Supplementary Material

"Synthesis of the Spirocyclic Cyclohexadienone Ring System of the Schiarisanrins"

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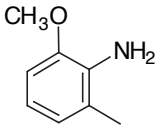
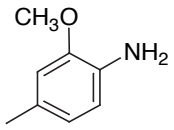
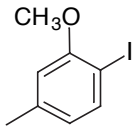


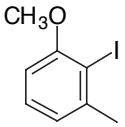
2-Methoxy-6-methylaniline. A solution of 3-methyl-2-nitroanisole (**17**) (50 mg, 0.299 mmol) in ethanol (5 mL) was treated with a catalytic amount of 10% palladium on carbon. Hydrogen gas was bubbled through the reaction mixture for 1 h. The reaction was filtered through Celite and concentrated *in vacuo* to give the desired aniline (40.6 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (m, 3H), 3.91 (s, 3H), 3.81 (br s, 2H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 134.7, 123.1, 123.0, 118.0, 108.6, 56.0, 17.6; IR (neat) ν_{max} 3465, 3377, 2938, 2835, 1618, 1488, 1278, 1238, 1169, 1056 cm^{-1}; HRMS (EI), *m/z* calcd for $C_8H_{11}NO$: 137.0841; found: 137.0838.



2-Methoxy-4-methylaniline. A solution of 5-methyl-2-nitroanisole (**18**) (50 mg, 0.299 mmol) in ethanol (5 mL) was treated with a catalytic amount of 10% palladium on carbon. Hydrogen gas was bubbled through the reaction mixture for 1 h. The reaction was filtered through Celite and concentrated *in vacuo* to give the desired aniline (40.6 mg, 99%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (m, 3H), 3.75 (s, 3H), 3.57 (br s, 2H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 133.9, 128.5, 121.6, 115.5, 112.0, 55.8, 21.4; IR (neat) ν_{max} 3449, 3365, 2936, 1623, 1590, 1519, 1465, 1279, 1243, 1158, 1037 cm^{-1}; HRMS (EI), *m/z* calcd for $C_8H_{11}NO$: 137.0841; found: 137.0858.

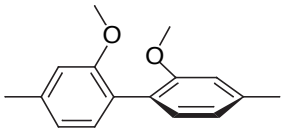


2-Iodo-5-methylanisole (19). A solution of the corresponding aniline (23.0 g, 168 mmol) in concentrated HCl (100 mL) was cooled to 0 °C. A solution of $NaNO_2$ (11.9 g, 173 mmol) in H_2O (200 mL) was added and the mixture was stirred at 0 °C for 1 h. This mixture was added dropwise over 30 min to a solution of KI (36.4 g, 218 mmol) in H_2O (200 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred at this temperature for 12 h. The mixture was extracted with Et_2O (3 x 150 mL). The combined extracts were washed with saturated aqueous NaCl (1 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a colorless oil. Purification by flash chromatography (silica, hexane) gave iodoanisole **19** (35.1 g, 84%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 6.69 (s, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 3.91 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.3, 140.3, 139.4, 123.8, 112.6, 82.3, 56.6, 21.9; IR (neat) ν_{max} 2937, 2855, 1576, 1479, 1398, 1281, 1256, 1173, 1045, 1016 cm^{-1}; HRMS (EI), *m/z* calcd for C_8H_9IO: 247.9698; found: 247.9695.

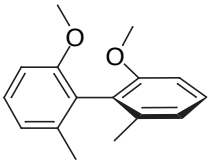


2-Iodo-3-methylanisole (20). A solution of the corresponding aniline (27.0 g, 197 mmol) in concentrated HCl (100 mL) was cooled to 0 °C. A solution of $NaNO_2$ (14.0 g, 203 mmol) in H_2O (200 mL) was added and the mixture was stirred at 0 °C for 1 h. This mixture was added dropwise over 30 min to a solution of KI (43.0 g, 256 mmol) in H_2O (200 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred at this temperature for 12 h. The mixture was extracted with Et_2O (3 x 150 mL). The combined extracts were washed with saturated aqueous NaCl (1 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a clear oil. Purification by flash chromatography (silica, hexane) gave iodoanisole **20** (38.0 g, 78%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (dd, *J* = 8.0, 7.9 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 3.81 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 143.9, 129.1, 122.8, 108.4, 93.5, 56.9, 29.1; IR (neat) ν_{max}

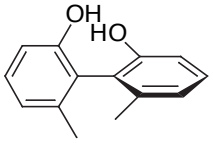
2938, 2835, 1588, 1566, 1467, 1410, 1295, 1263, 1080, 1014 cm^{-1}; HRMS (EI), *m/z* calcd for C_8H_9IO: 247.9698; found: 247.9695.



2,2′-Dimethoxy-4,4′-dimethylbiphenyl (21). A mixture of iodoaniline **19** (10.0 g, 40.3 mmol) and copper bronze (2 g) was stirred at 250 °C for 5 h. The mixture was allowed to cool to 25 °C and was triturated with $CHCl_3$ (150 mL), filtered and concentrated *in vacuo* to give a colorless oil. Purification by flash chromatography (silica, 0-2.5% ethyl acetate/hexane) gave biphenyl **21** (1.4 g, 14%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, *J* = 7.6 Hz, 2H), 6.74 (d, *J* = 7.6, 2H), 6.71 (s, 2H), 3.68 (s, 6H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 138.8, 131.7, 125.2, 121.4, 112.5, 56.1, 22.1; IR (neat) ν_{max} 2923, 2853, 1727, 1608, 1577, 1494, 1463, 1403, 1281, 1252, 1163, 1042 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{16}H_{18}O_2$: 242.1307; found: 242.1307.

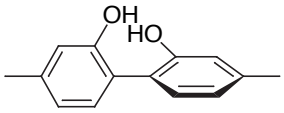


2,2′-Dimethoxy-6,6′-dimethylbiphenyl (22). A mixture of iodoanisole **20** (10 g, 40.3 mmol) and copper bronze (2 g) was stirred at 250 °C for 5 h. The mixture was allowed to cool to 25 °C and was triturated with $CHCl_3$ (150 mL), filtered and concentrated *in vacuo* to give a colorless oil. Purification by flash chromatography (silica, 0-2.5% ethyl acetate/hexane) gave biphenyl **22** (2.0 g, 20%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 8.2 Hz, 2H), 3.75 (s, 6H), 2.00 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 138.6, 128.3, 126.6, 122.6, 108.8, 56.2, 20.0; IR (neat) ν_{max} 2917, 2834, 1581, 1467, 1438, 1295, 1255, 1084, 1004 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{16}H_{18}O_2$: 242.1307; found: 242.1309.

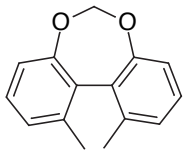


6,6′-Dimethyl-2,2′-biphenyldiol. A solution of biphenyl **22** (2.00 g, 8.26 mmol) in CH_2Cl_2 (50 mL) was cooled to –78 °C. BBr_3 (3.1 mL, 33.1 mmol) was added and the mixture was

stirred at –78 °C for 1 h. The mixture was allowed to warm to 25 °C and was stirred at this temperature for 1 h. The reaction mixture was washed with saturated aqueous NaCl (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 5-20% ethyl acetate/hexane) gave the biphenyldiol (1.50 g, 85%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, 2H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.94 (d, *J* = 8.3 Hz, 2H), 4.75 (s, 2H), 2.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 139.4, 130.5, 123.0, 120.0, 113.6, 19.9; IR (neat) ν_{max} 3464, 3413, 3032, 2971, 2915, 1574, 1465, 1281, 1250, 1176 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{14}H_{14}O_2$: 214.0994; found: 242.0993.

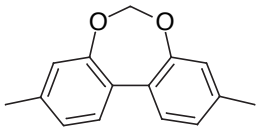


4,4′-Dimethyl-2,2′-biphenyldiol. A solution of biphenyl **21** (1.20 g, 4.96 mmol) in CH_2Cl_2 (50 mL) was cooled to –78 °C. BBr_3 (1.88 mL, 19.8 mmol) was added and the mixture was stirred at –78 °C for 1 h. The mixture was allowed to warm to 25 °C and was stirred at this temperature for 1 h. The reaction mixture was washed with saturated aqueous NaCl (2 x 30 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 5-20% ethyl acetate/hexane) gave the biphenyldiol (974 mg, 91%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 5.47 (s, 2H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 140.6, 131.4, 122.8, 120.7, 117.5, 21.6; IR (neat) ν_{max} 3244, 1620, 1564, 1499, 1415, 1285, 1233, 1159, 1113, 1007 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{14}H_{14}O_2$: 214.0994; found: 242.0996.

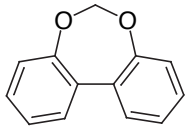


1,11-Dimethyldibenzo[*d,f*][1,3]dioxepin (8). A slurry of NaH (504 mg, 21.0 mmol) in DMF (100 mL) under N_2 was cooled to 0 °C and a solution of the corresponding biphenol (1.50 g, 7.00 mmol) in DMF (50 mL) was added dropwise over 15 min. The reaction mixture was stirred at 0 °C for an additional 15 min before a solution of CH_2BrCl (0.455 mL, 7.00 mmol) in DMF (50 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to 25 °C over 30 min and after 12 h

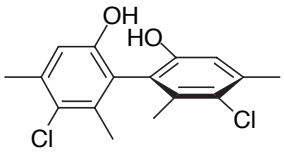
at this temperature the mixture was quenched by the addition of 1 N aqueous HCl (50 mL). The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 0-2.5% ethyl acetate/hexane) gave dioxepin **8** (1.16 g, 73%) as a white crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (app t, J = 7.8 Hz, 2H), 7.24 (d, J = 7.8 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 5.48 (s, 2H), 2.30 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 138.2, 132.1, 129.0, 127.9, 118.3, 102.3, 20.1; IR (neat) ν_{max} 3062, 2955, 2897, 1601, 1566, 1443, 1271, 1243, 1220, 1141, 1058, 1028 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{15}H_{14}O_2$: 226.0994; found: 226.0998.



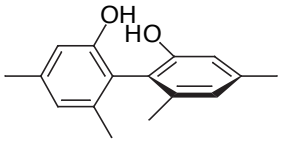
3,9-Dimethyl dibenzo[*d,f*][1,3]dioxepin (9). A slurry of NaH (326 mg, 13.6 mmol) in DMF (75 mL) under N_2 was cooled to 0 °C and a solution of the corresponding biphenol (970 mg, 4.53 mmol) in DMF (50 mL) was added dropwise over 15 min. The reaction mixture was stirred at 0 °C for an additional 15 min before a solution of CH_2BrCl (0.294 mL, 4.53 mmol) in DMF (25 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to 25 °C over 30 min and after 12 h at this temperature the reaction was quenched by the addition of 1 N aqueous HCl (25 mL). The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 0-2.5% ethyl acetate/hexane) gave dioxepin **9** (538 mg, 53%) as a white crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.1 Hz, 2H), 6.99 (s, 2H), 2.41 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 139.1, 128.6, 125.4, 125.3, 121.6, 98.1, 21.3; IR (neat) ν_{max} 2918, 1619, 1516, 1488, 1447, 1401, 1301, 1182, 1134, 1034 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{15}H_{14}O_2$: 226.0994; found: 226.0995.



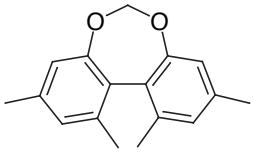
Dibenzo[*d,f*][1,3]dioxepin. A slurry of NaH (1.42 g, 59.1 mmol) in DMF (200 mL) under N_2 was cooled to 0 °C and a solution of 2,2′-biphenol (10.0 g, 53.7 mmol) in DMF (150 mL) was added dropwise over 30 min. This mixture was stirred at 0 °C for an additional 20 min. A solution of CH_2BrCl (3.84 mL, 59.1 mmol) in DMF (150 mL, 0.4 M) was added dropwise over 30 min. The reaction mixture was allowed to warm to 25 °C over 30 min and after 12 h at this temperature the mixture was quenched by the addition of 1 N aqueous HCl (300 mL). The mixture was extracted with Et_2O (3 x 100 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a pink oil. Purification by flash chromatography (silica, 0-1% acetone/hexane) gave dibenzo[*d,f*][1,3]dioxepin (3.7 g, 35%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 6.4 Hz, 2H), 7.36-7.34 (m, 2H), 7.30-7.26 (m, 2H). 7.20 (d, J = 6.4 Hz, 2H), 5.67 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7, 129.5, 129.3, 129.1, 124.9, 121.3, 99.6; IR (neat) ν_{max} 3066, 2904, 1502, 1481, 1434, 1283, 1183, 1025 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{13}H_{10}O_2$: 198.0681; found: 198.0682.



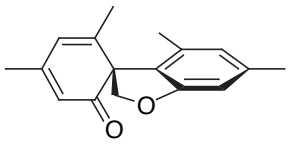
5,5′-Dichloro-4,4′,6,6′-tetramethyl-2,2′-biphenyldiol (15). A solution of 4-chloro-3,5-dimethylphenol (156 mg, 1.0 mmol) in chlorobenzene (10 mL) was treated with copper on K-10 Montmorillonite clay (500 mg). This mixture was brought to reflux and air was bubbled through the solution for 10 h. The reaction was then cooled to 25 °C and filtered. The residue was rinsed with CH_2Cl_2 (2 x 10 mL) and the combined filtrates were concentrated *in vacuo* to give a brown solid. Purification by flash chromatography (silica, 15-30% acetone/hexane) and subsequent recrystallization from hot 5% acetone/hexane gave biphenyldiol **15** (98.4 mg, 63%) as a white crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.72 (s, 2H), 4.45 (s, 2H), 2.29 (s, 6H), 1.94 (s, 6H).



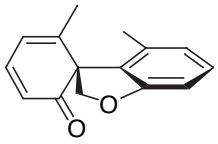
4,4′,6,6′-Tetramethyl-2,2′-biphenyldiol (16). A solution of biphenyldiol **15** (6.98 g, 22.41 mmol) in 10% aqueous NaOH (200 mL) was treated with Raney aluminum-nickel alloy (13.95 g) added over 1 h. The mixture was stirred for 12 h. at 25 °C. The reaction was then filtered through Celite and the filter cake was rinsed with H_2O. The filtrate was acidified to pH 1 by the addition of concentrated HCl. This mixture was extracted with Et_2O (4 x 100 mL) and the organic extracts were washed with saturated aqueous NaCl (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Recrystallization from hot 5% acetone/hexanes gave biphenyldiol **16** (5.6 g, 80%) as a white crystalline solid: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.63 (s, 2H), 6.60 (s, 2H), 4.56 (s, 2H), 2.21 (s, 6H), 1.85 (s, 6H).



1,3,9,11-Tetramethyldibenzo[*d,f*][1,3]dioxepin (7). A slurry of NaH (420 mg, 17.5 mmol) in DMF (100 mL) under N_2 was cooled to 0 °C and a solution of biphenyldiol **16** (3.86 g, 15.9 mmol) in DMF (60 mL) was added dropwise over 15 min. This mixture was stirred at 0 °C for an additional 15 min. A solution of CH_2BrCl (1.14 mL, 17.5 mmol) in DMF (60 mL) was added dropwise over 10 min. The reaction mixture was allowed to warm to 25 °C over 30 min and after 12 h at this temperature the mixture was quenched by the addition of 1 N aqueous HCl (100 mL). The mixture was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were washed with saturated aqueous NaCl (2 x 50 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 0-1% acetone/hexane) gave dioxepin **7** (2.58 g, 64%) as a white crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 6.79 (s, 2H), 5.33 (s, 2H), 2.31 (s, 6H), 2.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 138.8, 137.8, 129.1, 128.6, 119.0, 102.2, 21.5, 20.1; IR (neat) ν_{max} 2920, 1614, 1560, 1452, 1310, 1277, 1146, 1080, 1040 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{17}H_{18}O_2$: 254.1307; found: 254.1314.



3,5-Dimethyl-2,4-cyclohexadienone-6-spiro-3′-(4′,6′-dimethyl-2′,3′-dihydrobenzo[*b*]furan) (6). A solution of dioxepin **7** (100 mg, 0.392 mmol) in CH_2Cl_2 (8 mL) at 25 °C was treated with $AlCl_3$ (65.6 mg, 0.492 mmol) in one portion. The mixture was stirred at 25 °C for 5 min. CH_2Cl_2 was added (25 mL) and the mixture was washed with saturated aqueous NaCl (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a white solid. Purification by flash chromatography (silica, 0-1% acetone/hexane) gave cyclohexadienone **6** (95 mg, 95%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.43 (s, 1H), 6.01 (s, 1H), 5.97 (s, 1H), 4.53 (AB q, J = 8.6 Hz, Δν = 74.0 Hz, 2H), 2.24 (s, 3H), 2.09 (s, 3H), 1.84 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 161.0, 153.9, 150.8, 139.3, 133.5, 126.5, 123.1, 122.1, 120.9, 107.7, 81.6, 62.7, 22.6, 20.9, 19.0, 17.2; IR (neat) ν_{max} 2956, 2916, 1664, 1636, 1577, 1438, 1381, 1287, 1067, 990 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{17}H_{18}O_2$: 254.1307; found: 254.1311.



5-Methyl-2,4-cyclohexadienone-6-spiro-3′-(4′-methyl-2′,3′-dihydrobenzo[*b*]furan) (11). A solution of dioxepin **8** (100 mg, 0.442 mmol) in CH_2Cl_2 (3 mL) at 25 °C was treated with a solution of $EtAlCl_2$ (0.553 mL, 0.553 mmol, 1 M in CH_2Cl_2) in one portion. The mixture was stirred at 25 °C for 2 h. $CHCl_3$ was added (15 mL) and the mixture was washed with saturated aqueous NaCl (2 x 10 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give a yellow oil. Purification by flash chromatography (silica, 0-5% acetone/hexane) gave cyclohexadienone **11** (60.0 mg, 60%) as a light yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 10.1, 8.1 Hz, 2H), 6.78 (d, J = 8.1 Hz, 1H), 6.68 (d, J = 7.5 Hz, 1H), 6.21 (d, J = 7.5 Hz, 1H), 6.19 (d, J = 10.1 Hz, 1H), 4.64 (AB q, J = 8.6 Hz, Δν = 47.2 Hz, 2H), 1.97 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 161.6, 152.8, 142.7, 135.1, 130.4, 130.0, 123.9, 123.1, 119.2, 108.0, 82.5, 65.3, 20.1, 18.3; IR (neat) ν_{max} 3474, 3044, 2966, 1718, 1663, 1631, 1588, 1565, 1471, 1249, 1148, 1080 cm^{-1}; HRMS (EI), *m/z* calcd for $C_{15}H_{14}O_2$: 226.0994; found: 226.0994.