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Facile Synthesis of Natural Moracin Compounds using $Pd(OAc)_2/P(^tBu)_3$-HBF_4 as a Sonogashira Coupling Reagent

Jae Jun Lee, So-Ra Yun, and Jong-Gab Jun*

Department of Chemistry and Institute of Applied Chemistry, Hallym University, Chuncheon 200-702, Korea
**E-mail: jgjun@hallym.ac.kr*
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An efficient and practical synthesis of natural moracins, which have diverse range of biological properties including anticancer, antioxidant, and antibacterial activities, has been achieved using $Pd(OAc)_2/P(^tBu)_3$-HBF_4 as a Sonogashira coupling reagent which solved the unreactive problems in case of higher electron density of haloaryl compounds in the reaction. Lowering electron density of halophenol with acetylation and changing Sonogashira coupling reagent from $PdCl_2(PPh_3)_2$ to $Pd(OAc)_2/P(^tBu)_3$-HBF_4 smoothly produce the benzofuran structures in the syntheses of moracins M, N and S. The electron deficient halobenzaldehyde, however, easily forms the benzofuran using original Sonogashira conditions, and utilized for the first synthesis of moracin Y.

Key Words : Moracin, Sonogashira reaction, Benzofuran, $Pd(OAc)_2/P(^tBu)_3$-HBF_4, *Morus alba Linn*

Introduction

Moracins are active components of mulberry (*Morus alba Linn.*), and isolated and identified of the structures as many as A through Z.[1] Most of them show important biological effects including antioxidant,[2] anti-inflammatory,[3] anticancer,[4] asthma,[5] anxiolytic,[6] analgesic,[7] hyperlipidemic[8] and antibacterial activities.[9] Among them, moracin M (**1**) shows the most simple 2-arylbenzofuran structure and several synthetic reports with activity studies since the isolation from the heartwood of *Morus laevigata* in 1975.[10] Direct lithiation methods developed by Widdowson[11] or Watanabe[12] for moracin M synthesis encountered problems, such as commercially not available starting materials or a low overall yield (7%), respectively. Recently, Cossio *et al.* reported an interesting strategy for moracin M synthesis which showed the benzofuran formation using one-pot reaction between phenol and α-bromoacetophenone in the presence of Al_2O_3.[13] However, the benzofuran formation reaction showed only 26% yield with a low total yield. There were no reports for moracin M synthesis[14] by using Sonogashira coupling reaction which is often used for benzofuran ring formation.[15]

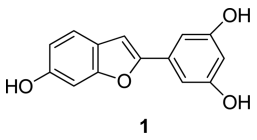

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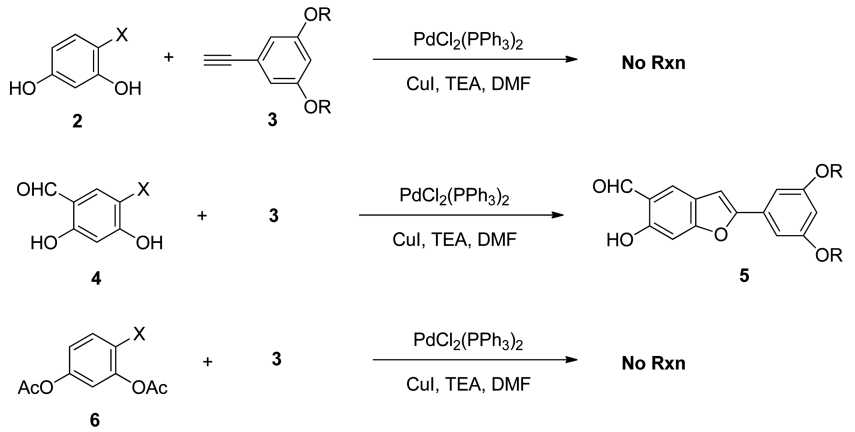
Figure 1. Moracin M (**1**).

Results and Discussion

We applied the Sonogashira coupling reaction of haloresorcinol **2** with aryl acetylene **3** using $PdCl_2(PPh_3)_2$ condition for moracin M synthesis. However, no reaction occurred despite every effort as shown in Scheme 1. Electron density of halophenol **2** in the reaction could be important. Halobenzaldehyde **4**, of which electron density was lowered by substitution of electron-withdrawing aldehyde comparing to **2**, was used once in our group[15d] for XH-14 synthesis, and



Scheme 1. Sonogashira coupling reaction of aryl halide with aryl acetylene derivatives.

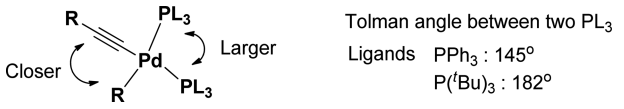


Figure 2. Tolman angle of Pd-acetylene complex.

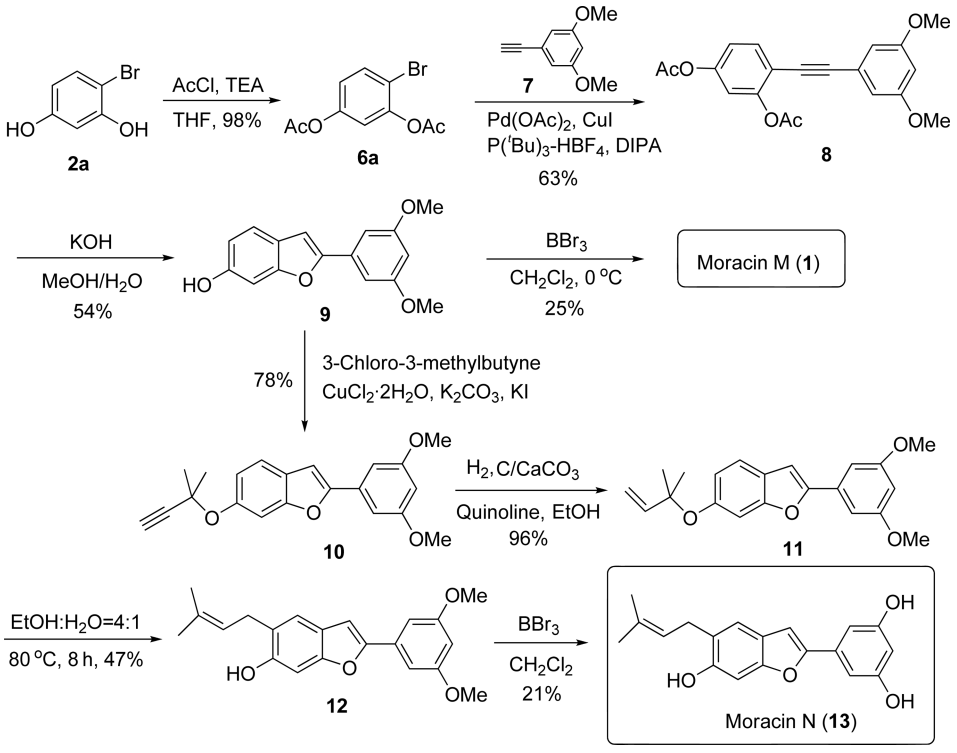
successfully applied with Sonogashira reagent to yield the expected benzofuran **5**. Acetylated haloresorcinol **6** for decreasing the electron density of **2**, however, did not give the expected benzofuran using original Sonogashira condition, and we assumed that the chloride anion produced from the reaction could be used as a nucleophile causing deacetylation to increase the electron density again and prohibit the coupling reaction.

Fu[16] introduced air-stable trialkylphosphonium salt and Kotschy[17] used this catalyst with $Pd(OAc)_2$ for benzofuran ring formation. Fagnou also introduced the optimal metal-ligand combination using $Pd(OAc)_2$ with $P(^tBu)_3$-HBF_4 to solve a cross-coupling problem.[18] Using bulky phosphine ligands exhibiting a large cone angle (known as Tolman angle)[19] has been known to accelerate the reductive elimination step in palladium catalysed coupling cycle (oxidative addition-transmetallation-reductive elimination) due to a decreased distance between the two R groups as shown in Figure 2. Changing the ligand from PPh_3 to $P(^tBu)_3$ increase the cone angle between two PL_3 from 145° to 182° in Pd-acetylene complex, and decrease the angle between two R groups which accelerate the reductive elimination step in the reaction pathway.

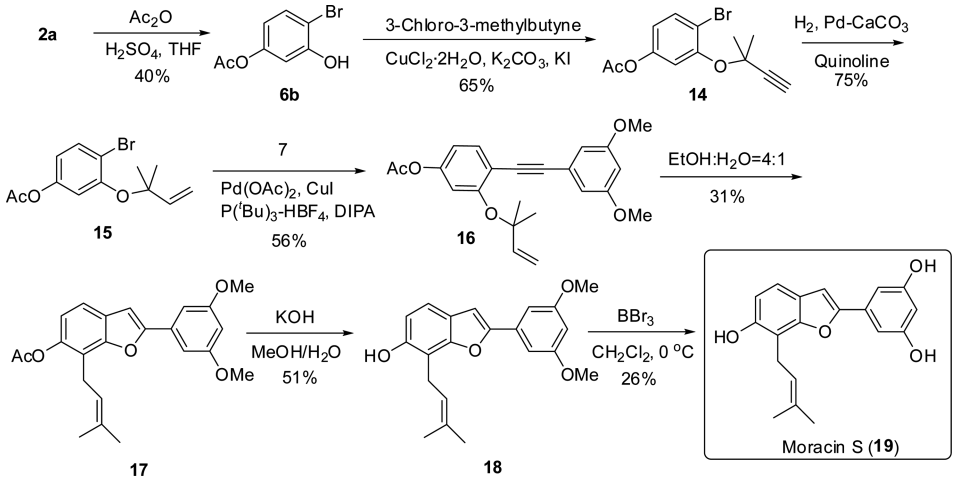
Sonogashira coupling of diacetylated bromoresorcinol **6a** with aryl acetylide **7** using $Pd(OAc)_2$/$P(^tBu)_3$-HBF_4, CuI and DIPA gave 63% yield of coupled product **8**, which was then deacetylated in basic condition to give the benzofuran **9** (Scheme 2). Demethylation of **9** using BBr_3 produced the moracin M in 25% yield as same as literature.[13] The intermediate benzofuran **9** was utilized for the first synthesis of moracin N (**13**) which was isolated from mulberry[20] and showed tyrosinase inhibitory activity[21] and better antifungal activity[22] than moracin M. Propargylation of **9** with 3-chloro-3-methylbutyne and following reduction using Lindlar catalyst gave the prenyl ether **11**. Water-accelerated [3,3]-sigmatropic rearrangement[23] of **11** produced 5-propenyl-benzofuran **12** in 47% yield regioselectively, and followed demethylation of **12** using BBr_3 gave the moracin N in 21% yield.

Moracin S (**19**), which is the regioisomer of moracin N, was isolated from black mulberry[1b] and showed similar antioxidant activity as vitamin E,[1b] however, no other reports on activity and synthesis are noticed. First total synthesis of moracin S is achieved using modified Sonogashira coupling reaction as shown in Scheme 3. Regioselective acetylation of **2a** with Ac_2O in acidic condition gave 40% yield of **6b** which was then propargylated to **14** in 65% yield and followed reduction with Lindlar catalyst produced **15** in 75% yield. Coupling reaction of **15** with aryl acetylide **7** using the modified Sonogashira reagent gave **16** in 56% yield and followed water-accelerated [3,3]-sigmatropic rearrangement produced the benzofuran **17** in one-step. Deacetylation of **17** with KOH and followed demethylation using BBr_3 produced the moracin S in 26% yield.

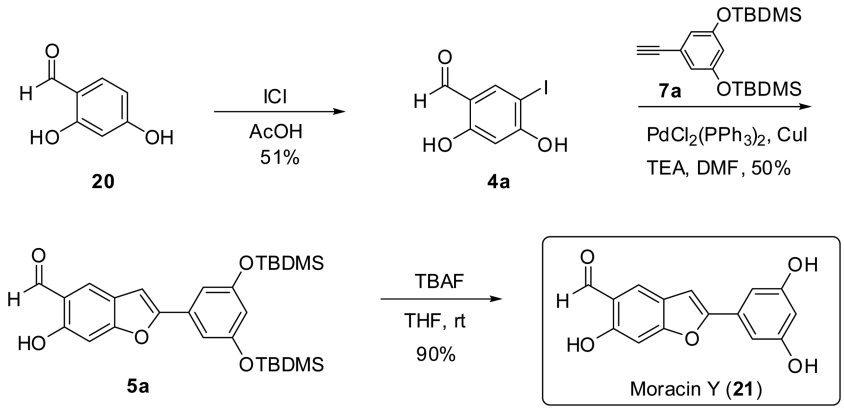
Moracin Y was extracted from mulberry leaves and only one bioactivity has been known.[1a] Benzofuran **5a** containing



Scheme 2. Synthesis of moracins M and N.



Scheme 3. Synthesis of moracin S.



Scheme 4. Synthesis of moracin Y.

electron withdrawing aldehyde, which was prepared in Scheme 1 using original Sonogashira coupling condition, is utilized for the first synthesis of moracin Y (**21**) as shown in Scheme 4. Benzaldehyde **20** was iodinated with ICl and coupled with aryl acetylide **7a** to give the benzofuran **5a**, which was then deprotected with TBAF to produce the moracin Y with overall 23% yield in 3 steps.

In conclusion, efficient and practical syntheses of moracins M, N, and S have been achieved using $Pd(OAc)_2/P(^tBu)_3$-HBF_4 and the spectral data of the synthetic moracins N, S and Y are well matched with the literatures.[20,1b,1a]

Experimental

All chemicals were purchased from Sigma-Aldrich Chemicals and were used without further purification unless noted otherwise. NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (J) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Mass spectra were recorded using a JMS-700 (JEOL) spectrometer. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

1,3-Diacetoxy-4-bromobenzene (6a). To a stirred solution 4-bromoresorcinol (**2a**) (0.50 g, 2.61 mmol) in THF (10 mL) was added triethylamine (0.74 mL, 5.31 mmol) under nitrogen atmosphere and stirred for 0.5 h at rt. AcCl (0.37 mL, 5.31 mmol) in THF (3 mL) was added slowly to this reaction mixture and stirred for 3 h at rt. The reaction mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by silica gel flash column chromatography (EtOAc/hexane = 1/10) to give a clean liquid. Yield: 0.69 g (98%); R_f 0.44 (EtOAc/hexane = 1/3); ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (1H, d, J = 8.4 Hz), 6.97 (1H, d, J = 0.9 Hz), 6.92 (1H, dd, J = 8.4, 0.9 Hz), 2.35 (3H, s), 2.29 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.51, 167.96, 150.05, 148.36, 133.20, 120.55, 117.49, 112.74, 21.17, 20.87.

1-(2,4-Diacetoxyphenyl)-2-(3,5-dimethoxyphenyl)acetylene (8). To **6a** (0.68 g, 2.53 mmol) were added $Pd(OAc)_2$ (30 mg, 0.12 mmol), CuI (30 mg, 0.12 mmol), $P(^tBu)_3$-HBF_4 (40 mg, 0.19 mmol) and 1-ethynyl-3,5-dimethoxybenzene **7** (0.52 g, 3.22 mmol) under nitrogen atmosphere and stirred for 3 d at 40 °C. The reaction mixture was dissolved with

ether, filtered with Celite® 545, concentrated *in vacuo*, extracted with ether, washed with brine, dried over $MgSO_4$ and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give the product as white solid. Yield: 0.57 g (63%); R_f 0.29 (EtOAc/hexane = 1/3); mp 178-180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (1H, d, *J* = 8.4 Hz), 7.01 (1H, dd, *J* = 8.4, 2.4 Hz), 6.96 (1H, d, *J* = 2.4 Hz), 6.62 (2H, d, *J* = 2.7 Hz), 6.46 (1H, t, *J* = 2.7 Hz), 3.79 (6H, s), 2.36 (3H, s), 2.30 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.50, 168.90, 151.84, 150.75, 133.15, 123.94, 119.17, 116.11, 114.72, 109.30, 101.79, 94.09, 83.10, 55.47, 21.14, 20.93.

2-(3,5-Dimethoxyphenyl)-6-hydroxybenzofuran (9). To a stirred solution of **8** (0.51 g, 1.44 mmol) in MeOH (5 mL) was added slowly KOH (0.28 g, 5.04 mmol) in H_2O (2 mL) under nitrogen atmosphere and refluxed for 5 h. The reaction was quenched with 1 N HCl, concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give a yellow solid. Yield: 0.21 g (54%); R_f 0.39 (EtOAc/hexane = 1/2); mp 218-221 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38 (1H, d, *J* = 8.3 Hz), 7.00 (1H, d, *J* = 1.8 Hz), 6.95 (2H, d, *J* = 2.4 Hz), 6.92 (1H, s), 6.77 (1H, dd, *J* = 2.4, 8.3 Hz), 6.43 (1H, t, *J* = 1.8 Hz), 3.86 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.96, 161.03, 156.94, 153.14, 135.36, 133.21, 132.36, 109.72, 106.54, 103.67, 100.96 99.10, 55.66.

6-Hydroxy-2-(3,5-dihydroxyphenyl)benzofuran; Moracin M (1). Procedure followed as reported.[13] Yield: (25%); R_f 0.53 (EtOAc/hexane = 1/1); mp 260-263 °C (lit.[10] mp 259-262 °C; lit.;[11a] ^{1}H NMR (300 MHz, methanol-d_4) δ 7.30 (1H, d, *J* = 8.4 Hz), 7.09 (1H, s), 6.95 (1H, d, *J* = 2.4 Hz), 6.68 (2H, d, *J* = 2.1 Hz), 6.55 (1H, dd, *J* = 8.4, 2.4 Hz), 6.22 (1H, t, *J* = 2.1 Hz); ^{13}C NMR (75 MHz, methanol-d_4) δ 160.1, 157.4, 157.0, 156.3, 134.0, 123.2, 122.2, 113.4, 104.1, 103.7, 102.4, 98.6. HRMS (EI): *m/z* $[M]^+$ calcd for $C_{14}H_{10}O_4$: 242.0579; found: 242.0580.

2-(3,5-Dimethoxyphenyl)-6-(1,1-dimethylprop-2-ynyloxy)benzofuran (10). To **9** (75 mg, 0.31 mmol) was added diisopropylethylamine (0.07 mL, 0.40 mmol) and stirred for 0.5 h at 0 °C. Cupper (II) chloride dihydrate (0.50 mg, 0.003 mmol) and 3-chloro-3-methylbutyne (0.04 mL, 0.34 mmol) was added slowly to this reaction mixture and stirred for 5 h at 0 °C. The reaction mixture was concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and purified by silica gel flash column chromatography (EtOAc/hexane = 1/8) to give a brown liquid. Yield: 81 mg (78%); R_f 0.60 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (1H, d, *J* = 9.3 Hz), 7.24 (1H, s), 6.87 (1H, d, *J* = 2.1 Hz), 6.62 (1H, dd, *J* = 9.3, 2.1 Hz), 6.40 (2H, d, *J* = 1.5 Hz), 6.35 (1H, t, *J* = 1.5 Hz), 3.74 (6H, s), 2.66 (1H, s), 1.71 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.75, 162.52, 160.76, 136.37, 131.49, 113.56, 111.13, 110.99, 107.35, 106.31, 98.82, 95.54, 84.53, 75.16, 72.31, 55.36.

2-(3,5-Dimethoxyphenyl)-6-(1,1-dimethylprop-2-enyloxy)benzofuran (11). To **10** (80 mg, 0.24 mmol) were added 5% mol Pd-$CaCO_3$ (5 mg), quinoline (1 mL, 0.01 mmol) in EtOH (2 mL) under hydrogen atmosphere and stirred for 4 h at rt. The reaction mixture was dissolved with MeOH, filtered with Celite® 545, concentrated *in vacuo*, extracted with CH_2Cl_2, dried over Na_2SO_4 and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give a brown liquid. Yield: 77 mg (96%); R_f 0.71 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J* = 8.4 Hz), 7.24 (1H, s), 6.53 (1H, d, *J* = 2.4 Hz), 6.44 (1H, dd, *J* = 8.4, 2.4 Hz), 6.40 (2H, d, *J* = 1.8 Hz), 6.35 (1H, t, *J* = 1.8 Hz), 6.14 (1H, dd, *J* = 16.5, 10.5 Hz), 5.27 (1H, d, *J* = 16.5 Hz), 5.20 (1H, d, *J* = 10.5 Hz), 3.76 (6H, s), 1.26 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.08, 163.87, 161.05, 159.25, 143.55, 136.78, 131.71, 114.50, 113.32, 111.65, 107.65, 106.54, 99.11, 81.12, 55.67, 27.63.

6-Hydroxy-2-(3,5-dimethoxyphenyl)-5-(3-methylbut-2-enyl)benzofuran (12). 11 (70 mg, 0.23 mmol) was dissolved in EtOH-H_2O (4:1 v/v, 4 mL) in a 35-mL Ace pressure tube with PTFE bushes and an FETFE O-ring seal. The tube was then placed in an electric furnace at 80 °C for 8 h. When the tube had cooled to rt, the screw-cap was loosened. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc-acetone (2:1), dried over $MgSO_4$ and purified by silica gel flash column chromatography (Acetone/hexane = 1/2) to give a yellow-green solid. Yield: 32 mg (47%); R_f 0.21 (EtOAc/hexane = 1/2); mp 232-234 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (1H, s), 6.91 (1H, s), 6.84 (1H, s), 6.59 (2H, d, *J* = 2.1 Hz), 6.31 (1H, t, *J* = 2.1 Hz), 1.61 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.53, 155.49, 155.00, 154.83, 131.11, 129.31, 125.44, 123.47, 122.82, 121.83, 105.43, 103.25, 99.80, 55.63, 27.00, 25.49, 17.64.

6-Hydroxy-2-(3,5-dihydroxyphenyl)-5-(3-methylbut-2-enyl)benzofuran (13); Moracin N. To a stirred solution of **12** (21 mg, 0.06 mmol) in CH_2Cl_2 (1 mL) was added slowly BBr_3 solution (0.25 mL, 0.25 mmol) (1 M in CH_2Cl_2) under nitrogen atmosphere and stirred for 1 h at −78 °C. Then the mixture was stirred for 19 h at 0 °C. MeOH was added to the reaction mixture and concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude was recrystallized from EtOAc-hexane to give the product as a brown solid.[20] Yield: 4 mg (21%); R_f 0.57 (EtOAc/hexane = 1/1); mp 220-221 °C (lit.[20b] mp 187-188 °C); ^{1}H NMR (300 MHz, Methanol-d_4) δ 7.24 (1H, s), 7.05 (2H, s), 6.79 (2H, d, *J* = 2.1 Hz), 6.41 (1H, t, *J* = 2.4 Hz), 5.27 (1H, t, *J* = 6.9 Hz), 3.77 (1H, d, *J* = 7.4 Hz), 1.78 (6H, s); ^{13}C NMR (75 MHz, Methanol-d_4) δ 166.65, 156.96, 150.25, 150.13, 134.01, 131.09, 130.55, 129.55, 128.54, 127.37, 105.35, 104.55, 104.18, 100.32, 29.34, 26.13, 18.25. HRMS (EI) calcd for $C_{19}H_{18}O_4$ M^+ 310.1205, found 310.1207.

5-Acetoxy-2-bromophenol (6b). Sulfuric acid (1 drop) was added to acetic anhydride (0.5 mL, 5.28 mmol) in one neck flask at rt and then cooled to −20 °C. After stirring for 10 min at −20 °C, 4-bromo resorcinol (**2a**) (1 g, 5.28 mmol) in THF was added and the resulting mixture was stirred for 7 h at this temperature. After completion of the reaction, H_2O was added. The reaction mixture was extracted with EtOAc, washed with brine, dried over anhydrous $MgSO_4$, concentrated *in vacuo*, and purified by silica gel flash column

chromatography (EtOAc/hexane = 1/8) to give a clean liquid. Yield: 0.48 g (40%); R_f 0.31 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 8.4 Hz), 7.07 (1H, dd, J = 8.4, 3 Hz), 6.89 (1H, d, J = 3 Hz), 2.19 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.31, 150.26, 149.16, 132.37, 118.65, 110.82, 108.14, 21.02.

4-Acetoxy-1-bromo-2-(1,1-dimethylprop-2-ynyloxy)benzene (14). 1,8-Diazabicycloundec-7-ene (0.32 mL, 2.07 mmol) was added to **6b** (0.41 g, 1.71 mmol) and stirred for 0.5 h at 0 °C. Cupper (II) chloride dihydrate (3 mg, 0.02 mmol) and 3-chloro-3-methylbutyne (0.21 mL, 1.81 mmol) was added slowly to this reaction mixture and stirred for 5 h at 0 °C. The reaction mixture was concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$ and purified by silica gel flash column chromatography (EtOAc/hexane = 1/8) to give a brown liquid. Yield: 0.33 g (65%); R_f 0.75 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (1H, d, J = 8.4 Hz), 6.87 (1H, dd, J = 8.4, 3 Hz), 6.78 (1H, d, J = 3 Hz), 2. 12 (1H, s), 1.78 (3H, s), 1.19 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.40, 157.76, 149.69, 133.93, 119.40, 112.97, 110.23, 84.87, 74.82, 72.45, 29.56, 21.02.

4-Acetoxy-1-bromo-2-(1,1-dimethylprop-2-enyloxy)benzene (15). To **14** (0.30 g, 1.03 mmol) were added 5% mol Pd-$CaCO_3$ (15 mg) and quinoline (0.01 mL, 0.01 mmol) in EtOH (2 mL) under hydrogen atmosphere and stirred for 4 h at rt. The reaction mixture was dissolved with MeOH, filtered with Celite® 545, concentrated *in vacuo*, extracted with CH_2Cl_2, dried over Na_2SO_4 and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give a brown liquid. Yield: 0.29 g (75%); R_f 0.81 (EtOAc/hexane = 1/3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, J = 8.7 Hz), 7.00 (1H, dd, J = 8.7, 3 Hz), 6.65 (1H, d, J = 3 Hz), 6.08 (1H, dd, J = 10.8, 10.8 Hz), 4.99 (2H, dd, J = 10.8, 10.8 Hz), 2.32 (3H, s), 1.28 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.40, 157.65, 149.88, 143.41, 134.11, 119.41, 114.42, 111.14, 107.74, 81.17, 27.07, 21.02.

1-(4-Acetoxy-2-(1,1-dimethylprop-2-enyloxy)phenyl)-2-(3,5-dimethoxyphenyl)acetylene (16). To a stirred solution of **15** (0.25 g, 0.83 mmol) in diisopropylamine (5 mL) were added slowly $Pd(OAc)_2$ (10 mg, 0.41 mmol), CuI (8 mg, 0.41 mmol), P(^{t}Bu)$_3$-HBF_4 (12 mg, 0.06 mmol) and 1-ethynyl-3,5-dimethoxybenzene **7** (0.18 g, 1.08 mmol) under nitrogen atmosphere and stirred for 3 d at 40 °C. The reaction mixture was dissolved with ether, filtered with Celite® 545, concentrated *in vacuo* at 80 °C, extracted with ether, washed with brine, dried over $MgSO_4$ and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give a white solid. Yield: 0.18 g (56%); R_f 0.43 (EtOAc/hexane = 1/3); mp 197-198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (1H, d, J = 8.9 Hz), 6.82 (1H, dd, J = 8.9, 2.8 Hz), 6.74 (1H, d, J = 2.8 Hz), 6.69 (2H, d, J = 2.3 Hz), 6.36 (1H, t, J = 2.3 Hz), 6.03 (1H, dd, J = 10.4, 10.4 Hz), 4.91 (2H, dd, J = 10.4, 10.4 Hz), 3.43 (6H, s), 2.24 (3H, s), 1.38 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.40, 163.97, 163.04, 149.72, 143.41, 134.76, 127.14, 117.37, 115.37, 114.42, 110.10, 108.02, 100.93, 98.38, 92.63, 82.43, 55.31, 27.53, 21.78.

6-Acetoxy-2-(3,5-dimethoxyphenyl)-7-(3-methylbut-2-enyl)benzofuran (17). 16 (0.17 g, 0.47 mmol) was dissolved in EtOH-H_2O (4:1 v/v, 4 mL) in a 35-mL Ace pressure tube with PTFE bushes and an FETFE O-ring seal. The tube was then placed in an electric furnace at 100 °C for 9 h. When the tube had cooled to rt, the screw-cap was loosened. The reaction mixture was concentrated *in vacuo*, extracted with EtOAc-acetone (2:1), dried over $MgSO_4$ and purified by silica gel flash column chromatography (Acetone/hexane = 1/2) to give a green solid product. Yield: 55 mg (31%); R_f 0.61 (EtOAc/hexane = 1/2); mp 195-198 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (1H, d, J = 8.7 Hz), 7.29 (1H, s), 7.06 (1H, d, J = 2.7 Hz), 6.37 (2H, d, J = 2.4 Hz), 6.30 (1H, t, J = 2.4 Hz), 5.24 (1H, m), 3.64 (6H, s), 3.51 (2H, d, J = 7.4 Hz), 2.35 (3H, s), 1.84 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.07, 161.33, 155.78, 154.53, 153.55, 130.71, 128.65, 125.21, 124.12, 121.25, 119.36, 112.32, 105.37, 105.11, 99.83, 55.67, 25.53, 20.11, 20.02, 18.36.

6-Hydroxy-2-(3,5-dimethoxyphenyl)-7-(3-methylbut-2-enyl)benzofuran (18). To a stirred solution of **17** (55 mg, 0.14 mmol) in MeOH (5 mL) was added slowly KOH (16 mg, 0.29 mmol) in H_2O (2 mL) under nitrogen atmosphere and refluxed for 5 h. The reaction was quenched with 1N HCl, concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and purified by silica gel flash column chromatography (EtOAc/hexane = 1/6) to give a yellow solid. Yield: 25 mg (51%); R_f 0.84 (EtOAc/hexane = 1/1); mp 242-244 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (1H, d, J = 8.9 Hz), 7.23 (1H, s), 6.82 (1H, d, J = 8.9 Hz), 6.75 (2H, d, J = 2.4 Hz), 6.41 (1H, t, J = 2.4 Hz), 5.22 (1H, m), 3.41 (6H, s), 3.35 (2H, d, J = 7.1 Hz), 1.72 (6H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.52, 156.22, 155.64, 150.65, 135.29, 128.51, 122.21, 121.42, 119.26, 117.32, 108.12, 105.21, 103.67, 97.51, 53.55, 25.60, 20.73, 17.47.

6-Hydroxy-2-(3,5-dihydroxyphenyl)-7-(3-methylbut-2-enyl)benzofuran (19); Moracin S. To a stirred solution of **18** (20 mg, 0.059 mmol) in CH_2Cl_2 (1 mL) was added slowly BBr_3 solution (0.23 mL, 0.23 mmol) (1 M in CH_2Cl_2) under nitrogen atmosphere and stirred for 1 h at −78 °C. Then the mixture was stirred for 19 h at 0 °C. MeOH was added to the reaction and concentrated *in vacuo*, extracted with CH_2Cl_2, washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude product was recrystallized from EtOAc-hexane to give the product as orange solid. Yield: 4.7 mg (26%); R_f 0.63 (EtOAc/hexane = 1/1); mp 217-220 °C.[1b]; ^{1}H NMR (300 MHz, methanol-d_4) δ 7.27 (1H, d, J = 8.4 Hz), 7.12 (1H, s), 6.85 (1H, d, J = 8.4 Hz), 6.72 (2H, d, J = 2.1 Hz), 6.39 (1H, t, J = 2.1 Hz), 5.05 (1H, m), 3.66 (2H, d, J = 7.2 Hz), 1.90 (6H, s); ^{13}C NMR (75 MHz, methanol-d_4) δ 160.12, 156.11, 155.02, 152.21, 133.41, 133.11, 124.43, 123.71, 119.01, 113.34, 113.12, 104.01, 103.74, 103.18, 26.54, 24.01, 17.96. HRMS (EI) calcd for $C_{19}H_{18}O_4$ M^+ 310.1205, found 310.1207.

2,4-Dihydroxy-5-iodobenzaldehyde (4a). To a stirred solution of 2,4-dihydroxybenzaldehyde (**20**) (1.50 g, 10.9 mmol) in AcOH (7.5 mL) was added slowly ICl (17.32 mL, 17.31 mmol) in CH_2Cl_2 under nitrogen atmosphere and

stirred for 5 h at rt. The reaction was quenched with sodium thiosulfate-H_2O (4:1) resulted solid product and the solid was filtered and washed with water resulted the product as brown solid. Yield: 2.87 g (51%); R_f 0.63 (EtOAc/hexane = 1/2); mp 167-170 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.67 (1H, s), 7.95 (1H, s), 6.36 (1H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 193.02, 157.65, 156.77, 143.92, 117.75, 102.05, 70.61.

6-Hydroxy-2-(3-hydroxy-5-(*tert*-butyldimethylsilyl)oxyphenyl)benzofuran-5carbaldehyde (5a). To a stirred solution of **4a** (0.1 g, 0.37 mmol) in DMF (2 mL) were added slowly $PdCl_2(PPh_3)_2$ (13 mg, 0.02 mmol), CuI (1.4 mg, 0.01 mmol), TEA (0.10 mL, 0.76 mmol) and ((5-ethynyl-1,3-phenylene)bis(oxy))bis(tert-butyldimethylsilane) **7** (0.52 g, 3.22 mmol) under nitrogen atmosphere and stirred for 2 d at 70 °C. The reaction mixture was dissolved with ether, filtered with Celite® 545, concentrated *in vacuo* at 80 °C, extracted with ether, washed with brine, dried over $MgSO_4$. The crude product was recrystallized from acetone-hexane and brown solid. Yield: 73 mg (50%); R_f 0.38 (EtOAc/hexane = 1/3); mp 246-248 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 10.99 (1H, s), 9.79 (1H, s), 7.78 (1H, s), 7.03 (1H, s), 6.83 (1H, s), 6.68 (2H, d, J = 1.8 Hz), 6.17 (1H, t, J = 1.8 Hz), 0.78 (18H, s), 0.03 (12H, s); ^{13}C NMR (75 MHz, acetone-d_6) δ 196.88, 160.36, 159.67, 157.40, 156.92, 131.60, 127.80, 123.05, 118.85, 108.24, 108.10, 105.37, 101.92, 98.87, 30.09, 25.52, –4.70.

6-Hydroxy-2-(3,5-dihydroxyphenyl)benzofuran-5carbaldehyde (21); Moracin Y. To a stirred solution of **5a** (34 mg, 0.07 mmol) in THF (1 mL) was added slowly TBAF (0.1 mL, 0.28 mmol) under nitrogen atmosphere and was stirred for 5 h at rt. After completion of the reaction, solvent was removed *in vacuo*, Acetone was added to the crude and filtered the solid TBAF. The filtrate was concentrated and addition of ether-MeOH to the crude offered the solid product moracin Y as yellow solid.[1a] Yield: 17 mg (90%); R_f 0.32 (EtOAc/hexane = 1/1); mp 235-238 °C; ^{1}H NMR (300 MHz, methanol-d_4) δ 10.23 (1H, s), 7.72 (1H, s), 6.85 (1H, s), 6.73 (1H, s), 6.65 (2H, d, J = 2.1 Hz), 6.19 (1H, t, J = 2.1 Hz); ^{13}C NMR (75 MHz, Methanol-d_4) δ 193.70, 169.51, 161.71, 159.56, 155.79, 131.88, 122.12, 121.50, 120.03, 103.21, 102.71, 101.08, 100.62. HRMS (EI) calcd for $C_{15}H_{10}O_5$ M^+ 270.0528, found 270.0529.

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