Diversity Oriented Synthesis of Natural 2-Arylbenzofuran, Moracin F

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Diversity oriented synthesis of natural 2-arylbenzofuran, moracin F (**1**) has been carried out from the commercially available starting materials using Sonogashira coupling, Suzuki coupling, neutral Al_2O_3 mediated cyclization, and intramolecular Wittig reaction as key steps.

Keywords: Moracin F, Sonogashira coupling, Suzuki coupling, Neutral Al_2O_3 mediated cyclization, Intramolecular Wittig reaction

Introduction

Heterocyclic compounds share more than half of the existing organic compounds and can play a key role in medicinal chemistry and drug discovery. Benzofuran, a fused heterocyclic compound, occurs in a large number of natural products and occupies a prominent position among the plant phenols in view of its medicinal and biological significance.[1] In particular, several natural and non-natural 2-substituted benzofurans display potent biological properties including anti-inflammatory,[2] antioxidant,[3] anticancer,[4] antifungal,[5] antimicrobial,[6] anti-platelet,[7] and antiviral activity.[8] In addition, some derivatives are investigated as enzyme inhibitors[9] and diagnostic imaging agents targeting amyloid plaques in Alzheimer's disease (AD).[10] Some benzofuran compounds are explored in organic semiconductors.[11] They also find applications as brightening agents[12] and in agriculture as pesticides and insecticides.[13]

The genus *Morus* belongs to flowering plants family, Moraceae. It contains around 16 species with worldwide distribution. It has gained considerable attention due to its medicinal and economical value.[14] In the recent review, Naik *et al*. highlighted the isolation of benzofurans (moracins A–Z) from the genus *Morus* and outlined the different synthetic methods used to construct the scaffold.[15] Moracin F (**1**) (Figure 1) was isolated[16] from acetone extracts of the cortex and phloem tissues of mulberry shoots infected with *F. solani f. sp. mori* and to the best of our knowledge, its synthesis is not yet reported.

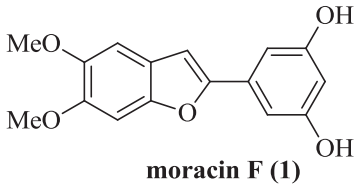
Continuing our interest on the synthesis and biological evaluation of benzofurans as anti-inflammatory agents,[17] herein, we describe the synthesis of natural 2-arylbenzofuran, moracin F using diverse methods which utilize Sonogashira coupling, Suzuki coupling, Al_2O_3 mediated cyclization, and intramolecular Wittig reaction as key steps.

Experimental

All chemicals were obtained from commercial suppliers and were used without further purification unless stated otherwise. All solvents used for reactions were freshly distilled from proper dehydrating agents under nitrogen gas. All solvents used for chromatography were purchased and directly used without further purification. ^{1}H-NMR spectra were recorded on Varian Mercury-300 MHz FT-NMR (Palo alto, CA, USA) and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) downfield relative to TMS and the coupling constants (*J*) quoted in Hz. $CDCl_3$/CD_3OD was used as a solvent and an internal standard. Mass spectra were recorded on a JMS-700 (JEOL, Tokyo, Japan) spectrometer. Melting points were measured on a MEL-TEMP II apparatus (Triad Scientific, Manasquan, NJ, USA) and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (layer thickness 0.2 mm; Merck, Darmstadt, Germany) plastic-backed silica gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde and phosphomolybdic acid (PMA) stain. Chromatographic purification was carried out using Kieselgel 60 (60–120 mesh, Merck).

***tert*-Butyl(3,4-dimethoxyphenoxy)dimethylsilane (3).** TBSCl (0.29 g, 1.95 mmol) in anhyd. DMF (1.5 mL) was added to a stirred solution of 3,4-dimethoxyphenol (**2**) (0.20 g, 1.30 mmol) and imidazole (0.22 g, 3.25 mmol) in anhyd. DMF (6.0 mL). The reaction mixture was stirred at 40°C for 4 h. After completion of the reaction, diluted with ether (20 mL), washed water (3 × 25 mL), brine (3 × 25 mL), dried over anhyd. Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/hexane = 1/15) to afford the pure product **3** (0.33 g, 94%) as colorless liquid. R_f = 0.48 (EtOAc/hexane = 1/15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* = 8.1 Hz), 6.41 (1H, d, *J* = 2.4 Hz), 6.35 (1H, dd, *J* = 8.1, 2.4 Hz), 3.83 (3H, s), 3.82 (3H, s), 0.98 (9H, s), 0.18 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 149.3, 143.5, 111.6, 110.5, 104.8, 56.3, 55.8, 25.8, 18.3, −4.3.

2-Iodo-4,5-dimethoxyphenol (4). To a stirred solution of compound **3** (0.20 g, 0.76 mmol) in ethyl alcohol (6 mL)



moracin F (1)

Figure 1. Structure of moracin F (**1**).

were added molecular iodine (0.21 g, 0.84 mmol) and silver sulfate (0.24 g, 0.84 mmol). The reaction was stirred for 48 h at room temperature. After completion of the reaction, it was diluted with saturated sodium thiosulphate solution and ethanol solvent was removed *in vacuo*. The compound was then extracted with EtOAc (2 × 25 mL), washed with brine (2 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography (EtOAc/hexane = 1/6) to afford the pure product **4** (0.14 g, 67%) as brown liquid. R_f = 0.28 (EtOAc/hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.02 (1H, s), 6.59 (1H, s), 5.25 (1H, s), 3.84 (3H, s), 3.80 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 149.8, 144.1, 119.9, 99.6, 71.8, 56.9, 56.3.

3,5-Bis(ethoxymethoxy)benzaldehyde (6). To a stirred solution of 3,5-dihydroxybenzaldehyde (0.14 g, 1.0 mmol) in anhydrous DMF (7 mL) was added K_2CO_3 (0.55 g, 4.0 mmol) under nitrogen atmosphere at room temperature. After stirring for 15 min, chloromethyl ethyl ether (0.28 mL, 3.0 mmol) was added dropwise and stirred for overnight at room temperature. After completion of the reaction, reaction mixture was diluted with ether (40 mL) and washed with water (3 × 15 mL). The organic layer was washed successively with water (3 × 30 mL), brine (3 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/6) to afford the pure compound (0.19 g, 76%) as colorless liquid. R_f = 0.54 (EtOAc/hexane = 1/5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.89 (1H, s), 7.19 (2H, d, *J* = 2.4 Hz), 6.98 (1H, t, *J* = 2.4 Hz), 5.24 (4H, s), 3.73 (4H, q, *J* = 6.9 Hz), 1.23 (6H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 159.0, 138.6, 111.4, 110.6, 93.5, 64.8, 15.5.

1,3-Bis(ethoxymethoxy)-5-ethynylbenzene (7). To a stirred solution of (trimethylsilyl)diazomethane (2.0 M solution in diethyl ether, 0.75 mL, 1.5 mmol) in anhyd. THF (3 mL) at −78 °C was added *n*-BuLi (2.0 M solution in cyclohexane, 1.5 mL, 1.5 mmol) dropwise and stirred for 30 min. To this, compound **6** (0.13 g, 0.5 mmol) in anhyd. THF (3 mL) was added dropwise and stirred for 1 h. After completion of the reaction, aqueous saturated NH_4Cl solution (1 mL) was added slowly and the reaction mixture warmed to room temperature. The reaction mixture was extracted with EtOAc (2 × 20 mL). Combined organic layer was washed with brine (2 × 15 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to afford the pure product (0.10 g, 79%) as colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (2H, d, *J* = 2.4 Hz), 6.75 (1H, t, *J* = 2.4 Hz), 5.20 (4H, s), 3.73 (4H, q, *J* = 6.9 Hz), 3.06 (1H, s), 1.25 (6H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 123.3, 113.2, 106.2, 93.1, 83.3, 64.4, 15.2.

2-(3,5-Bis(ethoxymethoxy)phenyl)-5,6-dimethoxybenzofuran (8). Compound **4** (0.07 g, 0.26 mmol), compound **7** (0.08 g, 0.32 mmol), and trimethylamine (0.11 mL, 0.78 mmol) were placed in sealed tube and anhydrous DMF was added to it. $PdCl_2(PPh_3)_2$ (0.01 g, 0.02 mmol) and CuI (0.01 g, 0.02 mmol) were added to the mixture and degassed for 2 min. The reaction was stirred at 80°C for 15 h. After completion of the reaction, cooled to room temperature and the solvent was removed under reduced pressure. The crude was purified by column chromatography (EtOAc/hexane = 1/8) to afford the pure product **8** (0.03 g, 20 %) as brown liquid. R_f = 0.28 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (2H, d, *J* = 1.8 Hz), 7.11, (1H, s), 7.01 (1H, s), 6.93 (1H, s), 6.72 (1H, t, *J* = 2.1 Hz), 5.26 (4H, s), 3.94 (3H, s), 3.92 (3H, s), 3.76 (4H, q, *J* = 6.9 Hz), 1.25 (6H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 154.4, 149.5, 148.0, 146.4, 132.4, 120.8, 105.6, 104.5, 102.0, 95.2, 93.2, 93.1, 64.4, 56.3, 56.2, 15.2 [Note: compound **8** was also obtained from **21** and **23** using $PdCl_2$(dppf).CH_2Cl_2/anhyd.K_3PO_4 system by Suzuki coupling reaction[17b]].

5-(5,6-Dimethoxybenzofuran-2-yl)benzene-1,3-diol (Moracin F) (1). To a stirred solution of **8** (0.03 g, 0.06 mmol) in anhydrous MeOH (2 mL) was added Dowex® 50X2-100 (Sigma-Aldrich, St.Louis, Missouri, USA) resin (0.03 g) under nitrogen atmosphere. The mixture was stirred at room temperature for 12 h. After completion of the reaction, resin was filtered and washed with EtOAc (15 mL). The filtrate was concentrated *in vacuo*. Crude residue was purified by column chromatography (EtOAc/hexane = 1/1) to yield the pure compound **1** (0.01 g, 75%) as white solid. R_f = 0.32 (EtOAc/hexane = 1/1); mp 186–188°C; ^{1}H NMR (300 MHz, CD_3OD) δ 7.15 (1H, s), 7.08 (1H, s), 6.92 (1H, s), 6.74 (2H, d, *J* = 1.2 Hz), 6.21 (1H, t, *J* = 1.2 Hz), 3.88 (3H, s), 3.86 (3H, s); ^{13}C NMR (75 MHz, CD_3OD) δ 158.7, 155.4, 149.7, 148.4, 146.9, 132.5, 121.5, 103.0, 102.7, 102.3, 101.3, 95.4, 55.9, 55.7; EI-MS *m/z* 286 (M^+, base), 271, 257; HRMS calcd for $C_{16}H_{14}O_5$ (M^+) 286.0841, found 286.0835.

1-(3,5-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)ethanone (10). 3,5-Dihydroxyacetophenone (0.08 g, 0.5 mmol), TBSCl (0.23 g, 1.5 mmol), and imidazole (0.17 g, 2.5 mmol) in anhyd. DMF (6 mL) reacted for 4.5 h, following the procedure described for compound **3** preparation to afford the compound **10** (0.18 g, 98%) as colorless liquid. R_f = 048 (EtOAc/hexane = 1/15); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (2H, d, *J* = 2.1 Hz), 6.51 (1H, t, *J* = 2.1 Hz), 2.53 (3H, s), 0.98 (18H, s), 0.21 (12H, s); ^{13}C NMR (75 MHz, CDCl3) δ 197.7, 156.8, 139.2, 117.0, 113.5, 27.1, 26.0, 18.6, −4.0.

1-(3,5-Bis((*tert*-butyldimethylsilyl)oxy)phenyl)-2-bromoethanone (11). To a stirred solution of substituted acetophenone **10** (0.19 g, 0.5 mmol) in EtOAc (5 mL) was added copper(II) bromide (0.28 g, 1.25 mmol) at room temperature, and the mixture was refluxed for 2.5 h. After cooling to room temperature, the mixture was filtered through a Celite® pad (Samchun Chemical, pyeongtaek, South Korea) and washed with EtOAc (10 mL). The filtrate was concentrated *in vacuo*. The crude product was purified on a short column (EtOAc/hexane = 1/15) to yield the corresponding pure compound **11** (0.2 g, 87%) as pale yellow liquid. R_f = 0.64 (EtOAc/hexane = 1/10); 1H NMR (300 MHz, $CDCl_3$) δ 7.12 (2H, s), 6.56 (1H, s), 4.37 (2H, s), 0.98 (18H, s), 0.22 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 160.8, 133.8, 114.2, 110.9, 34.7, 25.3, 14.3, −4.20.

((5-(5,6-Dimethoxybenzofuran-2-yl)-1,3-phenylene)bis(oxy))bis(*tert*-butyldimethylsilane) (12). A mixture of **2** (0.07 g, 0.44 mmol), phenacyl bromide **11** (0.20 g, 0.44 mmol), and neutral aluminum oxide (0.16 g, 1.53 mmol) was refluxed in xylene (3 mL) for 48 h. The resulting mixture was filtered through a Celite® pad and evaporated. The residue was purified by column chromatography on silica gel using ethyl acetate/hexane as eluent to yield the corresponding benzofuran (0.02 g, 8%) as brown liquid. R_f = 0.22 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (1H, s), 6.98 (1H, s), 6.89 (2H, d, J = 1.8 Hz), 6.85 (1H, s), 6.28 (1H, t, J = 1.8 Hz), 3.94 (3H, s), 3.92 (3H, s), 1.00 (18H, s), 0.23 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 154.9, 149.8, 148.2, 146.7, 132.5, 121.2, 112.1, 109.8, 102.3, 102.0, 95.5, 56.6, 56.5, 26.1, 18.6, −3.9.

5-(5,6-Dimethoxybenzofuran-2-yl)benzene-1,3-diol (Moracin F) (1). To a stirred solution of TBS-protected benzofuran **12** (0.02 g, 0.03 mmol) in anhyd. THF was added 1.0 M TBAF (0.07 mL, 0.07 mmol) and stirred for 4 h at room temperature. After completion of the reaction, solvent was removed *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/1) to afford the pure compound **1** (0.01 g, 90%) as white solid.

3,5-Bis(allyloxy)benzoic acid (14). To a stirred suspension of 3,5-dihydroxybenzoic acid (**13**) (0.2 g, 1.30 mmol) and K_2CO_3 (0.90 g, 6.49 mmol) in anhydrous DMF (8 mL) was added allyl bromide (0.34 mL, 3.80 mmol) slowly under nitrogen atmosphere at room temperature. The reaction mixture was stirred for 3 h. After completion of the reaction, filtered through Celite® pad and washed with ether (30 mL). The filtrate was washed with water (3 × 15 mL), brine (3 × 15 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to yield allyl 3,5-bis(allyloxy)benzoate (0.33 g, 92%) as colorless liquid. R_f = 0.80 (EtOAc/hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (2H, d, J = 2.4 Hz), 6.68 (1H, t, J = 2.4 Hz), 6.02 (3H, m), 5.40 (3H, dd, J = 17.1, 1.5 Hz), 5.28 (3H, dd, J = 10.2, 1.5 Hz), 4.80 (2H, dt, J = 5.4, 1.5 Hz), 4.54 (4H, dt, J = 4.8, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 159.7, 133.0, 132.3, 132.1, 118.4, 118.1 108.5, 107.3, 69.4, 66.0. To a stirred solution of the above ester (0.18 g, 0.64 mmol) in MeOH (5 mL) was added 1.0 N NaOH (1.91 mL) and refluxed for 2 h. After cooling to room temperature, solvent was removed under reduced pressure. The crude pH was adjusted to 2 with 1 N HCl and extracted with EtOAc (2 × 25 mL). The combined organic layer was washed with brine (2 × 30 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude acid **14** (0.13 g, 85%) obtained as white solid was utilized in the next step without further purification. mp 64–66°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (2H, d, J = 2.4 Hz), 6.70 (1H, t, J = 2.4 Hz), 6.06 (2H, m), 5.44 (2H, dd, J = 17.1, 1.5 Hz), 5.32 (2H, dd, J = 10.5, 1.5 Hz), 4.58 (4H, dt, J = 5.5, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 159.6, 132.7, 131.0, 118.1, 108.6, 108.0, 69.1

2-(Hydroxymethyl)-4,5-dimethoxyphenol (17). To a stirred solution of 2-hydroxy-4,5-dimethoxybenzaldehyde (**16**) (0.10 g, 0.54 mmol) in EtOH (3 mL) was added sodium borohydride (0.02 g, 0.55 mmol) at 0°C. The reaction mixture was stirred at room temperature for 1 h. After the solvent was removed, aq. 1 N HCl solution (4 mL) was added to the residue and extracted with CH_2Cl_2 (2 × 20 mL). The organic phase was dried over anhyd. Na_2SO_4 and filtered. The filtrate was concentrated to give the alcohol **17** (0.09 g, 90%) as clear liquid. R_f = 0.20 (EtOAc/hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.74 (1H, s), 5.93 (1H, s), 5.82 (1H, br s), 4.58 (2H, br d, J = 4.5 Hz), 4.15 (1H, br s), 3.86 (3H, s), 3.83 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.8, 159.0, 147.9, 129.4, 108.2, 107.3, 60.0, 59.0, 56.8.

2-((Bromotriphenylphosphoranyl)methyl)-4,5-dimethoxyphenol (18). To a stirred solution of compound **17** (0.08 g, 0.41 mmol) in acetonitrile (3 mL) was added triphenylphosphine hydrobromide (0.14 g, 0.41 mmol) and the mixture was refluxed for 2 h. After completion of the reaction, cooled to room temperature, filtered and washed with acetonitrile (8 mL) and dried to give the solid **18** (0.20 g, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78–7.39 (15H, m), 6.89 (1H, s), 6.37 (1H, s), 5.39 (1H, s), 4.49 (2H, d, J = 12.0 Hz), 3.71 (3H, s), 3.68 (3H, s).

2-(3,5-Bis(allyloxy)phenyl)-5,6-dimethoxybenzofuran (19). Thionyl chloride (0.07 mL, 0.96 mmol) was added to the acid **14** (0.15 g, 0.64 mmol) and refluxed for 2 h. After cool to room temperature, the excess thionyl chloride was removed under reduced pressure to give acid chloride **15** (0.15 g, 93%) as brown liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 2.1 Hz), 6.77 (1H, t, J = 2.1 Hz), 6.03 (2H, m), 5.42 (2H, dd, J = 17.1, 0.9 Hz), 5.31 (2H, dd, J = 10.8, 0.9 Hz), 4.56 (4H, d, J = 5.4 Hz) ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 159.5, 134.7, 132.2, 118.2, 109.8, 109.1, 69.2. To the above acid chloride was added the Wittig salt **18** (0.30 g, 0.44 mmol), triethylamine (0.20 mL), and toluene (10 mL) and refluxed for 3 h. After cool to room temperature, the precipitate was filtered and

washed with EtOAc (10 mL). The filtrate was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/7) to afford the pure benzofuran **19** (0.03 g, 15%) as clear liquid. R_f = 0.28 (EtOAc/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.07 (1H, s), 6.99 (1H, s), 6.96 (2H, d, *J* = 2.1 Hz), 6.88 (1H, s), 6.46 (1H, t, *J* = 2.4 Hz), 6.07 (2H, m), 5.44 (2H, dd, *J* = 17.1, 1.2 Hz), 5.31 (2H, dd, *J* = 10.2, 1.2 Hz), 4.58 (4H, dt, *J* = 5.4 Hz), 3.94 (3H, s), 3.93 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 154.5, 149.3, 147.3, 146.3, 132.8, 132.2, 120.7, 117.6, 103.2, 101.9, 101.7, 101.5, 95.0, 68.8, 56.2, 56.1.

5-(5,6-Dimethoxybenzofuran-2-yl)benzene-1,3-diol (Moracin F) (1). $Pd(PPh_3)_4$ (0.002 g, 2 mmol%) was added to a stirred suspension of **19** (0.03 g, 0.07 mmol) and K_2CO_3 (0.06 g 0.41 mmol) in anhydrous MeOH (3 mL) under nitrogen atmosphere. The mixture was stirred at 60°C for 3 h. After cooling to room temperature, solvent was removed under reduced pressure. The crude was neutralized with 1 N HCl and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with brine (2 × 10 mL), dried over anhyd. Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/2) to afford the pure benzofuran **1** (0.02 g, 86%) as white solid.

2-(2,2-Dibromovinyl)-4,5-dimethoxyphenol (20). Compound **20** was prepared from compound **16** following the literature procedure.[17b] Yield: 49%; brown liquid; R_f = 0.23 (EtOAc/hexane = 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (1H, s), 7.10 (1H, s), 6.43 (1H, s), 4.80 (1H, s), 3.87 (3H, s), 3.86 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.4, 147.3, 143.0, 132.0, 113.8, 111.5, 100.6, 90.7, 56.7.

2-Bromo-5,6-dimethoxybenzofuran (21). Compound **21** was prepared from compound **20** following the literature procedure.[17b] Yield: 81%; brown liquid; R_f = 0.64 (EtOAc/hexane = 1/1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, s), 6.92 (1H, s), 6.60 (1H, s), 3.90 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.3, 150.3, 146.7, 125.2, 120.5, 108.0, 101.2, 95.0, 56.4, 56.2.

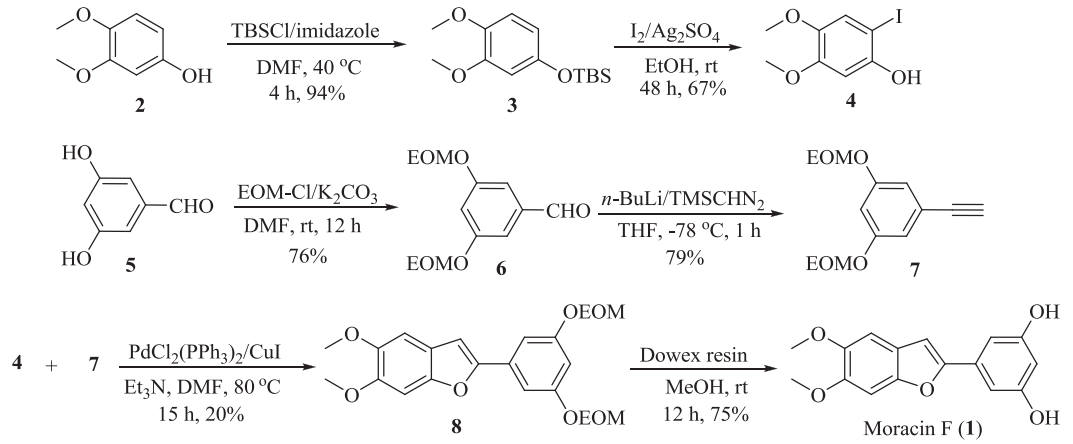
2-(3,5-Bis(ethoxymethoxy)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (23). Compound **23** was prepared from compound **22** following the literature procedure.[17b] Yield: 91%; clear liquid; R_f = 0.65 (EtOAc/hexane = 1/2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, d, *J* = 2.4 Hz), 6.82 (1H, t, *J* = 2.4 Hz), 5.21 (4H, s), 3.72 (4H, q, *J* = 6.9 Hz), 1.32 (12H, s) 1.22 (6H, t, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 115.3, 108.2, 93.1, 83.8, 64.3, 24.9, 15.2.

Results and Discussion

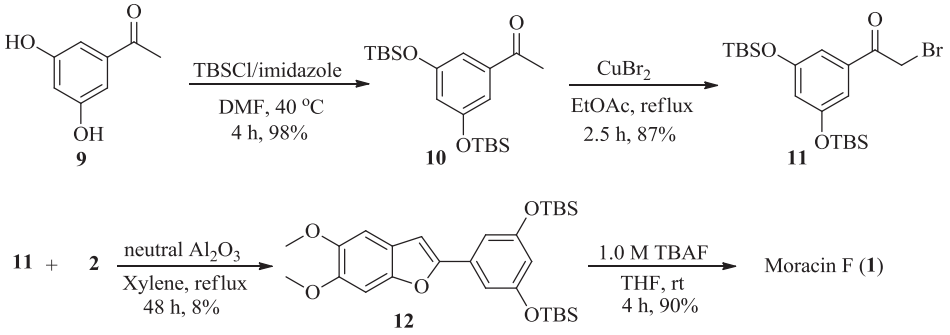
Synthesis of **1** using Sonogashira coupling as a key reaction[17a] was commenced with protection of 3,4-dimethoxyphenol (**2**) using *tert*-butyldimethylsilyl chloride (TBDMS-Cl) (Scheme 1). Regioselective iodination of **3** using $I_2/AgSO_4$ system offered the *tert*-butyldimethylsilyl (TBS)-free iodo compound **4**. 3,5-Dihydroxybenzaldehyde (**5**) was treated with chloromethyl ethyl ether (EOM-Cl) in presence of K_2CO_3 and the resulting ethoxymethyl (EOM)-protected aldehyde **6** was then converted as its homologous alkyne by Colvin rearrangement.[18] Next, Sonogashira coupling between **4** and **7** gave the EOM-protected benzofuran **8** which upon treatment with Dowex® resin led to the target compound, moracin F (**1**).

Next, the synthesis of **1** using neutral Al_2O_3 mediated cyclization as a key step in which the yields are generally low to moderate[19] was began with TBS-protection of 3,5-dihydroxyacetophenone[9] (Scheme 2). The resulting compound **10** was transformed as its phenacyl bromide **11** using copper bromide ($CuBr_2$). Regioselective cyclization of **2** with **11** was facilitated with neutral Al_2O_3 to afford the TBS-protected benzofuran **12** which was subsequently treated with 1.0 M tetrabutylammonium fluoride (TBAF) (in THF) to yield the desired compound **1** in high yield.

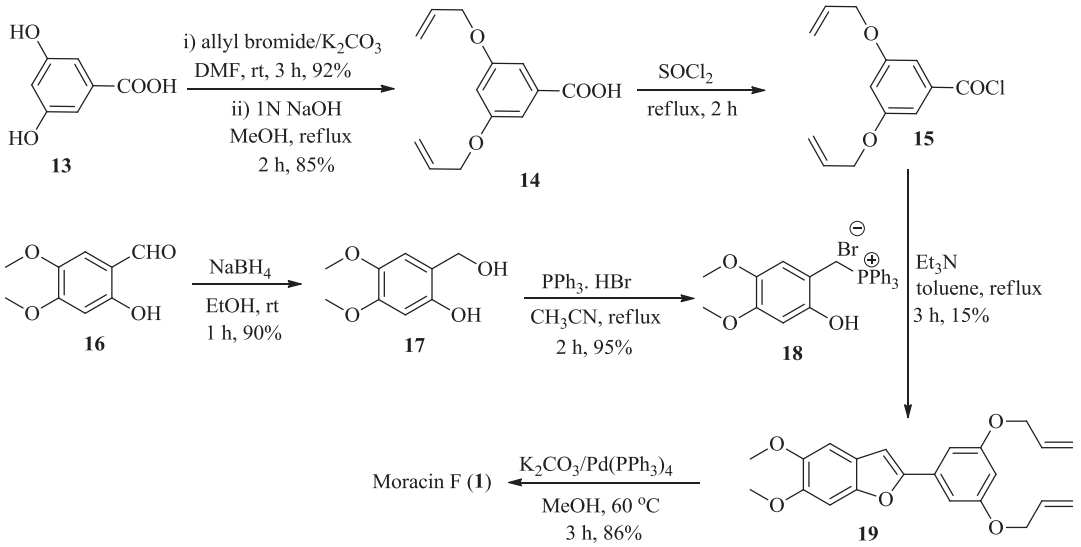
Synthesis of the natural benzofuran, **1** was also carried out by another approach which is outlined in Scheme 3. The key step for the formation of the benzofuran backbone was achieved by an intramolecular Wittig reaction[20] between triphenylphosphonium salt **18** and 3,5-bis



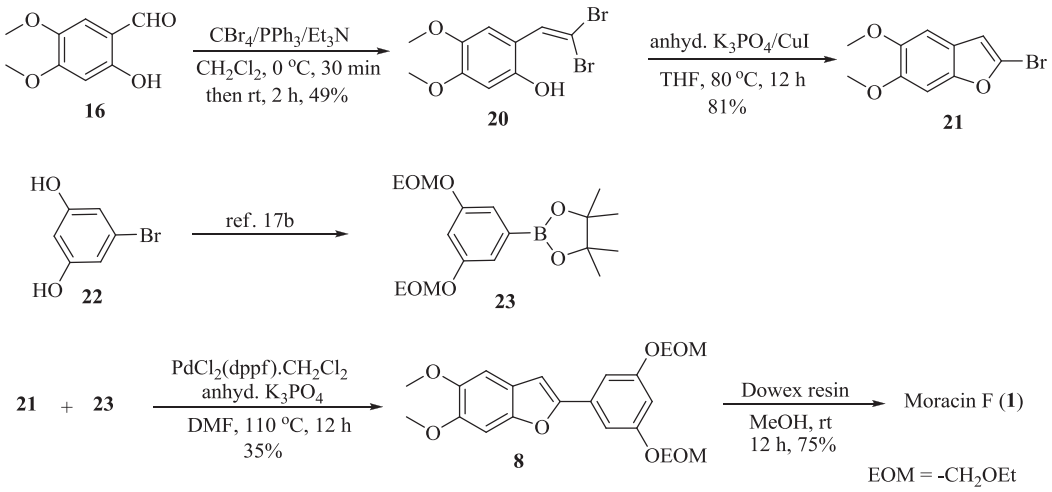
Scheme 1. Synthesis of moracin F (**1**) using Sonogashira reaction as a key step.



Scheme 2. Synthesis of moracin F (**1**) using neutral Al_2O_3 mediated cyclization as a key step.



Scheme 3. Synthesis of moracin F (**1**) using intramolecular Wittig reaction as a key step.



Scheme 4. Synthesis of moracin F (**1**) using Suzuki coupling as a key step.

(allyloxy)benzoyl chloride **15** (Scheme 3). The desired Wittig reagent **18** was readily prepared from triphenylphosphine hydrobromide (PPh_3.HBr) and the benzyl alcohol **17**, which in turn was obtained from the corresponding aldehyde by reduction. The acid chloride **15** was generated from its 3, 5-dihydroxybenzoic acid **13** by allyl protection, ester hydrolysis followed by chlorination synthetic sequence. Wittig reaction afforded the allyl-protected benzofuran **19**, which upon treatment with K_2CO_3 and catalytic $Pd(PPh_3)_4$ gave the target compound **1** in 86% yield.

Finally, we verified the Suzuki coupling approach[17d] for the synthesis of **1**. This method was initiated with the

Ramirez *gem*-dibromoolefination of aldehyde **16** (Scheme 4). The resulting *gem*-dibromoolefin **20** underwent intramolecular cross-coupling using anhydrous K_3PO_4/CuI system to yield 2-bromobenzofuran **21**. The corresponding boronic ester coupling agent **23** was obtained from the commercial 5-bromoresorcinol (**22**).[17b] Suzuki coupling between **21** and **23** using $Pd(PPh_3)_4$ (10 mmol%) and aq. 2.0 M K_2CO_3 as base in sealed tube and THF as a solvent medium at 100°C gave the benzofuran **8** only in 10% yield. Next, we tried with $PdCl_2$(dppf).CH_2Cl_2 (5 mmol%) and anhydrous K_3PO_4 as base in *N,N*-dimethylformamide (DMF) solvent at 110°C in sealed tube and the benzofuran **8** was obtained in 35% yield, from which **1** was obtained as shown in Scheme 1.

Conclusion

We have described a diversity oriented synthesis of natural 2-arylbenzofuran, moracin F using four different approaches in which Sonogashira coupling, Suzuki coupling, neutral Al_2O_3 mediated cyclization, and intramolecular Wittig reaction employed as key steps. All the approaches were proceeded from the commercially available starting materials and we feel the Suzuki coupling approach is the viable method among the other approaches.

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