found: 370.1067 ([M+Na]$^+$).

Red solid, m.p. 208°C; $^1$H NMR (CDCl$_3$, 250 MHz): $\delta = 7.50$ (d, $J = 8.4$ Hz, 1H, $H_8$), 7.34 (d, $J = 8.4$ Hz, 1H, $H_1$), 7.07 (d, $J = 2.0$ Hz, 1H, $H_3$), 6.90 (m, 2H, $H_{4,7}$), 6.69 (dd, $J = 2.0$, 8.4 Hz, 1H, $H_2$),
6.26 (dd, \( J = 2.6, 6.2 \) Hz, 1H, \( H_c \)), 6.06 (d, \( J = 6.2 \) Hz, 1H, \( H_d \)), 5.99 (s, 1H, OH), 5.35 (d, \( J = 5.8 \) Hz, 1H, \( H_b \)), 4.61 (dd, \( J = 2.6, 5.8 \) Hz, 1H, \( H_d \)), 3.05 (s, 6H, N(CH\(_3\))\(_2\)), 3.03 ppm (s, 6H, N(CH\(_3\))\(_2\)); \(^{13}\)C NMR (CDCl\(_3\), 66 MHz): \( \delta = 169.1, 150.8, 150.1, 143.9, 134.8, 131.9, 128.6, 124.0, 122.8, 121.2, 120.4, 115.7, 112.7, 108.4, 106.9, 104.5, 101.4, 78.4, 66.5, 41.2, 41.15 \) ppm; HRMS m/z calcd for C\(_{23}\)H\(_{23}\)N\(_3\)O\(_2\): 373.1785, found: 396.1690 ([M+Na\(^+\)].

Green solid, m.p. > 200°C; \(^1\)H NMR (CDCl\(_3\), 400 MHz): \( \delta = 7.69 \) (dd, \( J_{H-H} = 8.4 \) Hz and \( J_{H-F} = 4.4 \) Hz, 1H, \( H_8 \)), 7.55 (dd, \( J_{H-H} = 2.0 \) Hz and \( J_{H-F} = 7.6 \) Hz, 1H, \( H_5 \)), 7.48 (t, \( J_{H-H} = 8.4 \) Hz and \( J_{H-F} = 4.8 \) Hz, 1H, \( H_1 \)), 7.33 (m, 2H, H\(_{2,7}\)), 7.08 (dd, \( J_{H-H} = 2.0 \) Hz and \( J_{H-F} = 8.8 \) Hz, 1H, \( H_4 \)), 6.48 (dd, \( J = 2.5, 6.0 \) Hz, 1H, \( H_c \)), 6.27 (d, \( J = 6.0 \) Hz, 1H, \( H_d \)), 5.62 (s, 1H, OH), 5.43 (d, \( J = 5.4 \) Hz, 1H, \( H_b \)), 4.71 ppm (dd, \( J = 2.5, 5.4 \) Hz, 1H, \( H_a \)); \(^{13}\)C NMR (CDCl\(_3\), 50 MHz): \( \delta = 166.5, 166.3, 165.7, 135.7, 132.9, 131.9, 122.2, 120.2, 119.7, 116.8, 116.3, 112.6, 112.2, 110.2, 109.8, 103.6, 78.0, 66.2 \) ppm; \(^{19}\)F NMR (CDCl\(_3\)/C\(_6\)F\(_6\), 188 MHz): \( \delta = -112.4 \) ppm; HRMS m/z calcd for C\(_{19}\)H\(_{11}\)F\(_2\)NO\(_2\): 323.0753, found: 346.0658 ([M+Na\(^+\)].

**General procedure for the preparation of aldehydes 6.**

![Image](image_url)

2-(6-chloro-pyridin-3-yl)-benzaldehyde 6a: To a degassed toluene solution (25 mL) containing Pd(PPh\(_3\))\(_4\) (173 mg, 0.15 mmol) and 4a (578 mg, 3 mmol), degassed solutions of 5a (450 mg, 3 mmol) in methanol (6 mL) and Na\(_2\)CO\(_3\) (636 mg, 6 mmol) in water (12 mL) were successively added. After heating for 12h at 100°C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and dried over MgSO\(_4\). After concentration, the residue was purified by
chromatography on silica gel (hexanes/ethyl acetate 3/1) to give compound 6a as a pale yellow powder (490 mg, 75%). M.p. 85°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 9.98$ (s, 1H, CHO), 8.42 (d, $J = 1.5$ Hz, 1H, H$_3$), 8.05 (dd, $J = 7.6$, 1.5 Hz, 1H, H$_2$), 7.80–7.65 (m, 2H, H$_{1,4}$), 7.60 (t, $J = 8.0$ Hz, 1H, H$_7$), 7.44 (t, $J = 8.0$ Hz, 2H, H$_{5,6}$); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta = 190.7$, 151.1, 149.5, 139.9, 133.8, 133.5, 132.6, 130.8, 129.0, 128.8, 123.7, 112.7 ppm; MS (70 eV): $m/z$ (%): 216 (100, [M-H]+), 182 (65), 154 (42), 127 (40); HRMS $m/z$ calcd for C$_{12}$H$_8$ClNO: 217.0288, found: 218.0366 (MH$^+$).

2-(6-Bromo-pyridin-3-yl)-benzaldehyde 6b. M.p. 86°C; $^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 9.98$ (s, 1H, CHO), 8.39 (s, 1H, H$_3$), 8.04 (d, $J = 7.4$ Hz, 1H, H$_2$), 7.80–7.55 (m, 4H, H$_{1,4,5,6}$), 7.41 (d, $J = 7.4$ Hz, 1H, H$_7$); $^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta = 190.7$, 150.0, 141.8, 139.9, 139.4, 133.9, 133.6, 133.0, 130.8, 129.2, 128.9, 127.5 ppm; MS (70 eV): $m/z$ (%): 261 (45), 182 (100), 153 (35), 127 (46); HRMS $m/z$ calcd for C$_{12}$H$_8$BrNO: 260.9783, found: 261.9861 (MH$^+$).

Pentacycle 8. Aldehyde 6b (175 mg, 0.8 mmol) was dissolved in dichloromethane (10 mL). $p$-Anisidine (98.4 mg, 0.8 mmol) and MgSO$_4$ (150 mg) were successively added and the mixture was stirred at room temperature overnight. After filtration and evaporation, [2-(6-chloropyridin-3-yl)-benzylidene]-(4-methoxy-phenyl)-amine was obtained quantitatively and used for the next step without further purification.

$^1$H NMR (CDCl$_3$, 200 MHz): $\delta = 8.39$ (m, 2H, H$_3$ and CHN), 8.30 (m, 1H, H$_2$), 7.60–7.45 (m, 4H, H$_{4,5,6,7}$), 7.31 (m, 1H, H$_1$), 7.11 (d, $J = 8.8$ Hz, 2H, H$_8$), 6.86 (d, $J = 8.8$ Hz, 2H, H$_9$), 3.77 (s, 3H).
To a degassed toluene solution (5 mL) containing Pd(PPh₃)₄ (29 mg, 0.025 mmol) and [2-(6-chloro-pyridin-3-yl)-benzylidene]-(4-methoxy-phenyl)-amine (183 mg, 0.5 mmol), degassed solutions of 5a (100 mg, 0.6 mmol) in methanol (1 mL) and Na₂CO₃ (110 mg, 1 mmol) in water (1.5 mL) were successively added. After heating for 12h at 100°C, the reaction mixture was cooled to room temperature, extracted with ethyl acetate and dried over MgSO₄. After concentration, the residue was purified by chromatography on silica gel (hexanes/ethyl acetate 9/1) to give 8 as a green solid (71 mg, 36%).

M.p. 80°C; ¹H NMR (CDCl₃, 250 MHz): δ = 7.80 (d, J = 7.5 Hz, 1H, H₅), 7.63 (dd, J = 2.0, 7.5 Hz, 1H, H₈), 7.62 (d, J = 7.5 Hz, 1H, H₁), 7.53 (m, 2H, H₄,7), 7.44 (dt, J = 2.0, 7.5 Hz, 1H, H₆), 7.36 (t, J = 7.5 Hz, 1H, H₂), 7.35 (t, J = 7.5 Hz, 1H, H₃), 6.68 (d, J = 9.2 Hz, 2H, H₉), 6.60 (d, J = 9.2 Hz, 2H, H₁₀), 6.53 (dd, J = 6.0, 2.5 Hz, 1H, H₄), 6.23 (d, J = 6.0 Hz, 1H, H₆), 5.16 (d, J = 6.5 Hz, 1H, H₆), 5.05 (dd, J = 6.5, 2.5 Hz, 1H, H₄), 3.67 ppm (s, 3H, OCH₃); ¹³C NMR (CDCl₃, 75 MHz): δ = 169.2, 152.8, 144.4, 141.4, 138.0, 136.5, 135.2, 134.8, 131.8, 129.8, 129.1, 128.5, 128.2, 125.8, 123.2, 121.0, 119.9, 117.9, 114.6, 113.2, 103.2, 65.3, 59.6, 55.6 ppm; MS (70 eV): m/z (%) = 269 (100) [M-NHp-MeOPh]⁺, 240 (18), 214 (16), 135 (15), 121 (30), 107 (38); HRMS m/z calcd for C₂₆H₂₀N₂O₂: 392.1525, found: 390.1359 (M-H₂).
B. Copies of $^1$H and $^{13}$C NMR spectra

**Compound 3b**: Only one diastereoisomer in the crude mixture
Compound 3d
Compound 3e

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Compound 3f

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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Compound 3g
Compound 3h
Compound 6a
Compound 6b

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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Compound 8

Supplementary Material (ESI) for Organic & Biomolecular Chemistry
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C. X-Ray diffraction of compounds 3a, 3c and 3f

Compounds 3a and 3c

The crystal structure analyses were performed on an Oxford Diffraction X'Calibur CCD diffractometer using MoKα radiation (λ=0.71073 Å). The structures were solved by direct methods with the program SIR-92 4 and full matrix least-square refinements on F² in SHELXL-97 5 were performed with anisotropic displacements for non-H atoms. Hydrogen atoms were located in difference Fourier maps and refined isotropically according to the riding model.

Figure C.1. ORTEP plot of 3a (up) and 3c (bottom) (hydrogen atoms, except those in trans relationship and in the internal hydrogen bond (shown as a broken line), are omitted for clarity; thermal ellipsoids set at 50% probability). Intramolecular hydrogen bond distances and angles: 3a : H…O = 1.998(1)Å, O…H…O = 149.10(8)°; 3c : H…O = 2.123(1)Å, O…H…O = 141.09(5)°.

3c: C₂₀H₁₅NO₂, Mᵣ=301.33, crystal dimensions: 0.27*0.20*0.12 mm, orthorhombic, space group P₂₁₂₁₂₁, a=6.03265(6) Å, b=14.26965(12) Å, c=16.47322(13) Å, V=1418.08(2) Å³, T=110(2) K, Z=4, ρ_calcd=1.411 g.cm⁻³, µ=0.09 mm⁻¹, 30002 reflections collected, 4835 unique reflections,
$R_{\text{int}}=0.021$, $2\theta_{\text{max}}=79.52^\circ$, 210 parameters, $R_1=0.037$, $wR_2=0.092$, $\Delta \rho_{\text{min}} = -0.237e.\text{Å}^{-3}$, $\Delta \rho_{\text{max}} = 0.492e.\text{Å}^{-3}$.

CCDC734891 contains the detailed crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**Compound 3f**

The crystal structure analysis was performed on an Oxford Diffraction Supernova diffractometer equipped with Atlas CCD detector, using Cu$K_\alpha$ radiation ($\lambda=1.54184\ \text{Å}$). The structure was solved by direct methods with the program SIR-92$^4$ and full matrix least-square refinements on $F^2$ in SHELXL-97$^5$ were performed with anisotropic displacements for non-H atoms. Hydrogen atoms were located in difference Fourier maps and refined isotropically according to the riding model (Fig. C.2).

3f: $2(\text{C}_2\text{H}_17\text{NO}_4)$, $\text{C}_2\text{H}_3\text{N}$, $M_r=735.77$, crystal dimensions: 0.36*0.14*0.11 mm, monoclinic, space group $P2_1/c$, $a=5.61290(10)\ \text{Å}$, $b=19.2298(3)\ \text{Å}$, $c=32.3685(5)\ \text{Å}$, $\beta=93.1660(10)^\circ$, $V=3488.36(10)\ \text{Å}^3$, $T=110(2)\ \text{K}$, $Z=4$, $\rho_{\text{calc}}=1.401\ \text{g.cm}^{-3}$, $\mu=0.795\ \text{mm}^{-1}$, 37426 reflections collected, 7394, unique reflections, $R_{\text{int}}=0.0185$, $2\theta_{\text{max}}=154.96^\circ$, 503 parameters, $R_1=0.0485$, $wR_2=0.1168$, $\Delta \rho_{\text{min}} = -0.373e.\text{Å}^{-3}$, $\Delta \rho_{\text{max}} = 0.473e.\text{Å}^{-3}$.

CCDC734893 contains the detailed crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Figure C.2. ORTEP plot of the asymmetric unit of 3f, including a co-crystallized acetonitrile solvent molecule (hydrogen atoms, except those in trans relationship and in the internal hydrogen bond, are omitted for clarity; thermal ellipsoids set at 50% probability).
**D. Theoretical calculations**

All calculations were performed in the gas phase, with the Gaussian03 program package\(^6\) using Density Functional Theory (DFT) with the hybrid exchange-correlation B3LYP functional.\(^7\)

Molecular structures of 3b and its hypothetical cis (named **C6cis**) counterpart and of C4 cyclization products (named **C4trans** & **C4cis** for trans & cis diastereomer respectively) were optimized at the B3LYP 6-311+G(d,p) level of theory (Fig. D.1, Table D.1). Frequency calculations were performed at the same level of theory on all investigated structures in order to check that they correspond to true energy minima and also to compute zero-point energy corrected gas phase free energy values at 373K (which is the experiment temperature).

**Figure D.1.** Optimized (B3LYP 6-311+G(d,p)) molecular structures of (a) 3b (O…H = 1.98Å; O…H…O = 146.81°), (b) **C6cis** (O…H = 2.04Å; O…H…O = 140.23°), (c) **C4trans**, (d) **C4cis** (internal hydrogen bond shown as a black broken line for 3b and **C6cis**; hydrogen atoms involved in the diastereomery in green).
Table D.1. Relative free energies at 373K of hypothetical cis C6 and trans & cis C4 cyclization products, compared to the 3b molecular structure (=C6trans) (B3LYP 6-311+G(d,p) level of theory).

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>$G^{373K}$ (kcal.mol$^{-1}$)[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b</td>
<td>0</td>
</tr>
<tr>
<td>C6cis</td>
<td>+3.48</td>
</tr>
<tr>
<td>C4trans</td>
<td>+4.82</td>
</tr>
<tr>
<td>C4cis</td>
<td>+5.56</td>
</tr>
</tbody>
</table>

[a] Free energy values referred to 3b

The final cyclization mechanism was investigated starting from four molecular structures of the intermediate C differing in their conformations (orientation of the benzene ring relative to the...
pyridine ring and of the aldehyde relative to the benzene ring). These four molecular conformations are thus precursors of the previously four cyclization products (C-3b for 3b, C-C6cis for C6cis, C-C4trans for C4trans, C-C4cis for C4cis), obtained by the formation of the C6 (C4) - CHO bond. Each conformation was optimized starting from B3LYP 6-31G(d,p) up to B3LYP 6-311+G(d,p) levels of theory. These optimized structures (depicted in Fig. D.2) show that the trans intermediates (C-3b & C4trans) are about the same free energy, and are more stable than cis intermediates (C6cis & C4cis) by ~2.2kcal.mol\(^{-1}\) (Table D.2).

**Figure D.2.** Optimized (B3LYP 6-311+G(d,p)) molecular structures of (a) **C-3b** (C6 – CHO = 3.19Å), (b) **C-C6cis** (C6 – CHO = 3.35Å), (c) **C-C4trans** (C4 – CHO = 3.24Å), (d) **C-C4cis** (C4 – CHO = 3.41Å). C6 & aldehyde hydrogen atom involved in the diastereomery of the final product are displayed in green. C6 (C4) - CHO interatomic distances are shown as a red broken line.
Table D.2. Relative free energies at 373K of the four optimized (B3LYP 6-311+G(d,p) level of theory) molecular structures of the intermediate C.

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>$G_{373K}$ (kcal.mol$^{-1}$)[$a$]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-3b</td>
<td>0</td>
</tr>
<tr>
<td>C-C6cis</td>
<td>+2.08</td>
</tr>
<tr>
<td>C-C4trans</td>
<td>+0.06</td>
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<tr>
<td>C-C4cis</td>
<td>+2.35</td>
</tr>
</tbody>
</table>

[a] Free energy values referred to C-3b

In order to investigate the C6 (C4) – CHO bond formation mechanism in details, a relaxed potential energy scan was performed starting from each four conformations of intermediate C (C-3b, C-C6cis, C-C4trans, C-C4cis), decreasing the C6 (C4) – CHO interatomic distance by 0.2Å while optimizing the remaining internal coordinates (B3LYP 6-31G(d,p)). As shown by Fig. D.3, only in the case of cyclization at C6 (with trans & cis configuration) a bond formation occurs together with a drop in energy, while no stable products are found when cyclization at C4 is attempted.
Figure D.3. Relaxed potential energy as a function of the C6 (C4) – CHO interatomic distance starting from (a) C-3b, (b) C-C6cis, (c) C-C4trans, (d) C-C4cis.
Starting from approximate structures derived from the previous relaxed potential energy scans, Transition States (TS) for the C6 – CHO bond formation were then fully optimized at the B3LYP 6-311+G(d,p) level of theory in the case of C-3b/3b & C-C6cis/C6cis (Fig. D.4). Frequency calculations performed at the same level confirmed the nature of the TS, characterized by only one imaginary frequency (-355cm\(^{-1}\) & -395cm\(^{-1}\) for C-3b/3b & C-C6cis/C6cis respectively). Both TS are characterized by a strong intramolecular hydrogen bond, which is more favourable in C-3b/3b case (shorter H..O bond length and closer to linearity O-H…O angle). Corresponding free activation energies are reported in Table D.3: the barrier height for the formation of the \textit{trans} product (i.e. 3b) is 8.2kcal.mol\(^{-1}\) smaller than the one necessary for the \textit{cis} product.
Figure D.4. Transition states molecular structures optimized at the 6-311+G(d,p) level of theory. (a) TS between 3b & C-3b (C6-CHO = 2.021Å, O…H = 1.716Å, O…H…O = 171.90°), (b) TS between C6cis & C-C6cis (C6-CHO = 2.092Å, O…H = 1.770Å, O…H…O = 158.65°). C6 & aldehyde hydrogen atom involved in the diastereomery of the final product are displayed in green.

Table D.3. Free activation energies (B3LYP 6-311+G(d,p) level of theory) for the C6 – CHO bond formation in the case of the trans (C-3b / 3b) and cis (C-C6cis / C6cis) configurations.

<table>
<thead>
<tr>
<th>Molecular structure</th>
<th>$\Delta^\ddagger G^{373K}$ (kcal.mol$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS C-3b / 3b</td>
<td>+21.55</td>
</tr>
<tr>
<td>TS C-C6cis / C6cis</td>
<td>+29.75</td>
</tr>
</tbody>
</table>
E. References


