Highly Effective Total Synthesis of Benzofuran Natural Product Egonol

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Benzo[*b*]furan natural products isolated from the Styracaceae family such as *Styrax japonicum*,[1] *S. formosanus*,[2] *S. obassia*,[3] *S. macranthus*[4] and *S. officinalis*[5] show variety of biological activities including insecticidal, fungicidal, antimicrobial, antisweet, antiproliferative, cytotoxic and antioxidant properties.[6] Egonol, 5-(3-hydroxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran, was first isolated in 1915 from the seed oil of *Styrax japonicum*[1] and first synthesized by Kawai[7] condensing an *o*-hydroxybenzaldehyde with an α-chlorophenylacetic acid and known to be an effective pyrethrum synergist.[8] A number of total synthesis of egonol have been reported by using Sonogashira coupling,[9] Lewis acid induced dehydrocyclization,[10] dienylacetylene coupling with carbene complex,[11] and palladium-catalyzed cross-coupling reaction.[12] We report herein the most effective total synthesis of egonol (**1**, Figure 1) in 5 steps with 74% overall yield from vanillin by using Sonogashira coupling reaction.

Vanillin (**2**) reacted with I_2/Ag_2SO_4 in EtOH at room temperature to give iodovanillin **3** in 80% yield (Scheme 1). Sonogashira coupling of **3** with 3,4-methylenedioxyphenylacetylene (**4**), which was easily prepared from piperonal *via* Colvin rearrangement,[13] by using $Pd(PPh_3)_4/CuI/Et_3N$ in DMF yielded benzofuran **5** in 95% yield through successive coupling and cyclization in one-step. Sonogashira coupling reactions were very sensitive to the haloaryl substituents as shown in Scheme 2. Bromovanillin **8** was not reactive with acetylene **4** in Sonogashira coupling reaction, and Wittig coupled bromide **9** and iodide **10** were also not reactive with **4** in coupling reaction, which indicated that the reaction sequences were very important in egonol synthesis and Sonogashira coupling should be done before Wittig reaction. Wittig reaction of **5** with (carbethoxymethylene)triphenylphosphorane produced carbethoxyethenylbenzofuran **6** in 99% yield, which was reduced to **7** in 99% yield by H_2/Pd-C. Direct reduction of conjugated ester **6** to egonol **1** was performed by using $LiAlH_4$ or $LiBH_4$ as shown in Scheme 3. Partially reduced alcohol **11** with egonol and some other by-products were formed in both cases and it was not easy to separate egonol from the alcohol **11** by column chromatography. Finally, reduction of ester **7** with DIBAL-H gave egonol (**1**) in 99% yield.

Khan isolated a new egonol derivative, 5-(3-propanoyloxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (**12**), from *Styrax obassia* (Scheme 4).[14] The newly found benzofuran **12** was easily prepared from our synthetic egonol **1** by esterification with propanoic acid using DCC in 99% yield and confirmed by NMR data with literature.

In conclusion, the 5 steps reaction procedures including iodination, Sonogashira coupling, Wittig reaction, hydrogenation and metal hydride reduction produced egonol in

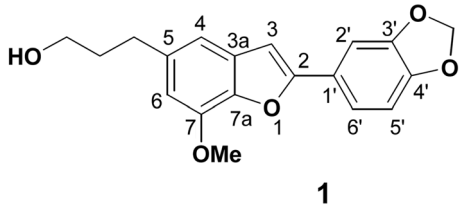
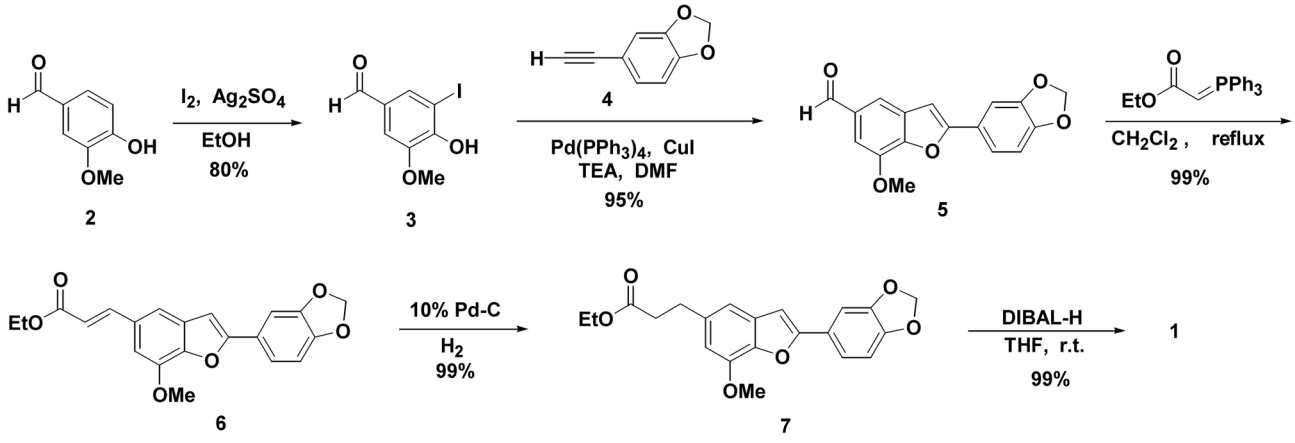
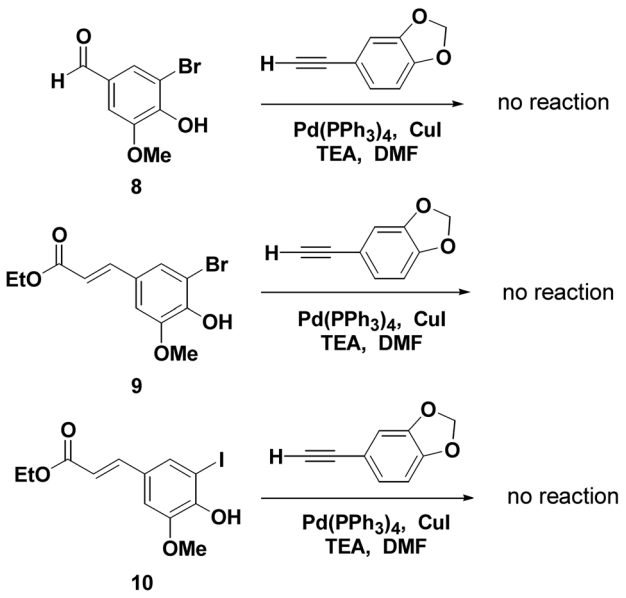


Figure 1. Chemical structure of egonol.



Scheme 1



Scheme 2

74% overall yield from vanillin and the new benzofuran egonol derivative **12** was synthesized using this methodology for biological tests. This synthetic method provides the most effective egonol total synthesis in our best knowledge.

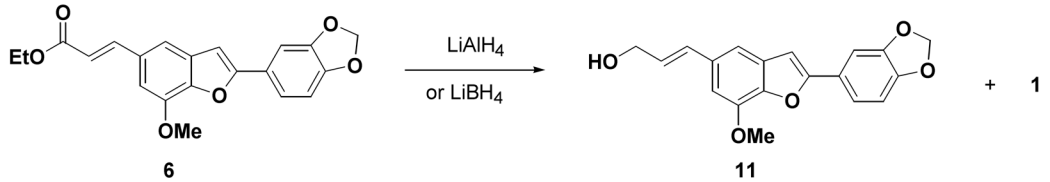
Experimental Section

All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at Varian Mercury TM300 MHz FT-NMR for ^{1}H and 75 MHz for ^{13}C, with the chemical shifts (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. Flash chromatography was carried out using silica gel Merck 60 (230-400 mesh). Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed silica gel plates with visualization by UV light (254 nm) or by treatment with *p*-anisaldehyde. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected.

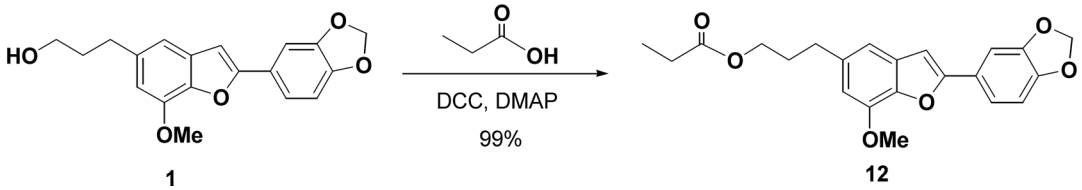
4-Hydroxy-3-iodo-5-methoxybenzaldehyde (3). To a solution of vanillin (**2**) (1.00 g, 6.57 mmol) in EtOH (50 mL) under nitrogen atmosphere was added I_2 (2.08 g, 7.89 mmol) with silver sulfate (2.46 g, 7.89 mmol) and stirred for 1 h at rt. Solvent was removed by evaporation and the organic product was extracted with CH_2Cl_2, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:2) to give the white solid **3** (1.47 g, 80%). R_f 0.34 (EtOAc:Hexane = 1:3); mp 179-182 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.97 (3H, s, OMe), 6.69 (1H, s, OH), 7.36 (1H, d, J = 1.5 Hz, C6-H), 7.81 (1H, d, J = 1.5 Hz, C2-H), 9.75 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.8 (OMe), 80.7 (C3-I), 108.8 (C6), 131.2 (C1), 136.4 (C2), 146.6 (C5), 151.5 (C4), 189.7 (C=O).

5-Formyl-7-methoxy-2-(3,4-methylenedioxyphenyl)-benzofuran (5). To a solution of iodovanillin (**3**) (0.06 g, 0.22 mmol), $Pd(PPh_3)_4$ (0.014 g, 0.02 mmol), 3,4-methylenedioxyphenylacetylene (**4**, 0.05 g, 0.32 mmol) and CuI (0.001 g, 0.004 mmol) in DMF (3 mL) under nitrogen atmosphere was added Et_3N (0.03 mL, 0.22 mmol) and stirred for 15 h at rt. The organic product was extracted with $CHCl_3$, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:4) to give the yellow solid **5** (0.04 g, 95%). R_f 0.28 (EtOAc:Hexane = 1:3); mp 176-178 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (3H, s, OMe), 6.02 (2H, s, O-CH_2-O), 6.88 (1H, d, J = 8.4 Hz, C5'-H), 6.93 (1H, s, C3-H), 7.31 (1H, d, J = 1.8 Hz, C2'-H), 7.33 (1H, br d, C6-H), 7.41 (1H, dd, J = 1.8, 8.0 Hz, C6'-H), 7.66 (1H, d, J = 0.6 Hz, C4-H), 9.97 (1H, s, CHO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.5 (OMe), 100.9 (C3), 101.7 (O-CH_2-O), 104.6 (C2'), 105.8 (C6), 108.2 (C5), 109.0 (C5'), 119.3 (C4), 119.8 (C6'), 123.9 (C1'), 131.1 (C3a), 133.6 (C7a), 146.1 (C7), 148.4 (C4'), 148.8 (C3'), 157.8 (C2), 191.9 (CHO).

5-Carbethoxyethenyl-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (6). To a solution of **5** (0.05 g, 0.17 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere was added (carbethoxymethylene)triphenylphosphorane (0.09 g, 0.25 mmol) and refluxed for 7 h. The organic product was extracted with CH_2Cl_2, washed with brine, dried and con-



Scheme 3



Scheme 4

centrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:3) to give the white solid **6** (0.062 g, 99%). R_f 0.44 (EtOAc:Hexane = 1:3); mp 160-162 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (3H, t, J = 7.2 Hz, CH_3), 4.05 (3H, s, OMe), 4.27 (2H, q, J = 7.2 Hz, OCH_2), 6.01 (2H, s, O-CH_2-O), 6.39 (1H, d, J = 15.6 Hz, trans ethenyl C1-H), 6.83 (1H, s, C6-H), 6.86 (1H, d, J = 8.4 Hz, C5'-H), 6.94 (1H, br s, C3-H), 7.30 (2H, br s, C2'-H, C4-H), 7.39 (1H, dd, J = 1.5, 8.7 Hz, C6'-H), 7.73 (1H, d, J = 15.9 Hz, trans ethenyl C2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8 (CH_3), 56.4 (OCH_3), 60.7 (OCH_2), 100.7 (C3), 101.6 (O-CH_2-O), 105.5 (C2'), 105.8 (C6), 108.9 (C5'), 114.7 (C4), 117.1 (ethenyl C1), 119.6 (C6'), 124.3 (C1'), 128.8 (C5), 130.8 (C3a), 131.5 (C7a), 145.3 (C7), 145.5 (ethenyl C2), 148.3 (C4'), 148.5 (C3'), 157.1 (C2), 167.3 (C=O).

5-Carbethoxyethyl-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (7). To a solution of **6** (0.07 g, 1.19 mmol) in MeOH (1 mL) under hydrogen balloon atmosphere was added Pd-C (0.09 g, 10 wt% dry basis on activated carbon) and stirred for 3 h at rt. The organic product was filterd and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:3) to give the white solid **7** (0.07 g, 99%). R_f 0.60 (EtOAc:Hexane = 1:2); mp 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, J = 7.2 Hz, CH_3), 2.66 (2H, t, J = 8.1 Hz, CH_2), 3.01 (2H, t, J = 8.1 Hz, CH_2), 4.02 (3H, s, OCH_3), 4.13 (2H, q, J = 7.1 Hz, OCH_2), 6.00 (2H, s, O-CH_2-O), 6.62 (1H, br s, C6-H), 6.78 (1H, s, C3-H), 6.85 (1H, d, J = 8.4 Hz, C5'-H), 6.96 (1H, br s, C4-H), 7.30 (1H, d, J = 1.8 Hz, C2'-H), 7.38 (1H, dd, J = 8.1, 1.5 Hz, C6'-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0 (CH_3), 31.1 (CH_2), 36.3 (CH_2), 55.8 (OCH_3), 60.1 (OCH_2), 100.0 (C3), 100.9 (O-CH_2-O), 105.1 (C2'), 106.8 (C6), 108.2 (C5'), 111.8 (C4), 118.8 (C6'), 124.2 (C1'), 130.6 (C3a), 135.9 (x2, C5, C7a), 144.3 (C7), 147.5 (C4'), 147.6 (C3'), 155.6 (C2), 172.5 (C=O).

Egonol (1). To a solution of **7** (0.040 g, 0.11 mmol) in THF (4 mL) under nitrogen atmosphere was added DIBAL-H (1.0 M, 0.25 mL) and stirred for 1.5 h at rt. The reaction was quenched by addition of aqueous Na_2CO_3 solution. The organic product was extracted with CH_2Cl_2, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (MeOH:$CHCl_3$ = 1:15) to give the yellow solid **1** (0.035 g, 99%). R_f 0.22 (EtOAc:Hexane = 1:1); mp 100-103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.94 (2H, quintet, J = 6.7 Hz, propyl C2-H), 2.77 (2H, t, J = 7.5 Hz, propyl C1-H), 3.71 (2H, t, J = 6.5 Hz, CH_2OH), 4.02 (3H, s, OCH_3), 5.99 (2H, s, O-CH_2-O), 6.62 (1H, br s, C6-H), 6.77 (1H, s, C3-H), 6.85 (1H, d, J = 7.8 Hz, C5'-H), 6.95 (1H, br s, C4-H), 7.31 (1H, d, J = 1.5 Hz, C2'-H), 7.38 (1H, dd, J = 8.2, 1.5 Hz, C6'-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8 (propyl C2), 35.1 (propyl C1), 56.5 (OCH_3), 62.6 (CH_2OH), 100.6 (C3), 101.4 (O-CH_2-O), 101.5 (C2'), 107.6 (C6), 108.8 (C5'), 112.5 (C4), 119.4 (C6'), 124.9 (C1'), 131.2 (C3a), 137.7 (C5), 142.6 (C7a), 144.9 (C7), 148.1 (C4'), 148.2 (C3'), 156.2 (C2).

5-(3-Propanoyloxypropyl)-7-methoxy-2-(3,4-methylenedioxyphenyl)benzofuran (12). To a solution of **1** (0.010 g, 0.031 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere was added propionic acid (0.045 g, 0.061 mmol), *N,N*-dicyclohexylcarbodiimide (0.015 g, 0.077 mmol), dimethylaminopyridine (0.001 g, 0.0077 mmol) and refluxed for 10 h. The reaction mixture was filtered using celite filter and the organic product was extracted with CH_2Cl_2, washed with brine, dried and concentrated to give the solid. The solid was chromatographed (EtOAc:Hexane = 1:3) to give the white solid **12** (0.011 g, 99%). R_f 0.63 (EtOAc:Hexane = 1:2); mp 78-81 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16 (3H, t, J = 7.8 Hz, Me), 1.99 (2H, quintet, J = 6.6 Hz, propyl C2-H), 2.34 (2H, q, J = 7.5 Hz, CH_2Me), 2.74 (2H, t, J = 7.5 Hz, propyl C1-H), 4.02 (3H, s, OCH_3), 4.12 (2H, t, J = 6.6 Hz, propyl C3-H), 5.99 (2H, s, O-CH_2-O), 6.59 (1H, d, J = 1.2 Hz, C6-H), 6.77 (1H, s, C3-H), 6.85 (1H, d, J = 7.8 Hz, C5'-H), 6.94 (1H, br s, C4-H), 7.30 (1H, d, J = 1.5 Hz, C2'-H), 7.38 (1H, dd, J = 8.1, 1.5 Hz, C6'-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.6 (Me), 28.0 (propyl C2), 31.1 (propyl C1), 32.9 ($COCH_2$), 56.5 (OCH_3), 64.0 (propyl C3), 100.6 (C3), 101.5 (O-CH_2-O), 105.8 (C2'), 107.6 (C6), 108.8 (C5'), 112.5 (C4), 119.4 (C6'), 124.9 (C1'), 131.2 (C3a), 137.1 (C5), 142.7 (C7a), 144.9 (C7), 148.1 (C4'), 148.2 (C3'), 156.3 (C2), 174.7 (C=O).

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