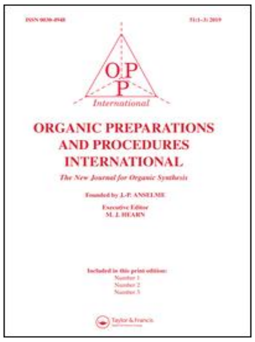

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OPPI BRIEF

Preparation of bis-Benzyne Precursor 2,5-bis(Trimethylsilyl)-1,4-Phenylene bis(Trifluoromethanesulfonate)

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Benzyne precursors are rapidly becoming well-used building-blocks for organic materials.[1] Our synthesis of conjugated oligoacene precursors by benzyne Diels-Alder reactions created a need for a reliable preparation of a bis-benzyne precursor (BBPC) able to form sequential benzyne intermediates. Kobayashi's technique was avoided as it requires organolithium reagents and low temperatures, which we found undesirable for a large-scale synthesis.[2–5] Alternatively, BBPC **6** was identified as a suitable precursor. The literature lacked a detailed and efficient synthesis that was suitable for large scale, so we optimized our own.[6,7]

Optimization of a route to prepare BBPC **6** (*Scheme 1*) was readily developed drawing on several literature sources.[7–9] In developing the route, key goals included eliminating the need for chromatographic purification and utilizing reactions that can easily be used on scale. Herein we report a detailed five-step synthetic route to bis-benzyne precursor 2,5-bis(trimethylsilyl)-1,4-phenylenebis(trifluoromethanesulfonate) **6** from commercially available hydroquinone **1** in 21% over-all yield. Our work describes a chromatography-free synthesis of **6** that should be suited for preparative, laboratory-scale, synthesis.

Experimental Section

All reagents and solvents were of reagent grade and used without further purification unless otherwise specified. All reactions were carried out using flame-dried glassware under a nitrogen atmosphere unless aqueous solutions were employed as reagents. Toluene, acetonitrile, pyridine, and trimethylsilylchloride (TMSCl) were dried by distillation from CaH_2 under nitrogen. All other chemicals were used as received unless otherwise noted. Analytical thin layer chromatography (TLC) was carried out using 0.25 mm silica plates from Silicycle. Eluted plates were visualized with UV light. ^{1}H

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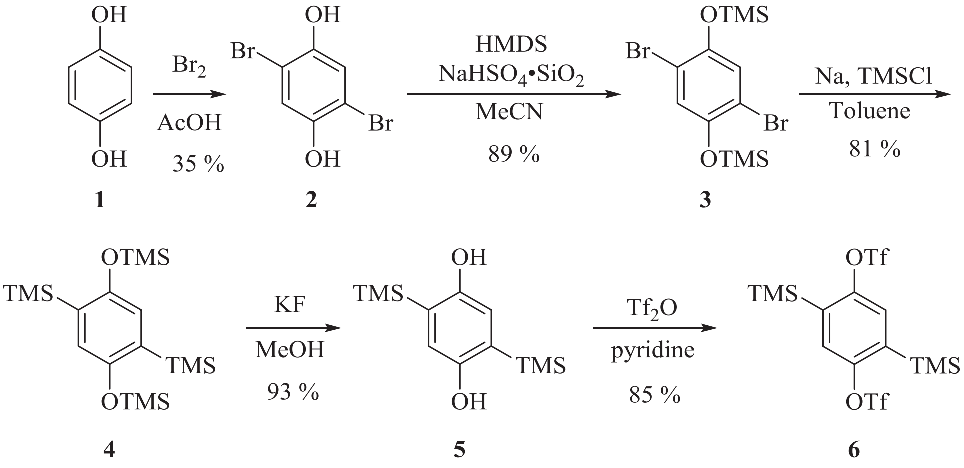

Scheme 1

NMR (500 MHz), ^{13}C NMR (126 MHz), and ^{19}F NMR (471 MHz) spectra were obtained on Varian FT NMR or Bruker FT NMR instruments. NMR spectra were reported as δ values in ppm relative to TMS for ^{1}H (0.00 ppm) and dimethyl sulfoxide (2.50 ppm), and chloroform for ^{13}C (77.16 ppm), and dimethyl sulfoxide (39.52 ppm). Melting points were obtained on a Mel-Temp apparatus (Cambridge, MA) and are uncorrected. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

2,5-Dibromohydroquinone (2)

In a 3-neck 250 mL round bottom flask equipped with an internal temperature probe, a 25-mL pressure-equilibrating addition funnel topped with a gas inlet adapter, and a gas outlet line submerged in a solution of 1M sodium thiosulfate (~50 mL), hydroquinone (5.50 g, 50.0 mmol, 1.00 eq.) was suspended in acetic acid (50 mL) at room temperature. The internal temperature was monitored to ensure that the temperature did not exceed 35 °C over the course of the reaction. The addition funnel was charged with a solution of bromine ***(Safety Note: Along with standard good practice (eye protection, fume hood, laboratory coat) the use of bromine requires impervious gloves and training for the operator.)*** (5.2 mL, 100 mmol, 2.00 eq.) in acetic acid (5 mL), while positive nitrogen pressure was applied, at 2–3 bubbles per second in the sodium thiosulfate solution. The bromine solution was added dropwise (1 drop/sec). Note: due to viscosity of the bromine solution, it was necessary to vary the N_2 pressure in order to deliver the full volume over 30 minutes. Additional acetic acid (~ 2 mL) was used to rinse the remaining bromine into the funnel. Upon addition of approximately one-third the volume of the bromine solution, the hydroquinone fully dissolved. Two hours after the complete addition of bromine, an off-white precipitate formed. The reaction mixture was stirred overnight. The precipitate was collected *via* vacuum filtration, washed with acetic acid (5 mL) and DI water (50 mL) until colorless providing **2** (4.67 g, 35%, 17.5 mmol, 98% pure by ^{1}H NMR) as a colorless solid. Additional product precipitated by allowing the filtrate to stand overnight at room temperature. However, this second crop of precipitate contained a mixture of 2,5-dibromohydroquinone **2** and 2,3-dibromohydroquinone. The ratio of these products varied batch-to-batch, from ~6:1 to ~3:1, favoring **2**. The 2,3-dibromo-regioisomer was significantly more soluble in acetic acid at room temperature, but co-precipitated with the desired regioisomer at lower temperatures. Purification by flash-chromatography proved challenging due to lack of solubility for both products; however, purity is imperative as the undesired regioisomer will generate persistent contaminants throughout subsequent reactions. A second crop of **2** could be achieved by recrystallizing the regioisomeric mixtures obtained from the filtrate in hot methanol, adding water as an anti-solvent until the mixture was turbid, yielding colorless crystals. This method was only successful, however, if the starting mixture significantly favored **2** (~6:1). mp 187–190 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (s, 2H), 7.04 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 147.7, 119.9, 108.7. IR (KBr) 3277, 2921, 1617, 1424, 1196, 1060, 852 cm^{-1}.

Anal. Calcd for $C_6H_4Br_2O_2$: C, 26.90; H, 1.51. Found: C, 26.91; H, 1.40.

((2,5-Dibromo-1,4-phenylene)bis(oxy))bis(trimethylsilane) (3)

To a flame-dried 25-mL flask under inert atmosphere, 2,5-dibromohydroquinone (**2**) (4.0 g, 15 mmol, 1.00 eq.) and $NaHSO_4 \cdot SiO_2$ (80 mg; freshly prepared catalyst provides best yields[10]) were added. The flask was evacuated and back-filled with nitrogen 3 times, then charged with dry acetonitrile (7.5 mL). While stirring at room temperature, hexamethyldisilazane (HMDS) (3.5 mL, 16.8 mmol, 1.12 eq.) was added dropwise over the course of 5 minutes. The reaction was stirred for an additional 5 minutes, then diluted with dichloromethane (7.5 mL) and filtered. Concentrating the filtrate yielded crude material as a light-yellow oil, which crystalized spontaneously. The product was purified *via* recrystallization in hexanes yielding **3** (5.49 g, 89%, 13.4 mmol) of colorless crystals. mp 63–66 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (s, 2H), 0.29 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4, 124.3, 114.1, 0.4. IR (film) 2959, 2898, 1055, 1476, 1254, 1210, 841 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}Br_2O_2Si_2$: C, 34.96; H, 4.89. Found: C, 34.97; H, 4.78.

(2,5-bis((Trimethylsilyl)oxy)-1,4-phenylene)bis(trimethylsilane) (4)

An oven-dried 3-neck 250 mL flask was equipped with a large-stir bar, glass-stoppered side arm, a septa-sealed side arm, and a reflux condenser. The round bottom flask was then charged with 10 mL of freshly distilled toluene, followed by freshly cut elemental sodium (1 g, 43.5 mmol, 4.00 eq., in several small blocks). The mixture was heated to reflux at 130 °C without stirring initially, which was a key step in the process to break the sodium into sodium sand. The sodium blocks sat in refluxing toluene until the edges and corners softened to rounded ends, then the mixture was stirred with a large stir-bar at a high rate (500–700 rpm), achieving fine particulates of molten sodium. A high yield was dependent on consistently stirring the molten sodium such that sodium droplets did not agglomerate. While stirring, distilled trimethylsilyl chloride (1.6 mL, 13.1 mmol, 1.20 eq.) was added dropwise (1 drop/2 s), followed by a dropwise addition (1 drop/2 s) of a solution of trimethylsilyl chloride (1.6 mL, 13.1 mmol, 1.20 eq.) and silyl ether (**3**) (4.50 g, 10.9 mmol, 1.00 eq.) in toluene (8 mL). After silyl ether addition, the solution turned blue. The reaction was refluxed for 1.5 hours then allowed to cool to room temperature, then filtered under an inert atmosphere *via* a Schlenk filter. The sodium salts were washed with fresh toluene (10 mL), followed by hexanes (10 mL). Combined filtrate and washes were concentrated to a crude yellow crystalline product. Crude product **3** was purified by dissolving in minimal CH_2Cl_2 in a suitable round bottom flask, then sheeting with hexanes to form two layers. The flask was capped with a septum and vacuum (~40 torr) was applied *via* a 20 gauge needle, slowly evaporating the CH_2Cl_2 layer. This method formed large, block crystals, which were rinsed with cold hexanes (pre-cooled in a –78 °C bath). We note at this point that small amounts of by-products persisting from formation of dibromohydroquinone **2** were removed during this recrystallization. The filtrate was concentrated and the above crystallization repeated to grow second and third crops of crystals, which were combined to yield **4** (3.52 g, 81%, 8.8 mmol) as colorless crystals, mp 123–126 °C. $R_f = 0.47$ (100% hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (s, 2H), 0.29 (s, 18H), 0.24 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 131.7, 122.6, 0.8, –0.9. IR (film) 2955, 1450, 1339, 1254, 1205, 1106, 935, 837, 746 cm^{-1}.

Anal. Calcd for $C_{18}H_{38}O_2Si_4$: C, 54.21; H, 9.60. Found: C, 53.94; H, 9.60.

2,5-bis(Trimethylsilyl)benzene-1,4-diol (5)

In a 100-mL oven-dried Schlenk tube, silyl ether **4** (2.36 g, 5.91 mmol, 1.00 eq.) and KF (0.72 g, 12.41 mmol, 2.10 eq.) were quickly added, then the flask was evacuated and back-filled with nitrogen 5 times. Deoxygenated methanol (65 mL, degassed by bubbling N_2 for 30 minutes) was charged to the flask and the solution was stirred at 25 °C for 1.25 h. The reaction mixture was poured into ice-cold water (225 mL) and extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were washed with brine (80 mL), dried over Na_2SO_4, filtered and concentrated to yield **5** (1.39 g, 93%, 5.48 mmol) as a tan solid, mp 178–183 °C. $R_f = 0.16$ (100% hexanes). ^1H NMR (500 MHz, $CDCl_3$) δ 6.67 (s, 2H), 4.46 (s, 2H), 0.29 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 128.1, 120.8, –0.9. IR (film) 3426, 2957, 1507, 1365, 1244, 1166, 1103, 836, 745 cm^{-1}. Elemental analysis was not attempted due to the instability of **5**. Compound **5** decomposes under ambient atmosphere and should be stored under an inert atmosphere at low temperatures (–20 °C). We recommend **5** be taken forward as soon as possible.

2,5-bis(Trimethylsilyl)-1,4-phenylene bis(trifluoromethanesulfonate) (6)

In an oven-dried 100-mL Schlenk tube, hydroquinone **5** (1.27 g, 4.97 mmol, 1.00 eq.) was dissolved in distilled pyridine (33 mL). The solution was then cooled to 0 °C, and while stirring triflic anhydride (2.1 mL, 12.40 mmol, 2.50 eq.) was added dropwise (1 drop/s). Following complete addition, the solution was allowed to warm to room temperature, then warmed to 50 °C and maintained for 2 hours. The reaction mixture was allowed to cool to room temperature and concentrated to yield a dark, viscous, oil. The crude product was triturated with hexanes (5 mL × 4) at 50 °C, collecting and combining the hexanes fractions, which were concentrated to yield **6** (2.2 g, 85%, 4.22 mmol) as a colorless solid, mp 107–108 °C. If necessary, **6** can be purified by recrystallization from hexanes. $R_f = 0.69$ (90% hexanes:10% EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (s, 2H), 0.38 (s, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.1, 137.4, 127.1 (q,

$J = 1.8$ Hz), 118.5 (q, $J = 320$ Hz), −1.3. ^{19}F NMR (471 MHz, $CDCl_3$) δ −76.90. IR (film) 2961, 2904, 1421, 1339, 1218, 1141, 1080, 909, 844, 734 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}F_6O_6S_2Si_2$: C, 32.43; H, 3.89. Found: C, 32.49; H, 3.96.

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