Supporting Information for the Paper

10-Hydroxy-10,9-Boroxarophenanthrenes: Versatile Synthetic Intermediates to 3,4-Benzocoumarins and Triaryls

Q. Jean Zhou,* Karin Worm and Roland Dolle

*Department of Chemistry, Adolor Corporation,
700 Pennsylvania Drive, Exton, PA 19341-1127*

jzhou@adolor.com

Table of Contents

Characterization of compounds 3, 4 and 7a	S2
Characterization of compounds 7b, 10, 13-17	S3
Characterization of compounds 18, 21, 23-25	S4
Characterization of compounds 26-34	S5
Characterization of compound 37-40	S6

Experimental Section

General Methods. All chemicals used were reagent grade and used as supplied. NMR spectra were recorded in CDCl₃, Acetone-d₆, or DMSO-d₆ on a 400 MHz spectrometer. Microwave heating was performed on a Milestone MicroSYNTH. LC/MS was performed under the following conditions: column: Michrom BioResources Inc. Magic C18 Macro Bullet; temperature: 40 °C; flow: 1.0 mL/min; detector: PDA 200 nm to 300 nm, total scan; mass detector: single quadrupole with Electrospray Ionization; mobile phase A: 10 mM ammonium acetate, pH 4.5; mobile phase B: acetonitrile; gradient (linear): 100% A to 99% B in 3.2 minutes, hold at 99% B until 3.6 minutes.

3-(1,1-Dimethylheptyl)-7,9-dimethyl-dibenzo[*c,e*][1,2]oxaborinin-6-ol (3). In a 100 mL round bottom flask, **1** (2.1 g, 6.21 mmol) was dissolved in 60 mL of anhydrous DCM. At 0 °C under N₂ atmosphere, a 1 M solution of BBr₃ in DCM (15.5 mL, 15.53 mmol) was added drop-wise. The reaction mixture was slowly warmed to 25 °C and stirred for 16 h. Water was added carefully to quench the reaction. A saturated aqueous solution of NaHCO₃ and diethyl ether were added, and the mixture was stirred for 10-20 min. The organic phase was separated, and the aqueous phase was extracted with diethyl ether (2x). The combined organic extracts were washed with NaHCO₃, brine, and dried over MgSO₄. The solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexane, hexane/EtOAc = 40/1, 30/1). A white solid was obtained (1.41 g, 65% yield): ¹H NMR (CDCl₃) δ 8.01 (d, 1 H, *J* = 9.1 Hz), 7.79 (s, 1 H), 7.14 (s, 1 H), 7.16 (d, 1 H, *J* = 9.0 Hz), 7.06 (s, 1 H), 4.70 (s, 1 H), 2.70 (s, 3 H), 2.45 (s, 3 H), 1.55-1.65 (m, 2 H), 1.33 (s, 6 H), 1.03-1.30 (m, 8 H), 0.83 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (CDCl₃) δ 151.3, 150.7, 145.9, 142.1, 141.7, 130.5, 123.4, 120.3, 120.3, 119.6, 116.4, 44.5, 37.7, 31.8, 30.0, 28.9, 24.7, 23.0, 22.7, 22.0, 14.1; LC/MS (99%), *m/z* 349.2 (M⁺); Anal. Calcd. for C₂₃H₃₁BO₂: C, 78.86; H, 8.92; found: C, 78.81; H, 9.02.

4'-(1,1-Dimethylheptyl)-3,5-dimethyl-biphenyl-2,2'-diol (4). To a mixture of **3** (0.72 g, 2.06 mmol) and NaOH (3N, 1 mL) in THF (10 mL) was added H₂O₂ (30%, 1 mL) drop-wise. The mixture was stirred at 25 °C for 16 h and then acidified to pH 2 with 1N HCl. H₂O/EtOAc was added, and the aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with brine, and dried over MgSO₄. Solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (hexane/EtOAc = 10/1, 10/2). A colorless oil was obtained (0.68 g, 94% yield): ¹H NMR (CDCl₃) δ 7.18 (d, 1 H, *J* = 9.1 Hz), 7.03 (s, 2 H), 7.00 (d, 1 H, *J* = 9.1 Hz), 6.92 (s, 1 H), 5.65 (b, 1 H), 5.40 (b, 1 H), 2.27 (s, 6 H), 1.57-1.66 (m, 2 H), 1.31 (s, 6 H), 1.03-1.36 (m, 8 H), 0.89 (t, 3 H, *J* = 6.8 Hz); ¹³C NMR (CDCl₃) δ 152.5, 152.4, 149.1, 131.8, 130.6, 130.2, 129.0, 125.4, 122.9, 120.5, 119.2, 114.1, 60.8, 44.5, 37.7, 31.8, 30.1, 28.9, 24.7, 22.7, 21.1, 20.5, 16.3, 14.1; LC/MS (98%), *m/z* 339.3 (M⁺).

Biphenyl-2-ol (7a). Same procedure as for **3** except 3 equiv of BBr₃ were used starting from **5a**. No column chromatography was necessary, and a white solid was obtained (100% yield): ¹H NMR (CDCl₃) δ 7.45-7.53 (m, 4 H), 7.38-7.44 (m, 1 H), 7.22-7.27 (m, 2 H), 6.97-7.02 (m, 2 H), 5.18 (s, 1 H); LC/MS (100%), *m/z* 169.2 (M⁺).

4'-Methyl-biphenyl-2-ol (7b). Same procedure as for **3** except 3 equiv of BBr₃ were used starting from **5b**. No column chromatography was necessary and a white solid was obtained (99% yield): ¹H NMR (CDCl₃) δ 7.36 (d, 2 H, *J* = 8.1 Hz), 7.30 (d, 2 H, *J* = 8.1 Hz), 7.21-7.27 (m, 2 H), 6.96-7.00 (m, 2 H), 5.21 (s, 1 H), 2.41 (s, 3 H); LC/MS (99%), *m/z* 183.4 (M⁺).

8,9-Dimethyldibenzo[*c,e*][1,2]oxaborinin-6-ol (10). Same procedure as for **3** except 3 equiv of BBr₃ were used starting from **5c**. No column chromatography was necessary; a white solid was obtained (99% yield): ¹H NMR (CDCl₃) δ 8.11 (dd, 1 H, *J* = 8.1 Hz, 1.5 Hz), 7.94 (s, 1 H), 7.80 (s, 1 H), 7.34 (dt, 1 H, *J* = 7.6 Hz, 1.5 Hz), 7.18-7.27 (m, 2 H), 4.65 (b, 1 H), 2.44 (s, 3 H), 2.38 (s, 3 H); LC/MS (99%), *m/z* 222.8 (M⁺).

Dibenzo[*c,e*][1,2]oxaborinin-6-ol (13). General procedure for boroxarene formation. Into a 250 mL oven-dried, 2-neck round bottom flask equipped with a drying tube and a septum was added 40 mL of anhydrous hexane. A solution of 1 M BCl₃ in hexane (7.41 mL, 7.41 mmol) was added via syringe. The starting 2-hydroxy-biphenyl (4.94 mmol) dissolved in anhydrous hexane (or anhydrous benzene) was added slowly via syringe. After the reaction mixture was stirred at 25 °C for 5-10 min, AlCl₃ (13-26 mg) was added quickly. The reaction mixture was heated to 70-75 °C for 6 h, and then cooled to 25 °C; ice was added slowly to quench the reaction. Diethyl ether (20 mL) was added, and the mixture was stirred for 20 min. The organic layer was separated, and the aqueous phase was extracted with diethyl ether (2 x 20 mL). All organic phases were combined, washed with H₂O (20 mL), brine (20 mL), and dried over anhydrous MgSO₄. The solvent was removed under reduced pressure. The product was an off-white solid (99% yield): ¹H NMR (CDCl₃) δ 8.18 (d, 1 H, *J* = 8.6 Hz), 8.14 (d, 1 H, *J* = 8.6 Hz), 8.07 (d, 1 H, *J* = 8.6 Hz), 7.71 (t, 1 H, *J* = 8.6 Hz), 7.48 (t, 1 H, *J* = 8.6 Hz), 7.38 (t, 1 H, *J* = 8.6 Hz), 7.21-7.29 (m, 2 H), 4.65 (s, 1 H); LC/MS (100%), *m/z* 195.1 (M⁺).

9-Methyldibenzo[*c,e*][1,2]oxaborinin-6-ol (14). Same procedure as for **13**; a white solid was obtained (98% yield): ¹H NMR (CDCl₃) δ 8.13 (d, 1 H, *J* = 8.5 Hz), 7.98 (s, 1 H), 7.95 (d, 1 H, *J* = 8.5 Hz), 7.20-7.39 (m, 4 H), 4.57 (s, 1 H), 2.53 (s, 3 H); LC/MS (97%), *m/z* 209.1 (M⁺).

8-Methyldibenzo[*c,e*][1,2]oxaborinin-6-ol (15). Same procedure as for **13**; an off white solid was obtained (98% yield): ¹H NMR (CDCl₃) δ 8.11 (d, 1 H, *J* = 8.1 Hz), 8.07 (d, 1 H, *J* = 8.1 Hz), 7.87 (s, 1 H), 7.53 (d, 1 H, *J* = 8.1 Hz), 7.20-7.39 (m, 3 H), 4.60 (s, 1 H), 2.47 (s, 3 H); LC/MS (97%), *m/z* 209.1 (M⁺).

2-Methyldibenzo[*c,e*][1,2]oxaborinin-6-ol (16). Same procedure as for **13**; a white solid was obtained (96% yield): ¹H NMR (CDCl₃) δ 8.16 (d, 1 H, *J* = 8.5 Hz), 8.05 (d, 1 H, *J* = 8.5 Hz), 7.95 (s, 1 H), 7.68-7.72 (m, 1 H), 7.42-7.49 (m, 1 H), 7.18 (s, 2 H), 4.59 (s, 1 H), 2.44 (s, 3 H); LC/MS (98%), *m/z* 209.0 (M⁺).

2-Fluorodibenzo[*c,e*][1,2]oxaborinin-6-ol (17). Same procedure as for **13**; a white solid was obtained (99% yield): ¹H NMR (CDCl₃) δ 8.07 (t, 2 H, *J* = 8.1 Hz), 7.71-7.80 (m, 2

H), 7.52 (t, 1 H, $J = 8.1$ Hz), 7.20-7.40 (m, 1 H), 7.05-7.10 (m, 1 H), 4.63 (s, 1 H); LC/MS (98%), m/z 213.1 (M^-).

8-Chlorodibenzo[*c,e*][1,2]oxaborinin-6-ol (18). Same procedure as for **13** (15% conversion as determined by LC/MS): LC/MS (15%), m/z 228.9 (M^-).

8-Fluoro-9-methyldibenzo[*c,e*][1,2]oxaborinin-6-ol (21). Same procedure as for **13** (80% conversion as determined by LC/MS): LC/MS (80%), m/z 227.0 (M^-).

3-(1,1-Dimethylheptyl)-dibenzo[*c,e*][1,2]oxaborinine-6,9-diol (23). Same procedure as for **13**; a white solid was obtained (80% yield): ^1H NMR (CDCl_3) δ 7.94 (d, 1 H, $J = 8.1$ Hz), 7.90 (d, 1 H, $J = 8.1$ Hz), 7.20 (s, 1 H), 7.17 (d, 1 H, $J = 8.1$ Hz), 7.14 (s, 1 H), 6.91 (d, 1 H, $J = 8.1$ Hz), 5.40 (b, 1H), 4.79 (b, 1 H), 1.58-1.62 (m, 2 H), 1.25 (s, 6 H), 1.04-1.35 (m, 8 H), 0.83 (t, 3 H, $J = 6.5$ Hz); LC/MS (94%), m/z 337.2 (M^-).

4-(1,1-Dimethylheptyl)-3''-methoxy-3',5'-dimethyl-[1,1',2',1'']terphenyl-2-ol (24). Into a 50 mL microwave reactor containing DME/ H_2O (10 mL, 3:1 v/v) were added **3** (0.14 g, 0.4 mmol), 3-methoxyphenyl iodide (0.113 g, 0.485 mmol), K_2CO_3 (0.112 g, 0.808 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (23 mg, 0.02 mmol). The mixture was de-gassed with N_2 for 5 min. The reactor was then capped and placed in the microwave oven. The temperature was ramped to 150 $^\circ\text{C}$ over 15 min, and kept at 150 $^\circ\text{C}$ for 15 min. After the reaction mixture was cooled to 25 $^\circ\text{C}$, EtOAc/ H_2O was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 x 20 mL). The combined organic phases were washed with H_2O , brine, and dried over anhydrous MgSO_4 . The residue was purified by column chromatography resulting in **24** as a colorless oil (108 mg, 63% yield): ^1H NMR (CDCl_3) δ 7.16 (s, 1 H), 7.05-7.10 (m, 2 H), 6.78 (b, 1 H), 6.70 (s, 1 H), 6.62-6.67 (m, 3 H), 6.52 (s, 1 H), 4.78 (b, 1 H), 3.60 (s, 3 H), 2.38 (s, 3 H), 2.20 (s, 3 H), 1.43-1.50 (m, 2 H), 1.19 (s, 6 H), 1.03-1.25 (m, 8 H), 0.86 (t, 3 H, $J = 7.0$ Hz); LC/MS (98%), m/z 429.2 (M^-).

3-(1,1-Dimethylheptyl)-7,9-dimethylbenzo[*c*]chromen-6-one (25). In a 100 mL round bottom flask, **3** (0.28 g, 0.8 mmol) was dissolved in DMSO (20 mL). MeOH (10 mL) and $\text{Pd}(\text{OAc})_2$ (0.180 g, 0.8 mmol) were added and the reaction mixture was evacuated and filled with CO three times. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 3 h until the brown catalyst turned to a black precipitate. The mixture was poured into an Erlenmeyer flask containing 200 mL of H_2O , which was then extracted with EtOAc (3 x 50 mL). The organic phases were combined and washed with H_2O , brine, and dried over MgSO_4 . The solvent was removed *in vacuo* and the residue was purified by column chromatography (hexane/EtOAc = 10/1) to give a white solid (0.24 g, 87% yield): ^1H NMR (CDCl_3) δ 7.94 (d, 1 H, $J = 8.6$ Hz), 7.76 (s, 1 H), 7.26 (d, 1 H, $J = 8.6$ Hz), 7.27 (s, 1 H), 7.17 (s, 1 H), 2.83 (s, 3 H), 2.49 (s, 3 H), 1.59-1.64 (m, 2 H), 1.32 (s, 6 H), 1.00-1.31 (m, 8 H), 0.83 (t, 3 H, $J = 6.5$ Hz); ^{13}C NMR (CDCl_3) δ 161.5, 153.1, 151.4, 144.7, 144.2, 136.3, 132.9, 122.5, 122.0, 119.8, 117.1, 115.6, 114.7, 44.4, 38.0, 31.8, 30.0, 28.8, 24.7, 23.7, 22.6, 22.0, 14.1; LC/MS (98%), m/z 392.2 ($M+\text{CH}_3\text{CN}$) $^+$.

Benzo[*c*]chromen-6-one (26). Same procedure as for **25** starting from **13**; a white solid

was obtained (90% yield): ^1H NMR (CDCl_3) δ 8.41 (d, 1 H, $J = 8.1$ Hz), 8.13 (d, 1 H, $J = 7.6$ Hz), 8.06 (d, 1 H, $J = 7.4$ Hz), 7.83 (m, 1 H), 7.59 (m, 1 H), 7.49 (m, 1 H), 7.31-7.38 (m, 2 H); LC/MS (100%), m/z 197.0 (M) $^+$, 238.0 ($\text{M} + \text{CH}_3\text{CN}$) $^+$.

9-Methylbenzo[*c*]chromen-6-one (27). Same procedure as for **25** starting from **14**. No column chromatography was necessary; a white solid was obtained (100% yield): ^1H NMR (CDCl_3) δ 8.31 (d, 1 H, $J = 8.1$ Hz), 8.07 (d, 1 H, $J = 7.6$ Hz), 7.93 (s, 1 H), 7.48 (dd, 1 H, $J = 7.6$ Hz, 8.6 Hz), 7.32-7.42 (m, 3 H), 2.57 (s, 3 H); ^{13}C NMR(CDCl_3) δ 161.3, 151.5, 145.9, 134.7, 130.6, 130.3, 130.2, 124.2, 122.7, 121.8, 118.8, 118.1, 117.8, 22.3; LC/MS (98%), m/z 210.9 (M) $^+$.

8-Methylbenzo[*c*]chromen-6-one (28). Same procedure as for **25** starting from **15**. No column chromatography was necessary; a white solid was obtained (96% yield): ^1H NMR (CDCl_3) δ 8.23 (s, 1 H), 8.02 (d, 1 H, $J = 7.6$ Hz), 7.65 (d, 1 H, $J = 7.6$ Hz), 7.47 (d, 1 H, $J = 7.6$ Hz), 7.45 (d, 1 H, $J = 8.0$ Hz), 7.31-7.38 (m, 2 H), 2.51 (s, 3 H); LC/MS (99%), m/z 210.9 (M) $^+$, 252.0 ($\text{M} + \text{CH}_3\text{CN}$) $^+$.

2-Methylbenzo[*c*]chromen-6-one (29). Same procedure as for **25** starting from **16**. Purification of the product was by column chromatography yielding a white solid (80% yield): ^1H NMR (CDCl_3) δ 8.41 (d, 1 H, $J = 7.6$ Hz), 8.12 (d, 1 H, $J = 7.6$ Hz), 7.86 (s, 1 H), 7.82 (t, 1 H, $J = 7.6$ Hz), 7.58 (t, 1 H, $J = 7.6$ Hz), 7.27 (m, 2 H), 2.47 (s, 3 H); LC/MS (99%), m/z 210.9 (M) $^+$, 252.1 ($\text{M} + \text{CH}_3\text{CN}$) $^+$.

2-Fluorobenzo[*c*]chromen-6-one (30). Same procedure as for **25** starting from **17**. No column chromatography was necessary; a slightly yellow solid was obtained (99% yield): ^1H NMR (CDCl_3) δ 8.44 (d, 1 H, $J = 7.6$ Hz), 8.05 (d, 1 H, $J = 8.1$ Hz), 7.87 (dd, 1 H, $J = 7.8$ Hz, 8.1 Hz), 7.74 (d, 1 H, $J = 8.1$ Hz), 7.64 (dd, 1 H, $J = 7.6$ Hz, 8.7 Hz), 7.33-7.40 (m, 1 H), 7.17-7.22 (m, 1 H); LC/MS (100%), m/z 215.0 (M) $^+$, 256.1 ($\text{M} + \text{CH}_3\text{CN}$) $^+$.

8-Chlorobenzo[*c*]chromen-6-one (31). Same procedure as for **25** starting from crude **18** (95% conversion determined by LC/MS): LC/MS (22%), m/z 231.0 (M) $^+$.

4'-Methyl-[1,1',2',1'']terphenyl-2-ol (32). Same procedure as for **24** starting from **15** and the reaction mixture was heated in an oil bath at 90 $^\circ\text{C}$ for 16 h. The residue was purified by column chromatography yielding a white solid (81% yield): ^1H NMR (CDCl_3) δ 7.32 (s, 1 H), 7.24-7.30 (m, 2 H), 7.10-7.21 (m, 6 H), 7.00 (d, 1 H, $J = 7.6$ Hz), 6.75-6.82 (m, 2 H), 4.85 (s, 1 H), 2.44 (s, 3 H); ^{13}C NMR(CDCl_3) δ 152.5, 141.6, 140.6, 138.6, 132.0, 131.6, 131.3, 130.8, 130.0, 129.1, 128.8, 128.0, 127.8, 127.0, 120.4, 115.4, 21.3; LC/MS (95%), m/z 259.2 (M) $^-$.

2-Hydroxy-[1,1',2',1'']terphenyl-3''-carbaldehyde (33). Same procedure as for **32** starting from **13** (85% yield as determined by LC/MS): LC/MS (85%), m/z 273.0 (M) $^-$.

4''-Methoxy-[1,1',2',1'']terphenyl-2-ol (34). Same procedure as for **33** (64% yield as determined by LC/MS): LC/MS (64%), m/z 274.9 (M) $^-$.

5H-Dibenzo[1,2]azaborinin-6-ol (37). Same procedure as for **13** except twice the amount of BCl_3 and AlCl_3 were used; a slightly brown solid was obtained (99% yield as determined by LC/MS). Re-crystallization was done on an aqueous solution of 50% acetic acid: ^1H NMR (Acetone- d_6) δ 8.29 (d, 1 H, $J = 8.6$ Hz), 8.19 (d, 1 H, $J = 8.6$ Hz), 8.09 (d, 1 H, $J = 8.1$ Hz), 7.52-7.56 (m, 1 H), 7.60 (br, 1 H), 7.30 (t, 1 H, $J = 7.3$ Hz), 7.13-7.20 (m, 2 H), 6.91-6.96 (m, 1 H); LC/MS (99%), m/z 194.3 (M) $^-$.

9-Methyl-5H-dibenzo[1,2]azaborinin-6-ol (38). Same procedure as for **13** except twice the amount of BCl_3 and AlCl_3 were used; a slightly brown solid was obtained (93% yield as determined by LC/MS): LC/MS (93%), m/z 208.0 (M) $^-$. When 1.5 equiv of BCl_3 and 4% of AlCl_3 were used and the reaction mixture was heated at 50 $^\circ\text{C}$ for 16 h, a 70% conversion resulted as determined by LC/MS.

5H-Phenanthridin-6-one (39). Same reaction conditions as described for **25** starting from **37**. After standard work up, the residue was dissolved in 50 mL of MeOH and 100 mL of 0.1 N H_2SO_4 . The mixture was heated at 60 $^\circ\text{C}$ for 3 h. After the mixture was cooled to room temperature, the solvent was removed and the aqueous phase was neutralized with saturated solution of Na_2CO_3 and extracted with Et_2O (3 x 20 mL). The solvent was removed *in vacuo* and the residue was analyzed by LC/MS (17 % yield, retention time was the same as the commercial compound): LC/MS (17%), m/z 195.9 (M) $^+$.

9-Methyl-5H-phenanthridin-6-one (phenaglydon; 40). Same reaction conditions as described for **39** (17% yield as determined by LC/MS): LC/MS (17%), m/z 210.1 (M) $^+$. The product mixture was re-dissolved in acetic acid (100 mL) with a few drops of water and $\text{Pd}(\text{OAc})_2$ (1 equiv) added. The reaction mixture was stirred at 50 $^\circ\text{C}$ under a CO atmosphere for 3 h. LC/MS indicated a yield increase of **40** to 37%. To this reaction mixture, an additional 10 mole% of $\text{Pd}(\text{OAc})_2$, and 20 mole% of DPPF were added, and was heated at 50 $^\circ\text{C}$ under a CO atmosphere for 16 h. A yield increase of **40** to 49% was observed as determined by LC/MS. Pure **40** was isolated by silica gel chromatography: ^1H NMR (DMSO- d_6) δ 11.60 (br. s, 1 H), 8.38 (d, 1 H, $J = 8.1$ Hz), 8.33 (s, 1 H), 8.21 (d, 1 H, $J = 8.1$ Hz), 7.45-7.49 (m, 2 H,), 7.35 (d, 1 H, $J = 8.6$ Hz), 7.25 (t, 1 H, $J = 7.8$ Hz), 2.54 (s, 3 H); ^{13}C NMR(DMSO- d_6) δ 160.8, 143.0, 136.7, 134.2, 129.4, 129.1, 127.4, 123.4, 123.2, 122.5, 122.1, 117.5, 116.0, 21.5; LC/MS (98%), m/z 210.2 (M) $^+$.