Total Synthesis of Garcifuran B

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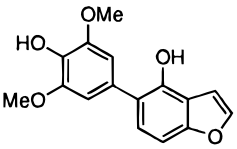
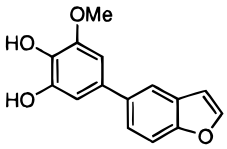
Studies on the constituents of plants of the *Garcinia* genus (Guttiferae), which are used in traditional herbal medicines in areas of southeastern Asia, showed them to contain a number of toxic components.[1] Garcifurans A (also known as garcinol[1]) and B were isolated from the roots of *Garcinia kola* Heckel collected in Nigeria by Niwa et al. in 1994.[2] The structures of garcifurans A and B were elucidated as **1a** and **1b** by examination of IR, UV,



1a



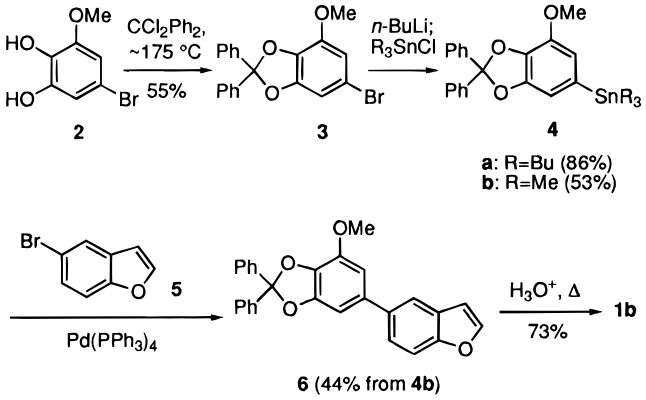
1b

NMR, and high-resolution mass spectra. To date, no garcifuran has been synthesized. Since the garcifurans are the first natural products claimed to possess a 5-arylbenzofuran nucleus, we undertook the synthesis of one member of this family—garcifuran B—to confirm the overall structure assignment.

Perhaps the easiest route to **1b** would have been to couple the known bromocatechol **2**[3] and the known bromobenzofuran **5**.[4] In previous projects[5] we have achieved such couplings by treating a mixture of two aryl bromides with a bis(trialkyltin) in the presence of a palladium catalyst. The reaction proceeds[5a] via in situ conversion of one aryl bromide to the corresponding stannane followed by coupling of the latter with the other aryl bromide. In the case of **2** and **5**, however, the palladium-catalyzed reaction with $(Me_3Sn)_2$ to give **1b** was unsuccessful. The major product was 5,5′-dibenzofuran, the product from the homocoupling of **5**. Consequently we sought to first convert **2** and **5** into a stannane in a separate step, but were unsuccessful. In the case of catechol **2**, we attributed our failure to obtain the stannane to not forming the desired trianion derived from **2** (≥3 equiv of *t*-BuLi or *n*-BuLi). This problem was overcome by protection[5e,6] of **2** with CCl_2Ph_2 to give **3** (Scheme 1). Lithiation and quenching with Bu_3SnCl or Me_3SnCl proceeded smoothly to give protected arylstannanes **4**.

With precursors **4a** and **5** in hand, palladium-catalyzed[7] coupling gave benzofuran **6**, but in low yield (18%).

Scheme 1



To our delight, the more reactive (but more decomposition prone) trimethylstannyl analog **4b** reacted smoothly with **5** to give in 44% yield the desired benzofuran **6**, which was then deprotected by heating under reflux in AcOH/H_2O to afford the natural product, garcifuran B (**1b**). IR and ^1H and ^{13}C NMR spectra of the synthetic product are in agreement with those reported for the naturally derived material.[2,8]

In conclusion, the structure of garcifuran B has now been confirmed by total synthesis, and a concise route to garcifuran B has been achieved in which the longest linear sequence is only five steps from commercially available materials.

Experimental Section[9]

5-Bromo-3-methoxycatechol (2). This compound was prepared as white wooly needles from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (Aldrich) according to the procedure of Larsson and Miksche:[3] mp 67−69 °C (lit.[3] mp 74−76 °C); ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H), 5.40 (br s, 2H), 6.60 (d, 1H, J = 2.1 Hz), 6.77 (d, 1H, J = 2.1 Hz); ^{13}C NMR ($CDCl_3$) δ 56.6, 107.1, 111.9, 112.5, 131.8, 144.8, 147.5.

6-Bromo-4-methoxy-2,2-diphenylbenzodioxole (3). Catechol **2** (0.60 g, 2.7 mmol) was placed together with dichlorodiphenylmethane (0.53 mL, 2.7 mmol, 1.0 equiv) into a 25-mL, two-necked, round-bottomed flask under a nitrogen atmosphere. The mixture was then heated to 170−180 °C (oil bath temperature) with stirring under nitrogen flux and maintained at that temperature for 5 min. The flask was removed from the oil bath and allowed to cool to ambient temperature. The dark brown residue was dissolved in dichloromethane, applied to a 3 × 30 cm SiO_2 column, and eluted with 1:1 diethyl ether/petroleum ether. The benzodioxole **3** was the first compound eluted, and appropriate fractions were collected and combined. The solvent was evaporated and the product recrystallized from hexane as white prisms (0.58 g, 55%): mp 87−89 °C; ^1H NMR ($CDCl_3$) δ 3.90 (s, 3H), 6.67 (d, 1H, J = 1.5 Hz), 6.75 (d, 1H, J = 1.5 Hz), 7.37−7.40 (m, 6H), 7.57−7.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 56.9, 106.4, 110.1, 113.4, 118.3, 126.5, 128.4, 129.4, 134.7, 139.8, 144.2, 149.1; HRMS (EI) calcd for $C_{20}H_{15}BrO_3$ (M^+) 382.0205, found 382.0202; Anal. Calcd for $C_{20}H_{15}O_3Br$: C, 62.68; H, 3.95. Found: C, 62.76; H, 3.78.

6-(Trialkylstannyl)-4-methoxy-2,2-diphenylbenzodioxoles (4). A solution of **3** (0.38 g, 1.0 mmol) in 4 mL of dry THF was placed in a dry, two-necked, 25-mL, round-bottomed flask under a nitrogen atmosphere with a small magnetic stirbar. The flask was immersed in an acetone/dry ice bath. *tert*-Butyllithium solution (1.0 mL, 1.7 M in pentane, 1.7 mmol, 1.7 equiv) was added slowly (1 drop/2 s) during which time the solution changed color from pale yellow to dark orange. The solution was stirred for 15 min at −78 °C, and then the reaction was quenched at

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(1) Niwa, M.; Terashima, K.; Aqil, M. *Heterocycles* **1993**, *36*, 671.
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(3) Larsson, S.; Miksche, G. E. *Acta Chem. Scand.* **1972**, *26*, 2031.
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(9) For general experimental procedures, see ref 5d.

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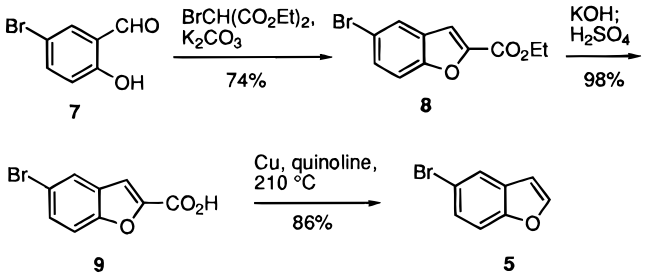
Scheme 2



this temperature with neat tributyltin chloride (0.50 mL, 1.8 mmol, 1.8 equiv) or trimethyltin chloride (1.8 mL, 1.0 M in THF, 1.8 mmol, 1.8 equiv, Aldrich). The solution was removed from the dry ice bath and allowed to reach room temperature. The reaction was quenched with 0.5 mL of H_2O and the solution concentrated in vacuo.

Stannane **4a** was isolated by flash column chromatography on a 3 × 30 cm SiO_2 column eluting with 9:1 hexanes/diethyl ether to give 0.51 g (86%) of **4a** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 9H, J = 7.6 Hz), 1.07 (t, 6H, J = 8.4 Hz), 1.37 (m, 6H), 1.58 (m, 6H), 3.99 (s, 3H), 6.62 (s, 1H), 6.74 (s, 1H), 7.38−7.40 (m, 6H), 7.65−7.67 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 10.0, 13.9, 27.6, 29.3, 56.9, 109.5, 115.3, 116.8, 126.6, 128.4, 129.1, 134.7, 135.4, 140.7, 143.9, 148.6; HRMS (EI) calcd for $C_{32}H_{42}O_3Sn$ (M^+) 590.2156, found 590.2145.

Stannane **4b** was purified by recrystallization from CH_2Cl_2 to give 0.26 g (53%) of **4b** as white crystals: mp 131−133 °C; ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 3.96 (s, 3H), 6.60 (s, 1H), 6.71 (s, 1H), 7.35−7.38 (m, 6H), 7.59−7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ −9.0, 57.0, 109.0, 114.7, 117.0, 126.6, 128.4, 129.2, 135.1, 135.6, 140.5, 144.0, 148.6; HRMS (CI) calcd for $C_{23}H_{25}O_3Sn$ ($M + H^+$) 469.0790, found 469.0812. Anal. Calcd for $C_{23}H_{24}O_3Sn$: C, 59.14; H, 5.18; Found: C, 58.87; H, 5.06.

5-Bromobenzofuran (5). This compound was prepared according to the literature (Scheme 2).[4]

NMR data for **8**, **9**, and **5** follow.

8: ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3H, J = 6.9 Hz), 4.42 (q, 2H, J = 6.9 Hz), 7.42 (s, 1H), 7.44 (s, 1H), 7.48 (d, 1H, J = 1.8 Hz), 7.77 (d, 1H, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$) δ 14.5, 61.9, 113.0, 114.0, 117.0, 125.5, 130.1, 130.7, 146.9, 154.5, 159.4.

9: ^{1}H NMR (DMSO) δ 7.60 (s, 1H), 7.63 (dd, 1H, J = 8.8, 2.0 Hz), 7.70 (d, 1H, J = 8.8 Hz), 8.00 (d, 1H, J = 2.0 Hz); ^{13}C NMR (DMSO) δ 112.6, 114.3, 116.0, 125.5, 129.1, 130.1, 147.7, 153.7, 159.9.

5: ^{1}H NMR ($CDCl_3$) δ 6.72 (d, 1H, J = 2.4 Hz), 7.39 (s, 2H), 7.63 (d, 1H, J = 2.4 Hz), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 106.3, 113.0, 116.0, 124.0, 127.4, 129.6, 146.3, 153.9.

6-(5-Benzofuranyl)-4-methoxy-2,2-diphenylbenzodioxole (6). A mixture of **4b** (50 mg, 0.11 mmol), **5** (21 mg, 0.10 mmol, 1.0 equiv), and freshly prepared tetrakis(triphenylphosphine)palladium(0)[10] (12 mg, 10 mol %) in 4 mL of dioxane was placed into a sealable tube equipped with a small magnetic stir bar. The tube was degassed by three cycles of evacuation and refilling with N_2 and sealed under vacuum. The vertical tube was partly immersed in an oil bath heated to 130−140 °C. The solution was heated under reflux for 24 h. After cooling, the reaction mixture was filtered and the filtrate evaporated. The product was isolated by flash column chromatography (SiO_2, 9:1 cyclohexane/diethyl ether) to give **6** (20 mg, 44%) as a white solid: mp 150−152 °C; ^{1}H NMR ($CDCl_3$) δ 4.00 (s, 3H), 6.75 (s, 1H), 6.80 (d, 1H, J = 1.6 Hz), 6.84 (d, 1H, J = 1.2 Hz), 7.35−7.42 (m, 6H), 7.43 and 7.52 (AB_q, 2H, J_{ab} = 8.8 Hz), 7.62−7.65 (m, 5H), 7.70 (d, 1H, J = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 56.9, 102.0, 106.9, 107.4, 111.6, 117.7, 119.7, 124.0, 126.6, 128.0, 128.4, 129.3, 134.4, 136.7, 136.8, 140.4, 143.8, 145.8, 149.0, 154.6; HRMS (EI) calcd for $C_{28}H_{20}O_4$ (M^+) 420.1362, found 420.1363.

5-(5-Benzofuranyl)-3-methoxy-1,2-benzenediol (1b, Garcifuran B). A solution of **6** (67 mg, 0.16 mmol) in 2.5 mL of glacial acetic acid and 0.5 mL of H_2O was refluxed for 6 h after which the solvent was evaporated in vacuo. The product was isolated by flash column chromatography (SiO_2, 1:1 hexanes/diethyl ether) to afford **1b** (29.8 mg, 73%) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 5.49 (br s, 2H), 6.72 (d, 1H, J = 2.0 Hz), 6.80 (dd, 1H, J = 2.0, 0.8 Hz), 6.88 (d, 1H, J = 2.0 Hz), 7.46 and 7.53 (AB_q, 2H, J_{ab} = 8.8 Hz), 7.64 (d, 1H, J = 2.0 Hz), 7.72 (d, 1H, J = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 56.5, 102.9, 106.9, 108.2, 111.6, 119.5, 123.9, 128.0, 131.9, 134.2, 136.6, 144.2, 145.7, 147.3, 154.5; IR (KBr) 3401, 2937, 2848, 1606, 1516, 1466, 1085 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{12}O_4$ (M^+) 256.0736, found 256.0736. The ^{1}H NMR and IR spectra are in agreement with those of natural garcifuran B provided by Dr. M. Niwa.[2]

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **3**, **4a**, **4b**, **6**, and **1b** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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