Supporting Information

Synthesis of Aromatic Bisabolane Natural Products via Palladium-Catalyzed Cross Couplings of Organozinc Reagents

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All reactions involving air- or moisture-sensitive compounds were conducted in oven- or flame-dried glassware under an atmosphere of dry argon using standard syringe/septa techniques. Ether and THF were distilled from sodium benzophenone ketyl immediately before use. The term “concentrated” refers to solvent removal on a rotary evaporator. Flash chromatography¹ was performed on hand packed columns of silica gel (230-400 mesh). Radial chromatography was performed under nitrogen using commercial silica rotors. Medium pressure liquid chromatography (MPLC) was performed with hand packed columns of silica gel (230-400 mesh) at 50-100 psi using combination RI/UV detection. 4-Bromo-2,5-dimethoxytoluene (**19a**),² alkenyl triflate **16**,³ and **26**⁴ were prepared according to literature procedures. Phenylzinc iodide, 4-methylphenylzinc iodide and 2-methoxyphenylzinc iodide were purchased from Aldrich.

2-(1,5-Dimethyl-4-hexenyl)-5-methylphenol [(±)-curcuphenol] (3).⁵ A solution of **35** (88 mg, 0.34 mmol) in methanol (4 mL) was added to a solution of TsOH · H₂O (8 mg) in methanol and the mixture was refluxed overnight. Solid NaHCO₃ was added and the solvent was removed by rotary evaporation. The residue was partitioned between ether and water. The layers were separated and the aqueous layer was extracted again with ether. The combined organic phases were washed with water and brine, dried over Na₂SO₄, and concentrated. Flash chromatography of the residue (6:1 hexanes/ethyl acetate) gave **3** (67 mg, 92%) as an oil whose spectra matched those previously reported.⁵

Curcuhydroquinone (8).^{5,6} Tetrahydrofuran (5 mL) and 10% HCl (5 mL) were mixed and enough isopropyl alcohol was added to create a homogenous solution. Dimethoxymethyl ether **20b** (0.10 g, 0.31 mmol) was added as a solution in THF (1 mL). The solution was stirred overnight. TLC analysis at that time indicated consumption of the starting material. The mixture

was poured into water and extracted repeatedly with ether. The combined organic layers were dried (Na_2SO_4) and concentrated to a viscous brown oil that was purified by radial chromatography (9:1 hexanes/ethyl acetate + 0.5 % ethanol) to yield **8** as an air sensitive pale yellow oil (0.065 g, 89%) whose spectra matched that previously reported.^{5,6}

Curcuquinone (9).^{5,6} Ceric ammonium nitrate (1.69 g, 3.09 mmol) was added to a solution of **20b** (0.322 g, 1.03 mmol) in H_2O (25 mL) and CH_3CN (25 mL). After 2h the mixture was diluted with H_2O and extracted repeatedly with CHCl_3 . The combined organic layers were washed (brine), dried (Na_2SO_4), and concentrated. Purification of the residue by radial chromatography (12 :1 hexanes/ethyl acetate) afforded **9** as a yellow oil (0.234 g, 98 %) whose spectral data matched that previously reported.^{5,6} Using the same procedure, dimethoxy ether **20a** was converted to **9** in 83% yield.

6-bromo-2-methylhept-2-ene (18a).⁷ A solution of 6-methyl-5-hepten-2-ol (25.0 g, 0.197 mol) and PPh_3 (57.4 g, 0.219 mol) in CH_2Cl_2 (250 mL) was cooled to 0 °C and placed in the dark. NBS (39.4 g, 0.221 mol) was added in ~ 2 g portions every 20 min. The mixture was stirred for 1 h after NBS addition was complete at which time TLC analysis (9:1 hexanes/ethyl acetate) showed the reaction was complete. The mixture was poured into cold pentane (900 mL) and filtered through a pad of silica gel. The filtrate was concentrated and purified by flash chromatography (hexanes) to give **18a** (26.8 g, 71%) as a colorless liquid. ^1H NMR (CDCl_3 , 300 MHz): δ 5.08 (br t, $J = 7.4$, 1H), 4.15 (m, 1H), 2.15 (m, 2H), 2.0-1.6 (m, 2H), 1.71 (d, $J = 6.3$, 3H), 1.69 (s, 3H), and 1.64 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 132.8, 122.8, 51.3, 41.2, 26.4, 26.3, 25.7, and 17.7. LRMS (EI): m/z . 192 (5, $\text{M}+2$)⁺, 190 (5, M^+), 111 (22), 69 (100).

6-iodo-2-methylhept-2-ene (18b).⁸ Triphenylphosphine (57.7 g, 0.220 mol) and imidazole (17.7 g, 0.260 mol) were added to a solution of 6-methyl-5-hepten-2-ol (25.6 g, 0.203 mol) in 3:1 Et₂O : MeCN (600 mL total volume). The mixture was cooled to 0 °C and I₂ (50.8 g, 0.20 mol) was added in portions over 3h. The mixture was stirred at 0 °C for an additional 1h after addition of the I₂ at which time GC analysis indicated consumption of the alcohol. The mixture was concentrated under reduced pressure, taken up in hexanes (200 mL) and filtered. The resulting filtrate was re-concentrated and distilled (b.p. 34-36 °C @ 2.8 mmHg) to give **18b** (37.6 g, 79%) as a colorless liquid. ¹H NMR (CDCl₃, 300 MHz): δ 5.05 (br t, *J* = 7.0, 1H), 4.17 (m, 1H), 2.14 (m, 2H), 1.92 (d, *J* = 7.0, 3H), 1.87 (obscured m, 2H), 1.68 (s, 3H), and 1.63 (s, 3H). ¹³C NMR (CDCl₃, 75 MHz): δ 132.8, 122.5, 42.9, 30.2, 28.9, 28.2, 25.7, and 17.9. Anal Calcd for C₈H₁₅I: C, 40.35; H, 6.35. Found: C, 40.51; H, 6.36.

2,5-bis(methoxymethoxy)-4-bromotoluene (19b). A solution of the 5-bromo-2-methylhydroquinone² (10.3 g, 50.7 mmol) in CH₂Cl₂ (150 mL) was placed in a flask fitted with a Soxhlet extractor charged with 3Å molecular sieves.⁹ A solution of TsOH·H₂O (0.20 g, 1.0 mmol, 2.5 mol%) in dimethoxymethane (75 mL, 0.85 mol) was added and the mixture heated to reflux. The reaction was monitored by TLC (3 : 1 hex : EtOAc) and additional portions of dimethoxymethane (3 × 25 mL) were added over a total reflux period of 105 h. The mixture was then diluted with H₂O and the organic phase was washed (10 % NaOH, Na₂CO₃, brine), dried (MgSO₄) and concentrated. The resulting solid was recrystallized (m.p. 72-74 °C, hexanes/CH₂Cl₂) to yield **19b** as large tan needles (11.8 g, 81%). TLC: R_f = 0.42 (3:1 hexanes/ethyl acetate). IR (film deposited from CH₂Cl₂): 2988, 2947, 2895, 1491, 1368, 1194, 1146, 1084, and 987 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz): δ 7.25 (s, 1H), 6.97 (s, 1H), 5.16 (s,

2H), 5.12 (s, 2H), 3.53 (s, 3H), 3.49 (s, 3H), and 2.19 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 150.9, 148.5, 128.0, 119.3(2C), 109.9, 95.9, 95.2, 56.3, 56.0, and 16.2. Anal Calcd for $\text{C}_{11}\text{H}_{15}\text{BrO}_4$: C, 45.38; H, 5.19. Found: C, 45.18; H, 5.30.

2-Bromo-4-methyl-1-(phenylmethoxy)benzene (36).¹⁰ A solution of 2-bromo-4-methylphenol (10.0 g, 53.0 mmol) in DMF (25 mL) was added to a slurry of sodium hydride (60% dispersion in mineral oil, 2.36 g, 59.0 mmol hydride) in DMF (25 mL) over 0.5 h. THF (50 mL) was added to dissipate the resulting solid. After 1 h of stirring, benzyl bromide (7.0 mL, 10 g, 59 mmol) in THF (10 mL) was added and the mixture was stirred overnight. The mixture was then diluted with ether, washed ($2 \times 10\%$ NaOH, $2 \times \text{sat. LiCl}$, brine), dried (Na_2SO_4) and concentrated to a light yellow oil that solidified upon standing. The solid was recrystallized (m.p. 42 - 43 °C) from petroleum ether to give **36** (13.4 g, 91 %) as a fluffy white solid. IR (dep. CDCl_3): 1603, 799, 773, 732, 692, and 668 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz): δ 7.45 (m, 2H), 7.35 (m, 3H), 6.99 (m, 1H), 6.79 (d, $J = 8.2$, 1H), 5.10 (s, 2H), and 2.24 (s, 3H). ^{13}C NMR (CDCl_3 , 75 MHz): δ 152.8, 136.7, 133.8, 131.8, 128.8, 128.5, 127.8, 127.0, 113.9, 112.2, 70.9 and 20.1. Anal Calcd for $\text{C}_{14}\text{H}_{13}\text{BrO}$: C, 60.67; H, 4.73. Found: C, 60.78; H, 4.79.

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