Total Syntheses of (±)-Preussomerin G and I.

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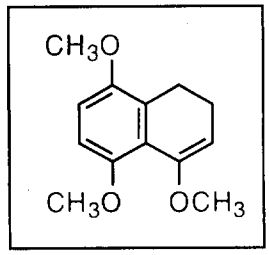
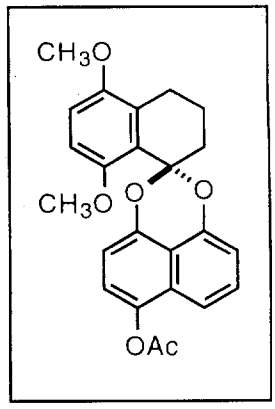
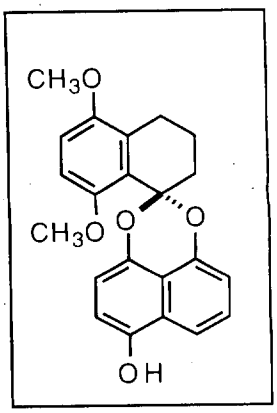
Supporting Information



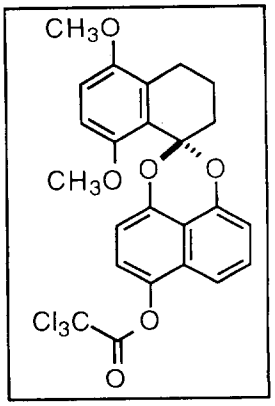
Enol ether (10). To a stirred solution of 5,8-Dimethoxytetralone **9** (1.0 g, 4.8 mmol) in a 4:1 mixture of methanol: trimethyl orthoformate (125 ml total) was added pyridinium *p*-toluene-sulfonate (PPTS) (270 mg, 1.1 mmol). The resulting suspension was purged with N_2 and stirred at room temperature. After 24h, additional trimethyl orthoformate (12 ml) was added and stirring continued for another 15h. Triethylamine (0.22 ml, 1.6 mmol) was added by syringe and the solution was concentrated to a brown residue which was purified by kugelrohr distillation to provide enol ether **10** (1.0 g, 94%) as a white solid. This material was used immediately in the next reaction. m.p. 68-70°; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J*=9 Hz, 1H), 6.76 (d, *J*=9 Hz, 1H), 5.13 (t, *J*=5 Hz, 1H), 3.79 (s, 6H), 3.64 (s, 3H), 2.67 (t, *J*=8 Hz, 2H), 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 150.6, 150.4, 128.8, 122.5, 112.6, 111.0, 97.6, 57.7, 56.0, 55.0, 21.8, 21.3; IR (KBr) 2999, 2953, 2833, 1634, 1582, 1261, 1087 cm^{-1}; Analysis calc'd for C13H16O3: C, 70.89; H, 7.32; found: C, 70.51; H, 7.25.



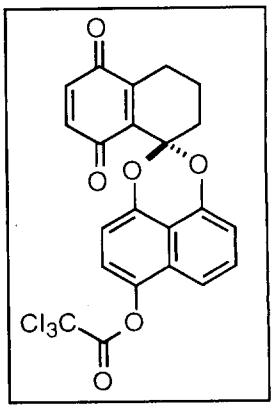
Monoacetal (11). Enol ether **10** (0.20 g, 0.9 mmol), 4-acetoxy-1,8-naphthalenediol (0.22 g, 1 mmol), and *p*-toluenesulfonic acid (20 mg, 0.1 mmol) were added to a flame dried flask. Dry benzene (25 ml) was added by syringe and the flask was fitted with a soxhelet extractor filled with dried 4Å molecular sieves and a reflux condensor. The resulting solution was degassed then heated at reflux for 42h. Upon cooling, the reaction was diluted with ether and washed with saturated aqueous $NaHCO_3$ solution, dried and concentrated to provide a dark brown residue. Flash chromatography (15->25% ethyl acetate/petroleum ether) provided monoacetal **11** (373 mg, 62 %)as a greenish white solid. An analytically pure sample was obtained by recrystallization from methanol. m.p. 210°; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J*=8 Hz, 1H), 7.40 (d, *J*=8.5 Hz, 1H), 7.18 (d, *J*=8 Hz, 1H), 6.95 (d, *J*=7.5 Hz, 1H), 6.55 (s, 2H), 6.87 (d, *J*=8.5 Hz, 1H), 3.83 (s, 3H), 3.73 (s, 3H), 2.78 (t, *J*=5.5 Hz, 2H), 2.46 (s, 3H), 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 153.7, 150.9, 148.4, 145.9, 139.9, 129.9, 128.0, 127.2, 124.5, 119.5, 113.6, 113.4, 111.9, 111.5, 109.6, 108.2, 101.4, 57.2, 55.9, 32.8, 24.1, 20.9, 18.9; IR (KBr) 2942, 2361, 2341, 1749, 1607, 1371, 1044 cm^{-1}; Analysis calc'd for C24H22O6: C, 70.93; H, 5.46; found: C, 71.39; H, 5.61.



Alcohol (12). Monoacetal **11** (600 mg, 1.48 mmol) was dissolved with methanol (40 ml) and the resulting solution was purged with N_2 for 1h. To this solution was added sodium methoxide (4M in methanol) by syringe and the reaction was stirred for 1.5h or until al the starting material was consumed. The solution turns a dark purple color. The reaction was quenched with 1N HCl solution and extracted with ethyl acetate. The organic layer was dried and concetrated to provide crude product as an off white solid. Flash chromatography (25% ethyl acetate/petroleum ether) provided the alcohol **12** (525 mg, 98%) as a white solid. m.p. 219-220°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J*=8.5 Hz, 1H), 7.43 (t, *J*=8.28, 7.59 Hz, 1H), 6.94 (d, *J*=7.49 Hz, 1H), 6.88 (s, 2H), 6.77 (d, *J*=8.1 Hz, 1H), 6.73 (d, *J*=8.0 Hz, 1H), 5.05 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 2.76 (m, 2H), 2.12 (m, 2H), 1.84 (t, *J*=5.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 151.0, 148.3, 145.3, 141.7, 129.8, 126.7, 125.0, 124.7, 113.9, 113.6, 112.3, 111.5, 109.9, 109.7, 108.4, 101.0, 57.4, 55.9, 32.7, 24.2, 19.0; IR (KBr) 3435, 2946, 2832, 1606, 1070, 965 cm^{-1}; Analysis calc'd for C22H20O5: C, 72.51; H, 5.53; found: C, 72.19; H, 5.51.

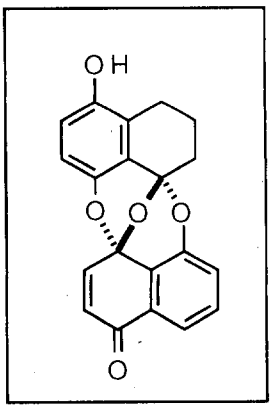


Trichloroacetate ester (13). To a solution of alcohol **12** (146 mg, 0.4 mmol) in CH_2Cl_2 (5 ml) was added trichloroacetic anhydride (88 µl, 0.5 mmol) and triethylamine (67 µl, 0.5 mmol). The reaction was stirred at room temperature and monitored by TLC. The reaction was diluted with CH_2Cl_2 and washed with saturated NH_4Cl solution then dried, and concentrated. Flash chromatography (20% ethyl acetate/petroleum ether) provided the trichloroacetate ester **13** (189 mg, 93%) as a yellow solid. m.p. 171-2°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.33 (d, *J*=8.3 Hz, 1H), 6.98 (dd, *J*=6.6, 1.8 Hz, 1H), 6.89 (d, *J*=8.1 Hz, 1H), 6.89 (s, 2H), 3.83 (s, 3H), 3.72 (s, 3H), 2.78 (t, *J*=6.2 Hz, 2H), 2.16 (m, 2H), 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 153.7, 150.9, 148.4, 139.6, 129.9, 128.8, 126.6, 124.3, 118.7, 113.4, 113.1, 111.9, 111.6, 110.1, 107.9, 101.6, 89.9, 57.2, 55.9, 32.9, 24.1, 18.9; IR (KBr) 2954, 2929, 1779, 1605, 1421, 1080, 1043 cm^{-1}; Analysis calc'd for C24H19Cl3O6: C, 56.55; H, 3.76; found: C, 56.96; H, 3.98.

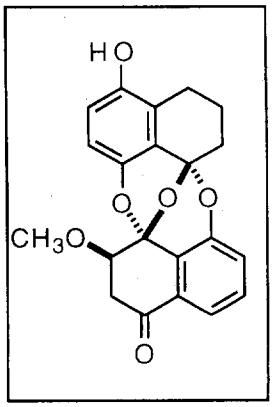


Quinone (14). Trichloroacetate ester **13** (583 mg, 1.1 mmol) was dissolved in acetonitrile (40 ml) with heating then cooled to room temperature. H_2O (13 ml) was then added to the reaction mixture which caused the starting material to precipate out. Further addition of CH_2Cl_2 (as needed) and reheating of the solution resolubilized **13**. This solution was again allow to cool slowly to room temperature then cooled further to 0°C with an ice bath (w/o precipitation of **13**). To this cooled solution was added ceric ammonium nitrate (1.38 g, 2.5 mmol) portionwise over 1.5h. The reaction was diluted with CH_2Cl_2 and washed with H_2O, dried, and concentrated to a red residue. Flash chromatography (15% ethyl acetate/petroleum ether) provided quinone **14** (477 mg, 87%) as a orange/red solid. m.p. 183-5°; ^{1}H

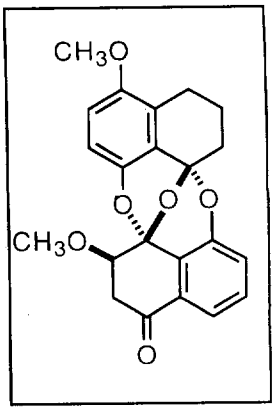
NMR (400 MHz, $CDCl_3$) δ 7.52 (m, 2H), 7.34 (d, *J*=8.3 Hz, 1H), 6.96 (d, *J*=7.4 Hz, 1H), 6.88 (d, *J*=8.2 Hz, 1H), 6.82 (dd, *J*=9.8, 0.7 Hz, 1H), 6.77 (dd, *J*=10.2, 0.7 Hz, 1H), 2.61 (t, *J*=6.0 Hz, 2H.), 2.08 (m, 2H), 1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.2, 183.3, 160.1, 147.2, 147.0, 145.5, 140.1, 137.9, 135.6, 135.1, 128.8, 126.6, 118.8, 113.9, 113.3, 110.4, 108.4, 99.4, 31.8, 29.7, 23.4, 17.5; IR (KBr) 1782, 1661, 1609, 1420, 1380, 1275, 1211 cm^{-1}; Analysis calc'd for C22H13Cl3O6: C, 55.08; H, 2.73; found: C, 55.22; H, 2.75.



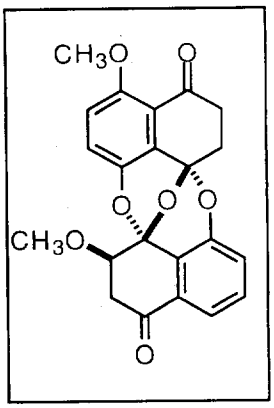
Bisacetal (15). Quinone **14** (455 mg, 1.0 mmol) was dissolved with THF (30 ml) and the resulting solution was purged with N_2 for 1h. Lithium hydroxide monohydrate (43 mg, 1.0 mmol) in H_2O (8 ml) was added by syringe. During this time the reaction solution turned from orange to purple. The reaction was complete immediately after the addition of lithium hydroxide. The reaction solution was quenched with aqueous 10% HCl solution and extracted with ethyl ether, dried and concentrated to provide bisacetal **15** (309 mg, 97%)as a yellow solid. m.p. dec >200°; ^1H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, *J*=7.5, 1 Hz, 1H), 7.34 (t, *J*=8.0, 1.0 Hz, 1H), 7.15 (d, *J*=10.0 Hz, 1H), 7.01 (dd, *J*=8.0, 1.0 Hz, 1H), 6.68 (d, *J*=8.5 Hz, 1H), 6.53 (d, *J*=8.5 Hz, 1H), 6.52 (d, *J*=10.0 Hz, 1H), 4.65 (s, 1H), 2.89 (m, 1H), 2.71 (m, 1H), 2.52 (m, 1H), 2.43 (m, 1H), 2.14 (m, 1H), 2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 149.9, 147.5, 143.2, 142.2, 132.8, 130.4, 130.6, 122.6, 121.3, 120.7, 119.6, 118.7, 116.7, 113.7, 95.5, 89.0, 31.9, 21.4, 16.7; IR (KBr) 3428, 2968, 1668, 1591, 1287 cm^{-1}; Analysis calc'd for C20H14O5: C, 71.85; H, 4.22; found: C, 71.64; H, 4.37.



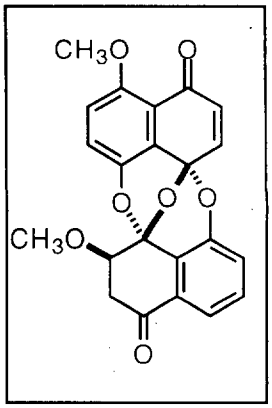
β-Methoxy adduct. Bisacetal **15** (82 mg, 0.25 mmol) was dissolved in methanol (3 ml) and the resultiing solution was purged with N_2 for 1h. To the purged solution was added 95% lithium methoxide (29 mg, 0.76 mmol) and the reaction mixture was stirred for 1h then quenched with saturated NH_4Cl solution, dried and concentrated to provide the methoxide adduct (103 mg, 100%) as a white solid. m.p. 229-30°; 1H NMR (400 MHz, CDCl3) d 7.58 (dd, *J*=7.6, 0.8 Hz, 1H), 7366 (t, *J*=8.0 Hz, 1H), 7.05 (dd, *J*=8.0, 0.8 Hz, 1H), 6.67 (d, *J*=8.4 Hz, 1H), 6.52 (d, *J*=8.4 Hz, 1H), 4.48 (s, 1H), 3.50 (s, 3H), 3.40 (dd, *J*=18.0, 3.2 Hz, 1H), 3.05 (dd, *J*=18.0, 2.7 Hz, 1H), 2.88 (m, 1H), 2.74 (m, 1H), 2.52 (m, 1H), 2.15 (m, 1H), 1.98 (m, 1H); 13C NMR (125 MHz, CDCl3) d 195.0, 151.1, 147.8, 142.7, 130.5, 130.4, 123.3, 121.8, 120.7, 119.5, 119.1, 116.7, 113.3, 95.0, 93.7, 79.6, 59.1, 40.4, 31.7, 21.1, 16.4; IR (KBr) 3414, 1671, 1464, 1291 cm-1; Analysis calc'd for C21H18O6: C, 68.85; H, 4.95; found: C, 68.57; H, 4.86.



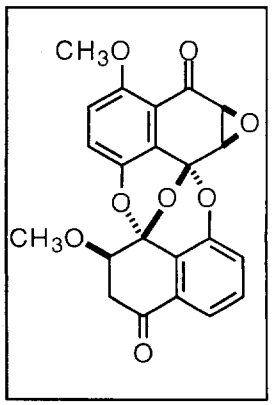
Ether (17). To a solution of methoxide adduct (77 mg, 0.21 mmol) in methanol (8 ml) was added excess diazomethane (as a solution in ethyl ether). The resulting solution was stirred at room temperature for 15h. The reaction mixture was then concentrated to provide a yellow residue which was purified by flash chromatography (20% ethyl acetate/petroleum ether) to provide the product **17** (67 mg, 84%) as a white solid. m.p. 151-52°; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, *J*=7.8, 0.8 Hz, 1H), 7.31 (t, *J*=8.0 Hz, 1H), 7.03 (dd, *J*=8.4, 0.8 Hz, 1H), 6.72 (d, *J*=8.9 Hz, 1H), 7.59 (d, *J*=9.2 Hz, 1H), 4.22 (t, *J*=2.9 Hz, 1H), 3.75 (s, 3H), 3.50 (s, 3H), 3.41 (dd, *J*=17.6, 2.8 Hz, 1H), 3.05 (dd, *J*=18.0, 2.7 Hz, 1H), 3.87 (m, 1H), 2.74 (m, 1H), 2.49 (m, 2H), 2.10 (m, 1H), 2.00 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.4, 151.6, 151.1, 142.5, 130.6, 130.3, 125.7, 121.6, 120.7, 119.4, 119.3, 112.8, 111.8, 95.0, 93.8, 79.7, 59.1, 55.6, 40.5, 31.8, 21.2, 16.5; IR (KBr) 2956, 1684, 1597, 1484, 1292 cm^{-1}; Analysis calc'd for C22H20O6: C, 69.47; H, 5.30; found: C, 69.2; H, 5.37.



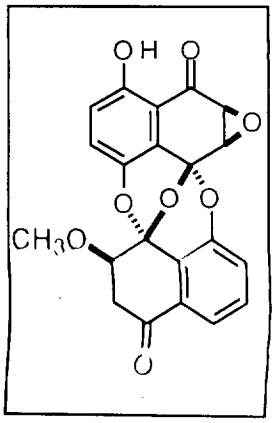
Ketone (18). To a solution of **17** (61.7 mg, 0.16 mmol) in CCl_4 (2 ml) heated at reflux, was added portionwise*N*-bromosuccinimide (32 mg, 0.18 mmol) and AIBN (10 mg, 0.06 mmol) over 1h. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O, dried and concentrated to provide the crude bromide. The crude bromide was dissolved in a 1:1 mixture of THF:H_2O (8 ml) and stirred at room temperature for 30 minutes. The reaction mixture was partitioned between ethyl ether/water and organic layer was dried, and concentrated to yield the crude alcohol. The crude alcohol was dissolved in CH_2Cl_2 (5 ml) and to this solution was added Dess-Martin periodinane (76 mg, 0.18 mmol). After 1.5h, the reaction mixture was diluted with CH_2Cl_2 and the organic layer washed with 10% NaOH solution, dried, and concentrated to provide an off white residue. Flash chromatography of the crude oxidation product (20->40% ethyl acetate/petroleum ether) provided the ketone **18** (36 mg, 56%) as a white solid. m.p. 198-200°; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J*=7.5, 1.0 Hz, 1H), 7.36 (t, *J*=8.0 Hz, 1H), 7.04 (dd, *J*=8.0, 1.0 Hz, 1H), 7.03 (d, *J*=9.5 Hz, 1H), 6.99 (d, *J*=9.0 Hz, 1H), 4.27 (t, *J*=3.0 Hz, 1H), 3.83 (s, 3H), 3.50 (s, 3H), 3.39 (dd, *J*=18.0, 2.5 Hz, 1H), 3.22 (ddd, *J*=19.0, 13.0, 6.5 Hz, 1H), 3.07 (dd, *J*=18.0, 2.5 Hz, 1H), 2.85 (ddd, *J*=19.0, 6.5, 1.0 Hz, 1H), 2.76 (ddd, *J*=13.5, 6.5, 1.0 Hz, 1H), 2.46 (dt, *J*=13.0, 6.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.5, 193.9, 154.5, 150.9, 141.8, 130.9 (2 carbons), 123.6, 122.8, 121.7, 120.2, 119.9, 118.7, 115.3, 94.2, 93.6, 79.2, 59.2, 56.5, 40.4, 34.1, 31.9; IR (KBr) 2999, 2363, 1687, 1684, 1558, 1286 cm^{-1}.



Enone (19). To a solution of diketone **18** (0.22 mg, 0.056 mmol) in CH_2Cl_2 (2 ml) cooled to -12°C, was added triethylamine (12 µl, 0.066 mmol) and trimethylsilyl trifluoromethanesulfonate (9 µl, 0.065 mmol). The reaction mixture was stirred at -12°C for 45 minutes then concentrated to provide the crude silyl enol ether. In a separate flask, $Pd(OAc)_2$ was dissolved with CH_3CN (4 ml). To this solution was added the crude silyl enol ether (dissolved in 4 ml CH_3CN) via cannula. The resulting reaction mixture was stirred at room temperature overnight. The reaction was then filtered and concentrated to provide the crude product **19** as a brown residue. Flash chromatography (20->40% ethyl acetate/petroleum ether) of the crude product provided enone **19** (14.2 mg, 65%) as a yellow solid. m.p. 210°; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (dd, *J*=7.5, 1.0 Hz, 1H), 7.38 (t, *J*=8.0 Hz, 1H), 7.13 (d, *J*=10.0 Hz, 1H), 7.06 (8.0, *J*=1.0 Hz, 1H), 7.03 (d, *J*=9.0 Hz, 1H), 6.99 (d, *J*=9.5 Hz, 1H), 6.54 (d, *J*=10.0 Hz, 1H), 4.29 (t, *J*=2.5 Hz, 1H), 3.90 (s, 3H), 3.53 (s, 3H), 3.39 (dd, *J*=18.5, 3.0 Hz, 1H), 3.10 (dd, *J*=18.0, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 183.0, 154.4, 150.8, 142.3, 138.4, 135.1, 130.9, 130.5, 122.6, 121.9, 121.8, 120.1, 119.3, 117.6, 115.6, 94.5, 90.1, 79.4, 59.3, 56.7, 40.4; IR (KBr) 1697, 1674, 1652, 1485, 1289 cm^{-1}.



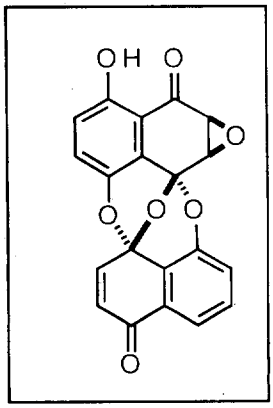
Expoxide (20). To a solution of enone **19** (12.4 mg, 0.031 mmol) in methanol (2.4 ml), cooled to 0°C, was added $NaHCO_3$ (27 mg, 0.32 mmol) and 30% aq. H_2O_2 (32 µl, 0.32 mmol). The reaction was stirred at 0°C for 5h then quenched with 1N HCl solution and extracted with ethyl ether. The organic layer was dried and concentrated to provide the crude product. Flash chromatography of the crude product (30% ethyl acetate/petroleum ether) provided expoxide **20** (10 mg, 80%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J*=8.0, 1.0 Hz, 1H), 7.38 (dd, *J*=8.0, 7.5 Hz, 1H), 7.04 (d, *J*=9.0 Hz, 1H), 7.04 (dd, *J*=7.5, 1 Hz, 1H), 6.99 (d, *J*=9.0 Hz, 1H), 4.34 (t, *J*=3.0 Hz, 1H), 4.26 (d, *J*=4.5 Hz, 1H), 3.89 (d, *J*=4.4 Hz, 1H), 3.85 (s, 3H), 3.54 (s, 3H), 3.38 (dd, *J*=18.0, 3 Hz, 1H), 3.10 (18.0, *J*=2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.5, 190.8, 153.5, 150.0, 143.1, 131.1, 130.8, 122.9, 121.7, 120.7, 119.8, 118.6, 115.9, 115.9, 94.5, 94.0, 79.2, 59.3, 56.6, 53.3, 53.0, 40.4.



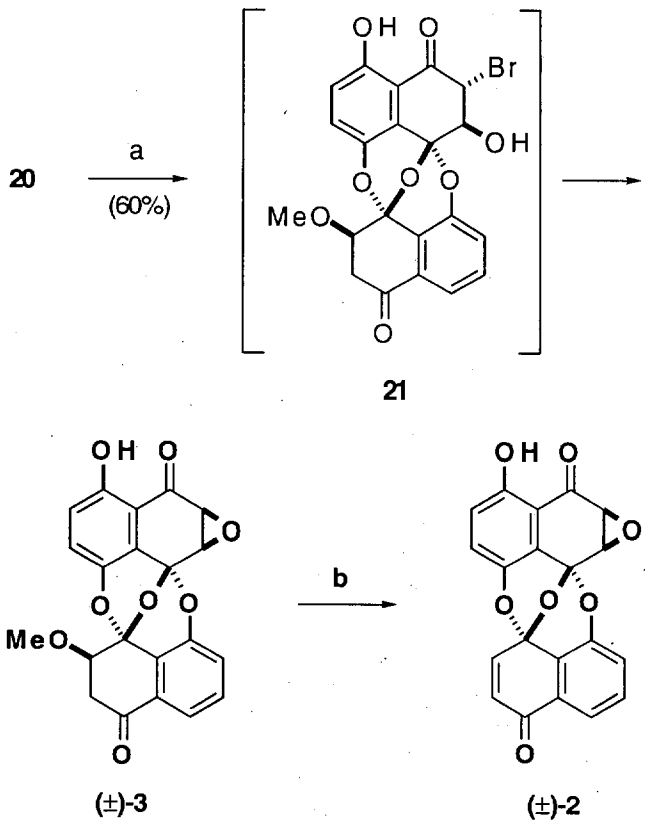
(±)-Preussomerin I (3). To a solution of epoxide **20** (8.7 mg, 0.021 mmol) in CH_2Cl_2 (1 ml), cooled to -78°C, was added excess solution of 2M BBr_3 in CH_2Cl_2. The resulting solution was stirred for 10 minutes then quenched with water and extracted with CH_2Cl_2. The organic layer was dried, and concentrated to provide the crude bromide **21**. The crude product was dissolved in methanol (2 ml). To this solution was added 95% lithium methoxide (2.6 mg, 0.064 mmol) and the resulting mixture was stirred for 10 minutes. The reaction solution was partition between ethyl acetate and 1N HCl solution. The organic layer was dried and concentrated. Flash chromatography (10% ethyl acetate/petroleum ether)

provided preussomerin I (**3**) (5 mg, 60%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1H), 7.66 (dd, *J*=8.0, 1.0 Hz, 1H), 7.40 (dt, *J*=8.5, 1.0 Hz, 1H), 7.07 (dd, *J*=8.5, 1.0 Hz, 1H), 7.04 (d, *J*=9.0 Hz, 1H), 6.96 (dd, *J*=9.9, 0.8 Hz, 1H), 4.35 (t, *J*=2.0 Hz, 1H), 4.30 (dd, *J*=4.0, 1.0 Hz, 1H), 3.85 (dd, *J*=4.0, 0.8 Hz, 1H), 3.55 (s, 3H), 3.37 (dd, *J*=18.2, 2.4 Hz, 1H), 3.10 (dd, *J*=18.2, 2.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.6, 193.4, 156.0, 149.6, 142.8, 131.1, 130.8, 126.4, 121.5, 121.3, 120.7, 119.8, 115.7, 110.7, 94.8, 93.5, 79.8, 59.3, 53.6, 52.1, 40.3.

(±)-Preussomerin G (2). To a solution of **3** (4.5 mg, 0.011 mmol) in CH_2Cl_2 (2 ml) was added trimethylsilyl trifluoromethanesufonate (31 µl, 0.17 mmol) and triethylamine (24 µl, 0.17 mmol). The resulting solution was stirred for 15 minutes then partitioned between CH_2Cl_2 and water. The organic layer was dried and concentrated to a yellow residue. Flash chromatography (5% ethyl acetate/petroleum ether) provided preussomerin G (**2**) (3.1 mg, 80%) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.63 (d, *J*=7.5 Hz, 1H), 7.40 (t, *J*=8.0 Hz, 1H), 7.24 (d, *J*=10.5 Hz, 1H), 7.04 (m, 2H), 6.96 (d, *J*=9.0 Hz, 1H), 6.60 (10.0, 1H), 4.24 (4.0, 1H), 3.85 (4.0, 1H).



Scheme 5



a. i. BBr_3, CH_2Cl_2, -78°C. ii. $LiOCH_3$, CH_3OH. b. TMSOTf 2 eq., TEA 2eq., CH_2Cl_2, rt.

In summary we have presented the first syntheses of members of the bis-spiroacetal family of fungal metabolites, (±)-preussomerin G (**2**), and (±)-preussomerin I (**3**). With the discovery of the rearrangement of quinone monoacetal **15** to bis-acetal **14a**, we believe we may have found the transformation that leads to this unique bis-acetal ring system in Nature. Future efforts in our laboratory will be directed at the development of an asymmetric approach to the preussomerins.

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Supporting Information: Experimental procedures and full characterization for all compounds reported (6 pages).

References:

1. a. Singh, S. B.; Zink, D. L.; Liesch, J. M.; Ball, R. G.; Goetz, M. A.; Bolessa, E. A.; Giacobbe, R. A.; Silverman, K. C.; Bills, G. F.; Pelaez, F.; Cascales, C.; Gibbs, J. B.; Lingham, R. B. *J.*