Synthesis, Enantiomeric Conformations and Stereodynamics of Aromatic *ortho*-Substituted Disulfones

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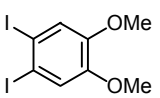
Supporting Information

General Methods and Materials: Solvents and chemicals were used without purification unless indicated. NMR spectral data were recorded on Bruker AMX-400 and Varian XL-200 spectrometers at ambient temperature, unless otherwise specified. Data are reported as follows: chemical shift (δ) in ppm from internal standard (tetramethylsilane for ^{1}H and ^{13}C NMR, H_3PO_4 for ^{31}P NMR) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, sept = septuplet and m = multiplet), coupling constant (Hz), integration. Infrared spectral data were recorded on a Perkin Elmer 1600 Series FT-IR spectrophotometer by using KBr. Analytical gas chromatography (GC) was carried out on a Hewlett-Packard HP6890 chromatograph using a 30 m by 0.32 mm by 0.25 μm (95% dimethylpolysiloxane, 5% diphenylpolysiloxane) non polar column from Alltech (HP5). Classical conditions: 2 minutes at 80 °C, slope 5 °C / minute, 5 minutes at 180 °C. Flash chromatography was performed under pressure (0.1-0.2 bar), using J. T. Baker silica gel (30-60 μm (230-400 mesh)) or Fluka neutral alumina type 507C (100-125 mesh). Electrospray mass spectral data were obtained on a Finnigan SSQ 7000 spectrometer. Mass spectral data were obtained with a Varian CH4 or SM1 spectrometer and relative intensities are given in parentheses (m/z, %). Melting points (M.p.) were measured in open capillary tubes with a Stuart Scientific SMP3 melting point apparatus. Toluene was distilled from sodium metal; methanol, hexane and dichloromethane from calcium hydride. Dimethyl formamide (DMF) was distilled from $MgSO_4$ at reduced pressure and stored over 4 Å molecular sieves under nitrogen. Chloroform (Fluka) and $CDCl_3$ were filtered through a plug of basic alumina prior to use.

Synthetic Procedures

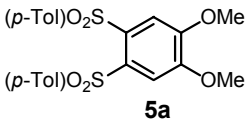


4

4,5-Diiodoveratrol (4): In a 50 mL round-bottomed flask, a solution of H_5IO_6 (Lancaster, 2.92 g, 12.8 mmol) in methanol (18.6 mL) was stirred for 15 minutes at 20 °C. Iodine (Lancaster, 6.38 g, 25.1 mmol) was then added and the mixture stirred vigorously for 10 minutes. Veratrol (Fluka, 4.00 mL, 31.4 mmol) was then added, and the mixture stirred for 4 hours at 70 °C (during the reaction, the formation of an important white precipitate was observed). The hot mixture was then poured into a diluted solution of sodium pyrosulfite, and the white solid formed was collected by filtration over a Büchner funnel and washed with methanol. The resulting product was then dissolved in ethyl acetate and dried (Na_2SO_4). Filtration and concentration *in vacuo* afforded 11.47 g (29.4 mmol, 94 %) of **4**. No further purification was required. **M.p.**: 133 °C (ethyl acetate / hexane). **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 7.21 (s, 2 H); 3.81 (s, 6 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ = 149.6; 121.6; 96.0; 56.1. **MS** (EI, 70 eV): m/z (%): 390 (M^+, 8 %); 264 (100 %); 249 (23 %). **MS** (H.R.): calc. 389.86139, found 389.86205 ($C_8H_8O_2I_2$). **GC**: 8.19 minutes.

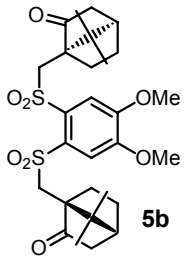
Sodium (+)-camphor-(10)-sulfinate: In a 25 mL round bottomed flask, a solution of sodium methanesulfinate using sodium sulfite (Fluka, 750 mg, 6.0 mmol, 1.0 eq) in water (9 mL) was vigorously stirred for 10 minutes at 20 °C. Sodium hydrogen carbonate (Fluka, 1.0 g, 12.0 mmol, 2.0 eq) was added and the mixture was stirred for 1 hour at 50 °C. (+)-Camphor-(10)-sulfonyl chloride (1.44 g, 5.70 mmol, 0.9 eq) was carefully added and after the addition was completed, the mixture was vigorously stirred at 50 °C for 4 hours. After cooling at 20 °C, the water was removed *in vacuo* for several hours. Methanol (Fluka, 5 mL) was added and the mixture was stirred overnight. After filtration

and concentration *in vacuo*, 1.36 g (5.70 mmol, Yield = 100 %) of substrate were obtained**.** **^{1}H-NMR** (CD_3OD, 200 MHz): δ = 2.62 (d, 1H, J=13 Hz); 2.40 – 2.26 (m, 2H); 2.12 (d, 1H, J=13 Hz); 2.10 – 1.99 (m, 2H); 1.87 (d, J=18 Hz, 1H); 1.60 – 1.53 (m, 1H); 1.46 – 1.40 (m, 1H); 1.06 (s, 3H); 0.90 (s, 3H). **^{13}C-NMR** (CD_3OD, 100 MHz): δ = 217.3; 77.1; 43.4; 42.9; 38.5; 29.6; 26.7; 26.4; 20.1; 20.0. **IR** (KBr): strong band at 1040-960 cm^{-1} (SO_2^-).



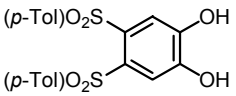
5a

4,5-Bis(*p*-toluenesulfonyl)veratrol (5a): In a 250 mL round-bottomed flask, a solution of 4,5-diiodoveratrol (**4**) (3.34 g, 8.50 mmol) in freshly distilled DMF (67.0 mL) was vigorously stirred under argon for 10 minutes at 20 °C. Cuprous iodide (Fluka, 5.00 g, 26.2 mmol, 3.0 equiv.) was added and the mixture was stirred for 10 minutes. Sodium *p*-toluenesulfinate (Lancaster, 5.00 g, 28.1 mmol, 3.0 equiv.) was added and the mixture was vigorously stirred under argon for 72 hours at 110 °C. The reaction mixture was allowed to cool to 20 °C and diluted with water (100 mL) and ethyl acetate (100 mL). The precipitate formed was removed by filtration over a Büchner funnel and discarded. The organic layer was washed with water (2 x 70 mL), saturated aqueous $NaHCO_3$ (2 x 50 mL) and dried (Na_2SO_4). After filtration and concentration *in vacuo*, 3.04 g (7.3 mmol, 88 %) of **5a** were obtained. Recrystallization from ethyl acetate / cyclohexane gave **5a** as white needles. **M.p.**: 193-194 °C (ethyl acetate / cyclohexane). **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 7.91 (s, 2 H); 7.81 (d, J = 4.0 Hz, 4 H); 7.27 (d, J = 4.0 Hz, 4 H); 4.03 (s, 6 H); 2.39 (s, 6 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ = 151.9; 143.9; 139.2; 133.0; 129.3; 127.8; 115.3; 56.8; 21.6. **MS** (EI, 70 eV): m/z (%): 446 (M^+, 100 %); 414 (31 %); 382 (70 %); 243 (60 %); 212 (59 %); 139 (73 %); 91 (89 %). **MS** (H.R.): calc. 446.08578, found 446.08817 ($C_{22}H_{22}O_6S_2$). **GC**: 9.66 minutes.



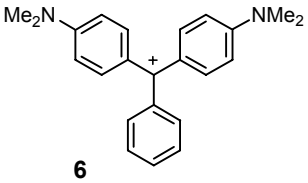
5b

4,5-Bis((+)-camphor-(10)-sulfonyl)veratrol (5b): Prepared following conditions reported for **5a** from **4** (299 mg, 0.76 mmol) in DMF (31 mL), cuprous iodide (Fluka, 432 mg, 2.26 mmol, 3.0 equiv.) and sodium camphor-(10)-sulfinate (4.54 g, 19.07 mmol, 25 equiv.) to afford 370 mg (0.65 mmol, 85 %) of **5b** as a yellow oil which was purified by chromatography over SiO_2 (ethyl acetate / cyclohexane 1:1). **^{1}H-NMR** ($CDCl_3$, 400 MHz): δ = 8.27 (s, 2H, minor (*m*)); 8.18 (s, 2H, major (*M*)); 5.19 (d, 2H, J=14.3 Hz, (*m*)), 4.98 (d, 2H, J=14.2 Hz (*M*)); 4.64 (d, 2H, J=14.3 Hz (m)); 4.63 (d, 2H, J=14.2 Hz, (M); 3.27 (s, 6H, (*M*)); 3.56 (d, 2H, J=14.9 Hz (M)); 3.36 (d, 2H, J=15.4 Hz (m)); 2.90 (d, 2H, J=14.9 Hz (M)); 2.79 (d, 2H, J=15.4 Hz, (m)); 3.15 (s, 6H, (*m*)); 2.43 – 1.43 (m, 10H); 1.04 (s, 6H, (*M*)); 1.03 (s, 6H, (*m*)); 0.90 (s, 6H, (*m*)); 0.89 (s, 6H, (*M*)). **^{13}C-NMR** ($CDCl_3$, 100 MHz) δ = 216.4 (m); 214.3 (M); 163.6; 162.9; 162.4; 70.8 (m); 65.6 (M); 60.3; 59.4 (m); 58.9 (M); 51.4 (M); 50.1 (m); 49.1 (m); 48.5 (M); 42.5; 36.6 (m); 35.9 (M); 32.3 (M); 31.5 (m); 27.0 (M); 26.8 (m); 26.1 (m); 25.5 (M); 19.7; 19.5 (M); 19.3 (m). **MS** (EI, 70 eV): m/z (%): 566 (M^+, 2 %); 534 (100 %); 502 (21 %); 216 (45 %); 151 (53 %). **GC**: 2.95minutes.

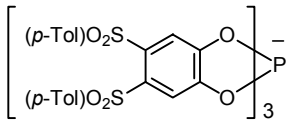


3

4,5-Bis(*p*-toluenesulfonyl)catechol (3): In a 250 mL round bottomed flask, a solution of 4,5-bis(*p*-toluenesulfonyl)veratrol (**5a,** 1.76 g, 3.9 mmol) in dichloromethane (80.0 ml) was stirred under argon for 10 minutes at 20 °C. Boron tribromide (Fluka, 2.40 mL, 39.5 mmol, 5 equiv.) was then slowly added, and the mixture was vigorously stirred, at 45 °C during 16 hrs. The mixture was cooled to 0 °C, and water was carefully added. The organic layer was washed with a diluted solution of HCl (10 %, 2 x 50 mL) and dried (Na_2SO_4). After concentration *in vacuo*, 1.52 g (3.63 mmol, Yield = 93 %) of **3** were obtained. **^{1}H-NMR** ($CDCl_3$, 200 MHz): δ = 7.98 (s, 2 H); 7.76 (d, J = 4 Hz, 4 H); 7.49 (s, 2 H); 7.22 (d, J = 4 Hz, 4 H); 2.35 (s, 6 H). **^{13}C-NMR** ($CDCl_3$, 50 MHz): δ = 147.2; 144.2; 138.7; 131.9; 129.4; 127.7; 120.1; 21.6. **MS** (EI, 70 eV): m/z (%): 418 (M^+, 15 %); 354 (11 %); 264 (53 %); 156 (17 %); 155 (30 %); 108 (37 %); 91 (100 %); 65 (37 %). **MS** (H.R.): calc. 418.05447, found 418.05277 ($C_{20}H_{18}O_6S_2$). **GC**: 9.43 minutes.



6



2

[Bis(dimethylaminophenyl)phenylmethinium][tris(4,5-bis(*p*-toluenesulphonyl) benzenediolato) phosphate] or [6][2]: In a flame-dried 10 mL two-necked round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser (topped with a gas outlet connected to a conc. NaOH trap), a solution of **3** (34.7 mg, 0.08 mmol) in CH_2Cl_2 (1 mL) was stirred for 10 minutes at room temperature under dinitrogen atmosphere. PCl_5 (5.7 mg, 0.03 mmol, 0.3 eq.) was added and the mixture was stirred for 10 minutes at room temperature. The CH_2Cl_2 was then removed under reduced pressure and freshly distilled DMF (1 mL) was added the mixture was stirred for 12 hrs at room temperature. Tri-*n*-butylamine (6.5 µL, 0.03 mmol, 0.3 eq) was added. After 8 hours of additional stirring at 25 °C, the solvent was evaporated under reduced pressure to afford brown oil. Purification was realized by cation exchange with malachite green in CH_2Cl_2 followed by flash chromatography (CH_2Cl_2) to afford the titled compound (27.5, 63%).[1] **^{1}H-NMR** (DMSO-d6, 400 MHz): δ = 8.07 (s, broad, 2H), 8.00 (s, 6H); 7.83 (d, broad, 16H, J=8.3 Hz); 7.75 (d, broad, 4H, J=1.8 Hz); 7.34 (d, broad, 4H, J=9.1 Hz); 7.30 – 7.26 (m, 17H); 6.83 (d, 4H, J=9.1 Hz); 3.21 (s, 12 H); 2.42 (s, 18 H). **^{13}C-NMR** (DMSO-d6, 100 MHz) δ = 155.5; 148.3, 148.2; 148.0; 143.7, 143.4; 139.7; 139.4, 139.2; 132.7, 131.9; 129.2; 129.1; 127.9; 127.7;

[1] Lacour, J.; Barchéchath, S.; Jodry, J. J.; Ginglinger, C. *Tetrahedron Lett.* **1998**, *39*, 567-570.

126.6; 120.2; 114.6; 114.4; 112.3; 77.2; 40.3; 21.5.[2] **^{31}P-NMR** (DMSO-d6, 162 MHz) δ = -76.72, -77.34, -77.53, -78.23. **MS-ES**: m/z (%): (+) 329 (100 %); (-) 1279 (36 %); 1115 (100 %); 141 (39 %); 125 (46 %); 79 (49 %); 63 (55 %).

[2] Only two sets of signals are observed in the ^{13}C spectrum whereas four are visible in ^{31}P NMR.