# High yield total syntheses of XH-14 derivatives using Sonogashira coupling reaction

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**Abstract**
A high yielding synthetic route to XH-14 derivatives is described using a Sonogashira reaction as a key step. Introduction of iodine into the structure and optimization of the synthetic sequence were essential for the successful syntheses of XH-14 derivatives. The nine-step reaction sequence gave **2** and **3** in 30% and 55% overall yields, respectively.

**Keywords:** XH-14, benzo[*b*]furan, Colvin rearrangement, Sonogashira coupling, iodocyclization.

## Introduction

XH-14 is known as a potent ingredient isolated from the root of *Salvia miltiorrhiza* Bunge (Chinese name 'Danshen'). Aqueous extracts of the root have been used widely in China for the treatment of cardiovascular diseases such as acute myocardiac infarction and angina pectoris.[1] It was the first reported non-nucleoside-type potent adenosine $A_1$ agonist and showed a high potency ($IC_{50}$ = 17 nM) in the bovine adenosine $A_1$ radioligand binding assay.[2] Chemically pure XH-14 (1 mg/kg) was isolated from the dried root of Danshen and structurally identified as a benzo[*b*]furan lignan.[3] Many biologically active benzo[*b*]furan compounds are found in nature.[4] The limited supply of XH-14 has prevented the diverse characterization of its biological activities. Several syntheses of XH-14 and its derivatives have been reported including Sonogashira coupling methodology.[5] However, emphasis was given only to the synthesis of C-2 and C-3 substituted analogs. Due to its high selectivity for the $A_1$ receptor subtype, the preparation of analogs for SAR tests was clearly of interest.[6] In order to prove the role of other substituents on XH-14 in biological selectivity, the modifications on benzofuran benzene unit were required. We report herein the convenient total syntheses of 6-methoxy- (**2**) and 5-

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methoxy-XH-14 (**3**) derivatives in nine steps from 2,4- and 2,5-dimethoxybenzaldehyde respectively (Figure 1).

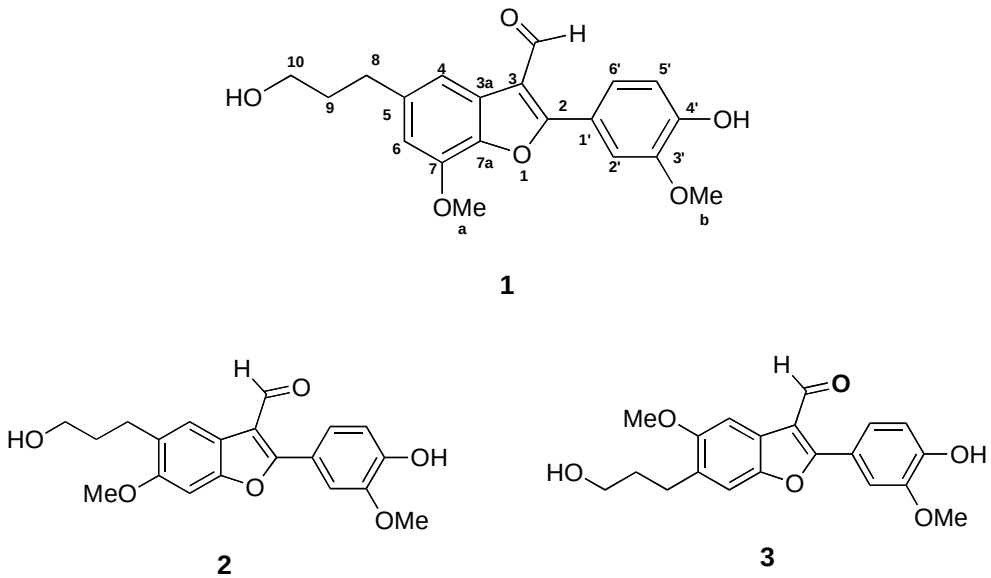



**Figure 1.** Structures of XH-14 (**1**), 6-methoxy- (**2**) and 5-methoxy-XH-14 (**3**) derivatives.

## Results and Discussion

In the present work, a key feature is the introduction of iodine into the dimethoxy compounds **8** and **18** as well as the optimization of the reaction sequence. The Wittig reaction of 2,4-dimethoxybenzaldehyde (**4**) with (carbethoxymethylene)triphenylphosphorane in methylene chloride under reflux produced conjugated ester **5** (*E:Z*=19:1) in 99% yield which was then reduced to **6** by hydrogenation (Scheme 1). Reduction of ester **6** with $LiAlH_4$ yielded alcohol **7** in 98% yield which was then benzylated to give **8** in 86% yield. The regioselective halogenation of **8** was essential for the Sonogashira reaction to give the desired product **10**.[7] Fortunately, the desired 5-position where the halogen needs to be introduced is *ortho* and *para* to both methoxy groups; hence, 5-bromo compound **9a** (X=Br) was easily obtained using Chern's method.[5e] However, the bromobenzene **9a** did not react in Sonogashira coupling with acetylene **10**.[8] The introduction of iodine was achieved using $I_2/Ag_2SO_4$ in EtOH to give **9b** in 88% yield. The earlier introduction of iodine in the reaction sequence (as shown in Scheme 2) was found to be unsuccessful.

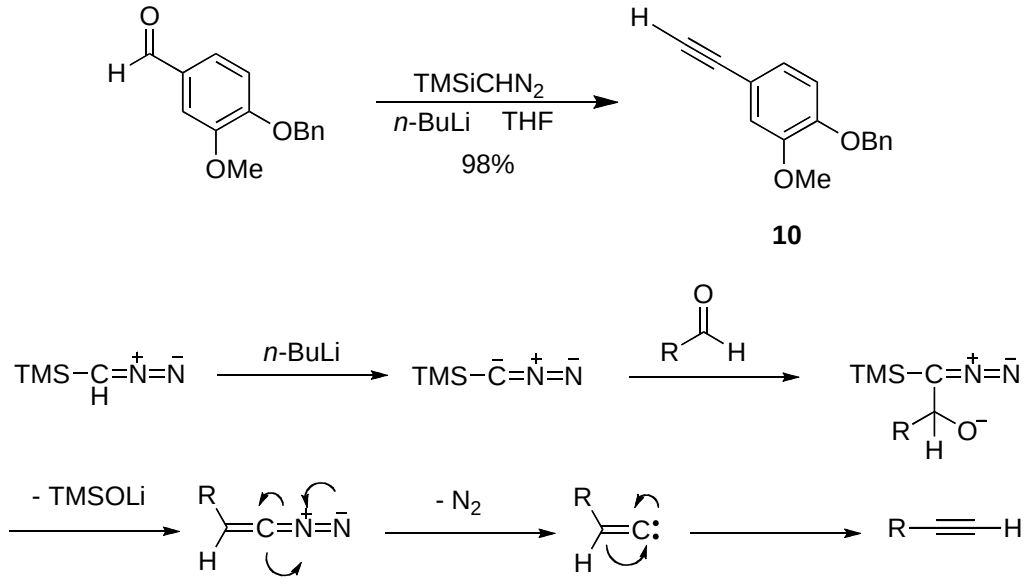
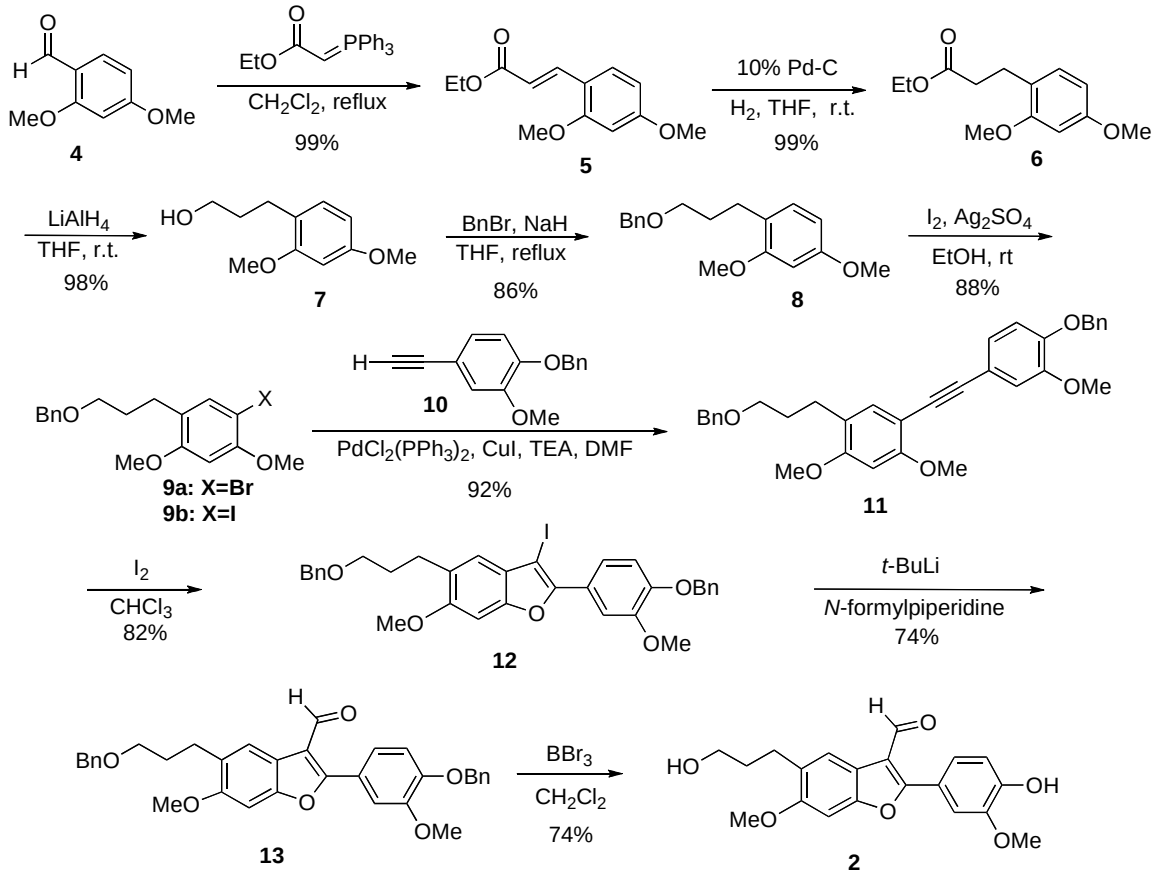
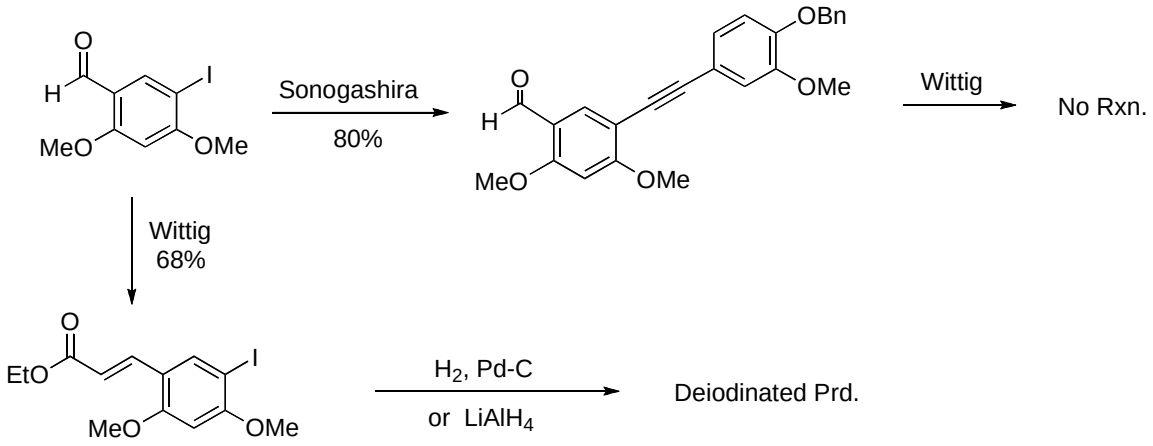



**Figure 2.** Colvin rearrangement of benzylated vanillin and reaction mechanism.

Compound **11** was obtained *via* conventional Sonogashira coupling[10] of iodobenzene **9b** with acetylene **10**, which was easily prepared from benzylated vanillin with trimethylsilyldiazomethane by Colvin rearrangement[9] (as shown in Figure 2). Iodine-induced cyclization of **11** produced 3-iodobenzofuran **12** in 82% yield.[7a] Iodobenzofuran **12** was easily converted into formyl-benzofuran **13** by reaction with *t*-BuLi then *N*-formylpiperidine in toluene (74%). Finally, careful debenzylation of **13** by $BBr_3$ at -78 $^oC$ gave 2-(4-hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-6methoxybenzofuran-3-carbaldehyde (**2**) in 74% yield.[5e]




**Scheme 1.** Synthesis of 6-methoxy-XH-14 from 2,4-dimethoxybenzaldehyde.

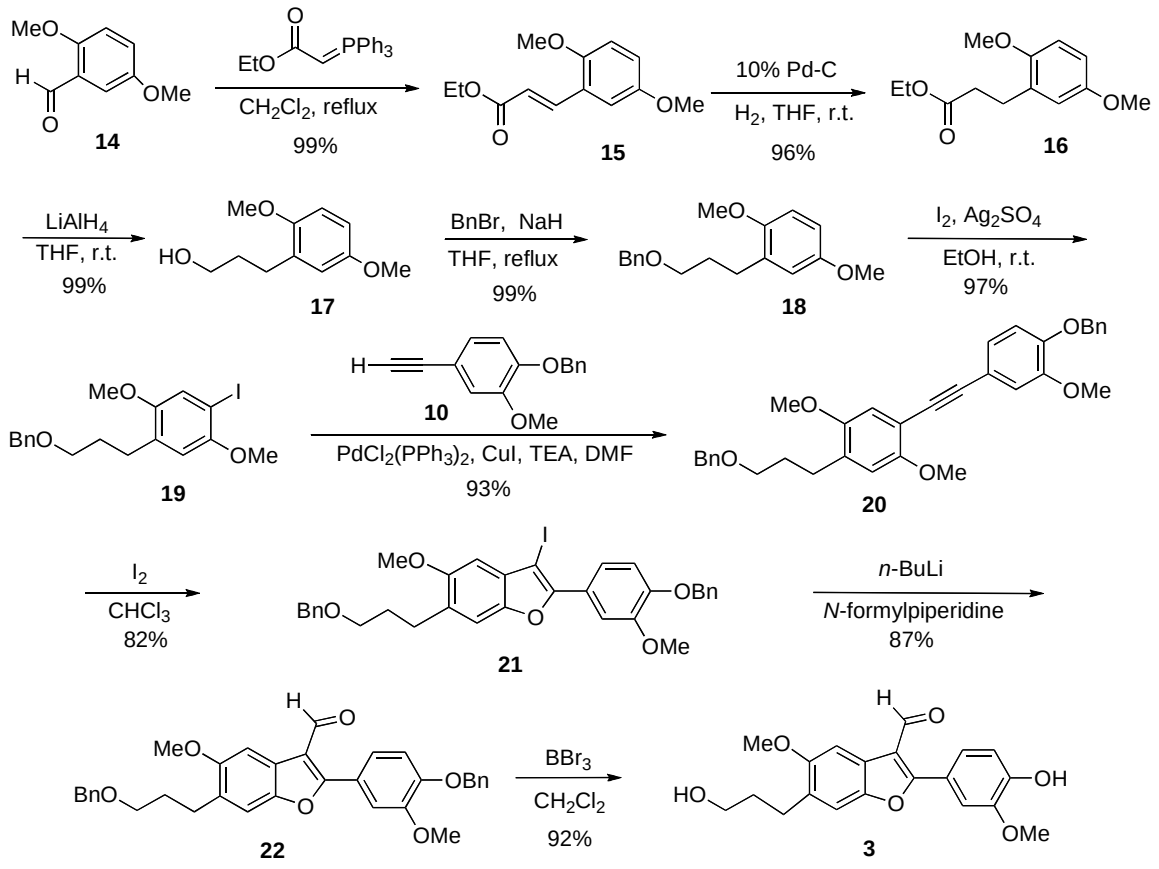



**Scheme 2.** Results of different reaction sequences.

5-Methoxy-XH-14 derivative (**3**) was easily prepared from 2,5-dimethoxybenzaldehyde (**14**) in nine steps using the same procedure as for 6-methoxy-XH-14 (Scheme 3). The Wittig reaction of **14** produced a 99% yield of conjugated ester **15** (*E:Z*=24:1) which was then converted to ester

**16** by hydrogenation in 96% yield. Reduction of **16** with $LiAlH_4$ yielded alcohol **17** followed by benzylation gave **18** in 99% yield. The regioselective iodination of **18** with $I_2/Ag_2SO_4$ in EtOH gave a 97% yield of iodobenzene **19** then Sonogashira coupling gave **20** in 93% yield. Iodine-induced cyclization of **20** produced 3-iodobenzofuran **21** in 82% yield, which was easily converted into formylbenzofuran **22** by reaction with *n*-BuLi then *N*-formylpiperidine (87%). Finally, careful debenzylation of **22** by $BBr_3$ gave 2-(4-hydroxy-3-methoxyphenyl)-6-(3-hydroxypropyl)-5-methoxybenzofuran-3-carbaldehyde (**3**) in 92% yield.

The $^1$H-NMR chemical shifts for the aromatic protons of XH-14 derivatives (**1-3**) enabled easy differentiation the various structural possibilities (Figure 3). The H-4 chemical shift of XH-14 at δ 7.50 (d, *J*=1.2 Hz) was compared to the H-4 chemical shifts of 6-methoxy (**2**) at δ 7.88 (s) and 5-methoxy (**3**) at δ 7.32 (s), and the H-6 chemical shift of XH-14 at δ 6.79 (d, *J*=1.2 Hz) was compared to the H-7 chemical shifts of 6-methoxy (**2**) at δ 7.18 (s) and 5-methoxy (**3**) at δ 7.58 (s).




**Scheme 3.** Synthesis of 5-methoxy-*apo*-XH-14 from 2,5-dimethoxybenzaldehyde.

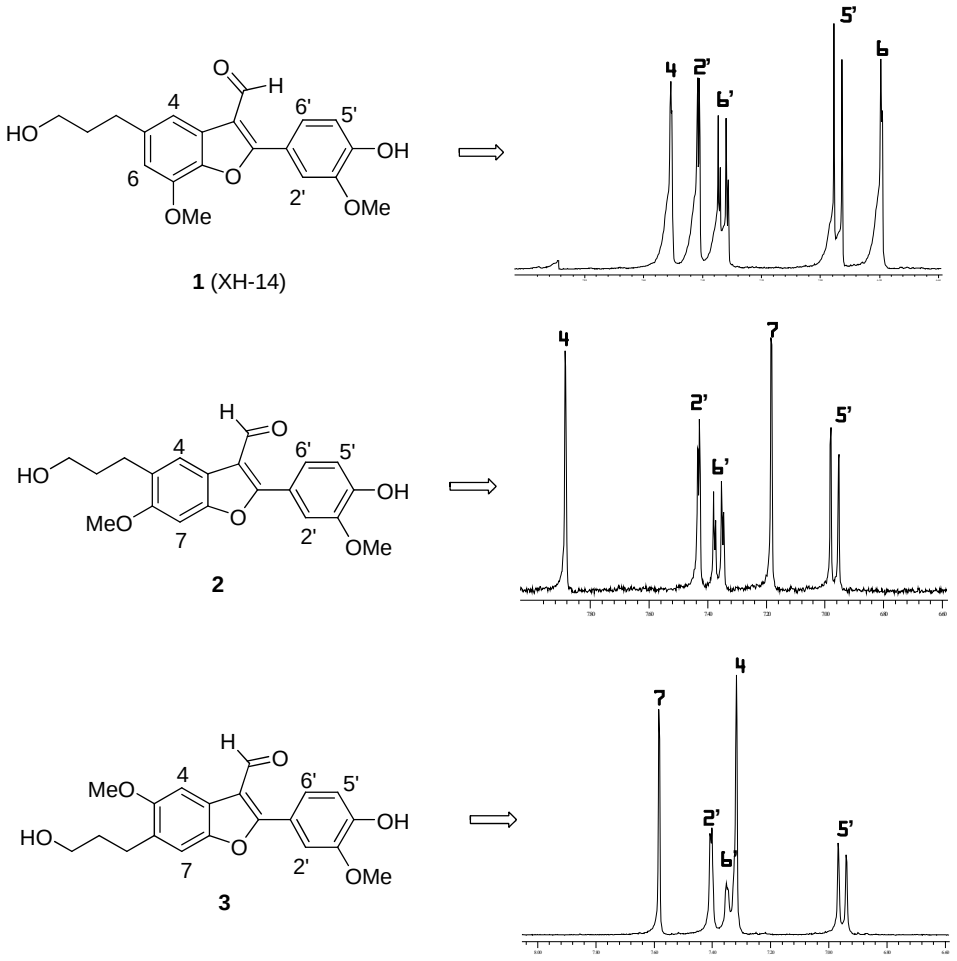



**Figure 3.** Comparison of $^{1}$H NMR chemical shifts for aromatic protons of XH-14 and derivatives.

## Conclusions

In conclusion, nine-step sequences produced 6-methoxy-XH-14 (**2**) and 5-methoxy-XH-14 (**3**) in 30% and 55% overall yields respectively. These compounds are now under investigation for their biological activities compared to XH-14.

## Experimental Section

**General Procedures.** All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded on a Varian Mercury-300 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 are uncorrected.

**1-(2-Carbethoxyethenyl)-2,4-dimethoxybenzene (5).** To a solution of 2,4-dimethoxybenzaldehyde (**4**) (1.00 g, 6.02 mmol) in $CH_2Cl_2$ (100 mL) was added (carbethoxymethylene)triphenylphosphorane (3.31 g, 9.03 mmol) and the mixture was refluxed for 3 days. Solvent was removed by evaporation and the organic phase was extracted with $CH_2Cl_2$, washed with brine, dried and concentrated to give a crude solid. The solid was purified by chromatography (EtOAc:hexane=1:4) to give the pure product as a white solid **5** (99%, *E:Z*=19:1). ***E*-5:** $R_f$ 0.53 (EtOAc:hexane=1:3); mp 50-52 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.33 (3H, t, *J*=7.2 Hz), 3.83 (3H, s, OMe), 3.86 (3H, s, OMe), 4.24 (2H, q, *J*=6.9 Hz, $OCH_2$), 6.42 (1H, d, *J*=15.6 Hz, *trans* ethenyl C1-H), 6.44 (1H, s, C3-H), 6.49 (1H, d, *J*=8.4 Hz, C5-H), 7.43 (1H, d, *J*=8.7 Hz, C6-H), 7.89 (1H, d, *J*=16.0 Hz, *trans* ethenyl C2-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.8 ($CH_3$), 55.7 (OMe), 55.8 (OMe), 60.5 ($OCH_2$), 98.6 (C3), 105.3 (C5), 116.3 (*trans* ethenyl C1), 116.8 (C1), 130.6 (C6), 140.1 (*trans* ethenyl C2), 159.9 (C2), 162.7 (C4), 168.1 (C=O); Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83% Found: C, 65.98, H, 6.65% ***Z*-5:** $R_f$ 0.59 (EtOAc:hexane=1:3); colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, *J*=7.2 Hz), 3.81 (3H, s, OMe), 3.82 (3H, s, OMe), 4.15 (2H, q, *J*=7.2 Hz, $OCH_2$), 5.85 (1H, d, *J*=12.6 Hz, *cis* ethenyl C1-H), 6.41 (1H, s, C3-H), 6.46 (1H, d, *J*=8.4 Hz, C5-H), 7.12 (1H, d, *J*=12.3 Hz, *cis* ethenyl C2-H), 7.70 (1H, d, *J*=8.7 Hz, C6-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.6 ($CH_3$), 55.7 (OMe), 55.8 (OMe), 60.3 ($OCH_2$), 98.0 (C3), 104.1 (C5), 116.9 (trans ethenyl C1), 117.8 (C1), 132.2 (C6), 138.9 (trans ethenyl C2), 158.8 (C2), 162.0 (C4), 166.7 (C=O); Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83% Found: C, 66.05, H, 6.61%

**1-(2-Carbethoxyethyl)-2,4-dimethoxybenzene (6).** To a solution **3b** (1.30 g, 5.50 mmol) in THF (30 mL) was added Pd/C (0.41 g, 10 wt% dry basis on activated carbon) and the mixture stirred for 10 h at rt under hydrogen atmosphere with a hydrogen balloon. The reaction mixture was filtered through Celite, the solvent was removed by evaporation and the residue was extracted with $CH_2Cl_2$, washed with brine, dried and concentrated to give an oil. The crude residue was purified by chromatography (EtOAc:hexane=1:4) to give a colorless oil **6** (1.30 g, 99%). $R_f$ 0.65 (EtOAc:hexane=1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.24 (3H, t, *J*=7.2 Hz), 2.55 (2H, t, *J*=7.5 Hz, ethyl C1-H), 2.86 (2H, t, *J*=7.5 Hz, ethyl C2-H), 3.78 (3H, s, OMe), 3.79 (3H, s, OMe), 4.11 (2H, q, *J*=6.9 Hz, $OCH_2$), 6.39 (1H, d, *J*=8.4 Hz, C5-H), 6.42 (1H, s, C3-H), 7.03 (1H, d, *J*=8.4 Hz, C6-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.6 ($CH_3$), 25.9 (ethyl C1), 34.9 (ethyl C-2), 55.5 (OMe), 55.7 (OMe), 60.5 ($OCH_2$), 98.7 (C3), 103.9 (C5), 121.5 (C1), 130.3 (C6), 158.5 (C4), 159.6 (C2), 173.6 (C=O); Anal. Calcd for $C_{13}H_{18}O_4$ (238.28): C, 65.53; H, 7.61% Found: C, 65.37, H, 7.49%

**1-(3-Hydroxypropyl)-2,4 dimethoxybenzene (7)**. To a solution of $LiAlH_4$ (0.33 g, 8.22 mmol) in THF (20 mL) was slowly added **6** (1.30 g, 5.48 mmol) and the mixture stirred for 30 min at 0 ˚C. The reaction was quenched by addition of 1N NaOH solution and filtered using Celite. The solvent was removed by evaporation and the organic phase was extracted with EtOAc, washed with brine, dried and concentrated to give a crude liquid, which was purified by chromatography (EtOAc:hexane=1:2) to give a colorless liquid **7** (1.05 g, 98%). $R_f$ 0.22 (EtOAc:hexane=1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.80 (2H, m, propyl C2-H), 2.65 (2H, t, *J*=7.2 Hz, propyl C1-H), 3.58 (2H, t, *J*=6.3 Hz, propyl C3-H), 3.79 (3H, s), 3.80 (3H, s), 6.43 (1H, d, *J*=7.5 Hz, C5-H), 6.44 (1H, s, C3-H), 7.03 (1H, d, *J*=7.5 Hz, C6-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 25.6 (propyl C2), 33.5 (propyl C1), 55.7 (2x$OCH_3$), 62.2 ($OCH_2$), 98.7 (C3), 104.3 (C5), 122.4 (C1), 130.5 (C6), 158.3 (C4), 159.3 (C2); Anal. Calcd for $C_{11}H_{16}O_3$ (196.24): C, 67.32; H, 8.22% Found: C, 67.17, H, 8.07%

**1-(3-Benzyloxypropyl)-2,4-dimethoxybenzene (8).** To a solution of **7** (0.88 g, 4.49 mmol) in THF (20 mL) was added NaH (0.54 g, 13.5 mmol) with BnBr (0.80 mL, 6.73 mmol) and the mixture heated at reflux for 10 h. Then, the solution was filtered through Celite, the solvent was removed by evaporation and the organic product was extracted with $CH_2Cl_2$, washed with brine, dried and concentrated to give a crude liquid, which was purified by chromatography (EtOAc:hexane=1:7) to give the colorless liquid **8** (1.10 g, 86%). $R_f$ 0.67 (EtOAc:hexane=1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.87 (2H, m), 2.63 (2H, t, *J*=7.5 Hz), 3.48 (2H, t, *J*=6.6 Hz), 3.77 (3H, s), 3.78 (3H, s), 4.50 (2H, s, benzyl-$CH_2$), 6.39 (1H, d, *J*=8.1 Hz, C5-H), 6.42 (1H, s, C3-H), 6.99 (1H, d, *J*=7.8 Hz, C6-H), 7.24-7.34 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.6 (propyl C2), 30.2 (propyl C1), 55.5 ($OCH_3$), 55.7 ($OCH_3$), 70.3 ($OCH_2$), 73.1 ($OCH_2$Ph), 98.7 (C3), 103.8 (C5), 122.9 (C1), 127.6 (benzyl C4), 127.9 (x2), 128.5 (x2), 130.3 (C6), 138.9 (benzyl C1), 158.5 (C4), 159.2 (C2); Anal. Calcd for $C_{18}H_{22}O_3$ (286.37): C, 75.50; H, 7.74. Found: C, 75.38, H, 7.65.

**1-(3-Benzyloxypropyl)-5-iodo-2,4-dimethoxybenzene (9b).** To a solution of **8** (0.77 g, 2.69 mmol) in EtOH (40 mL) was added $I_2$ (0.82 g, 3.22 mmol) and silver sulfate (1.01g, 3.22 mmol) and stirred for 2 h at rt. Solvent was removed by evaporation and the organic residue was extracted with $CH_2Cl_2$, washed with brine, dried and concentrated to give the solid. The solid was purified by chromatography (EtOAc:hexane=1:4) to give the white solid **9** (0.98 g, 88%). $R_f$ 0.58 (EtOAc:hexane=1:3); mp 57-59 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.85 (2H, m), 2.59 (2H, t, *J*=7.5 Hz), 3.46 (2H, t, *J*=6.6 Hz), 3.80 (3H, s), 3.86 (3H, s), 4.49 (2H, s), 6.38 (1H, s, C3-H), 7.24-7.35 (5H, m), 7.45 (1H, s, C6-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.3, 30.1, 55.8, 56.8, 70.1, 73.2, 74.0 (C5-I), 96.0 (C3), 125.1 (C1), 127.7, 127.9 (x2), 128.6 (x2), 138.8, 139.5 (C6), 157.5 (C2), 159.0 (C4); Anal. Calcd for $C_{18}H_{21}IO_3$ (412.26): C, 52.44; H, 5.13; I, 30.78% Found: C, 52.28, H, 5.06; I, 30.53%

**4-Benzyloxy-3-methoxyphenylacetylene (10).** To a stirred mixture of trimethylsilyldiazomethane (2 M solution in dichloromethane, 6 mL) at -78 ˚C in THF (45 mL) was added *n*-BuLi (5.1 mL, 1.6 M in hexane) and the mixture left for 0.5 h. 4-Benzyloxy-3-methoxybenzaldehyde (3.00 g, 12.4 mmol) in THF (150 mL) was added and the mixture stirred

for 3 h at the same temperature. The mixture was then quenched with saturated $NH_4Cl$, the organic phase was extracted with diethyl ether, washed with brine, dried and concentrated to give a solid. The solid was purified by chromatography (EtOAc:hexane=1:7) to give **10** as a yellow solid (2.90 g, 99%). $R_f$ 0.63 (EtOAc:hexane=1:3); mp 82-84 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 2.99 (1H, s, acetylene), 3.87 (3H, s, OMe), 5.15 (2H, s, $OCH_2$), 6.79 (1H, d, *J*=8.1 Hz), 7.01 (2H, d, *J*=8.1 Hz), 7.33-7.39 (5H, m, benzyl); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 56.3 (OMe), 71.1 ($OCH_2Ph$), 76.1 (acetylene), 84.0 (acetylene), 113.7 (C5), 114.9 (C1), 115.4 (C2), 125.5 (C6), 127.4, 128.2 (x2), 128.8 (x2), 136.8, 149.1 (C3), 149.3 (C4); Anal. Calcd for $C_{16}H_{14}O_2$ (238.28): C, 80.65; H, 5.92% Found: C, 80.29, H, 5.66%

**1-(4-Benzyloxy-3-methoxyphenyl)-2-[5-(3-benzyloxypropyl)-2,4-dimethoxyphenyl]acetylene (11).** To a solution of **9b** (0.23 g, 0.56 mmol), $PdCl_2(PPh_3)_2$ (0.019 g, 0.03 mmol), 4-benzyloxy-3-methoxyphenylacetylene **(10,** 0.20 g, 0.84 mmol) and CuI (0.005 g, 0.03 mmol) in DMF (3 mL) was added $Et_3N$ (0.16 mL, 1.12 mmol) and the mixture stirred for 48 h at rt. The reaction mixture was extracted with $CHCl_3$, washed with brine, dried and concentrated to give the crude oil. The crude product was purified by chromatography (EtOAc:hexane=1:4) to give a brownish oil **11** (0.27 g, 92%). $R_f$ 0.40 (EtOAc:hexane=1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.88 (2H, m), 2.62 (2H, t, J=7.5 Hz), 3.48 (2H, t, J=6.3 Hz), 3.84 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 4.50 (2H, s), 5.16 (2H, s), 6.40 (1H, s, C3'-H), 6.81 (1H, d, J=8.7 Hz, C4-H), 7.05 (1H, d, J=6.6 Hz, C5-H), 7.06 (1H, s, C1-H), 7.23-7.43 (10H, m), 7.41 (1H, C6'-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.4, 30.0, 55.7, 56.3, 56.4, 70.2, 71.1, 73.1, 84.8 (acetylene), 92.1 (acetylene), 95.1 (C3'), 103.9, 113.7, 114.9, 116.9, 122.7, 124.8, 127.5 (x2), 127.7, 127.9 (x2), 128.1, 128.5 (x2), 128.8 (x2), 134.5, 137.0, 138.8, 148.3, 149.2, 158.8, 159.7; Anal. Calcd for $C_{34}H_{34}O_5$ (522.63): C, 78.14; H, 6.56% Found: C, 77.96, H, 6.35%

**2-(4-Benzyloxy-3-methoxyphenyl)-5-(3-benzyloxypropyl)-3-iodo-6-methoxybenzofuran (12).** To a solution of **11** (1.20 g, 2.30 mmol) in $CHCl_3$ (50 mL) was slowly added $I_2$ (1.17 g, 4.59 mmol) at -20 ˚C and stirred for 5 h at rt. After addition of aqueous $NaHCO_3$, the reaction mixture was extracted with $CHCl_3$, washed with brine, dried and concentrated to give a solid. The crude solid was purified by chromatography (EtOAc:hexane=1:3) to give **12** as a white solid (1.20 g, 82%). $R_f$ 0.64 (EtOAc:hexane=1:3); mp 134-136 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.96 (2H, m), 2.81 (2H, t, *J*=7.5 Hz), 3.52 (2H, t, *J*=6.3 Hz), 3.85 (3H, s), 3.98 (3H, s), 4.52 (2H, s), 5.20 (2H, s), 6.94 (1H, d, *J*=8.7 Hz, C4'-H), 6.96 (1H, s, C7-H), 7.12 (1H, s), 7.23-7.44 (10H, m), 7.64 (1H, dd, *J*=1.8, 8.4 Hz, C5'-H), 7.68 (1H, br s); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.7, 30.3, 56.1, 56.4, 59.8, 70.3, 71.2, 73.2, 93.8, 110.7, 113.6, 120.1, 121.8, 123.8, 125.2, 127.5 (x2), 127.7, 127.9 (x2), 128.1, 128.2, 128.6 (x2), 128.8 (x2), 137.0, 138.9, 148.7, 149.4, 151.8, 153.2, 157.1; Anal. Calcd for $C_{33}H_{31}IO_5$ (634.50): C, 62.47; H, 4.92; I, 20.00% Found: C, 61.97, H, 4.65; I, 20.11%

**2-(4-Benzyloxy-3-methoxyphenyl)-5-(3-benzyloxypropyl)-6-methoxybenzofuran-3-carbaldehyde (13)**. To a solution of **12** (0.06 g, 0.09 mmol) in toluene (5 mL) was added *N*-formylpiperidine (0.10 mL, 0.95 mmol) and *t*-BuLi (0.56 mL, 1.7 M in pentane) and the mixture was stirred for 1 h at 0 ˚C. After the solution was neutralized with 1N HCl, the mixture was

extracted with diethyl ether, the extract washed with brine, dried and concentrated to give a solid. The solid was purified by chromatography (EtOAc:hexane=1:4) to give **13** as a yellow solid (0.037 g, 74%). $R_f$ 0.43 (EtOAc:hexane=1:3); mp 98-100 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.96 (2H, m), 2.81 (2H, t, *J*=7.5 Hz), 3.53 (2H, t, *J*= 6.3 Hz), 3.87 (3H, s), 3.99 (3H, s), 4.52 (2H, s), 5.25 (2H, s), 7.00 (1H, d, *J*= 6.9 Hz, C5'H), 7.01 (1H, s, C7-H), 7.24-7.47 (12H, m), 8.00 (1H, s, C4-H), 10.26 (1H, s, CHO); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.8, 30.3, 55.9, 56.5, 70.4, 71.2, 73.1, 93.7, 111.7, 113.7, 117.1, 118.1, 122.1, 122.4, 122.6, 127.4 (x2), 127.6, 127.9 (x2), 128.3, 128.5, 128.8 (x2), 128.9 (x2), 136.5, 138.9, 150.0, 150.6, 153.7, 157.1, 164.4, 186.9 (CHO); Anal. Calcd for $C_{34}H_{32}O_6$ (536.61): C, 76.10; H, 6.01% Found: C, 75.99, H, 5.89%

**2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-6-methoxybenzofuran-3-carbaldehyde (2).** To a solution of **13** (0.82 g, 0.15 mmol) in $CH_2Cl_2$ (20 mL) -78 ˚C was added $BBr_3$ (0.30 mL, 1.0 M in $CH_2Cl_2$) and the mixture stirred for 1 h. The organic phase was extracted with $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give a crude solid. The solid was purified by chromatography (MeOH:$CHCl_3$=1:15) to give the pure product as a yellow solid **2** (0.04 g, 74%). $R_f$ 0.48 (MeOH:$CHCl_3$=1:15); mp 200-202 ˚C; $^1$H NMR (300 MHz, $CD_3OD$) δ 1.84 (2H, m, propyl C2-H), 2.76 (2H, t, *J*=7.8 Hz, propyl C1-H), 3.59 (2H, t, *J*=6.6 Hz, $CH_2OH$), 3.90 (3H, s, C3'-$OCH_3$), 3.95 (3H, s, C6-$OCH_3$), 6.97 (1H, d, *J*=8.4 Hz, C5'-H), 7.18 (1H, s, C7-H), 7.36 (1H, dd, *J*=2.1, 8.4 Hz, C6'-H), 7.43 (1H, d, *J*=2.1 Hz, C2'-H), 7.88 (1H, s, C4-H), 10.20 (1H, s, CHO); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 27.4 (propyl C2), 33.7 (propyl C1), 56.5 (C3'-$OCH_3$), 56.6 (C6-$OCH_3$), 61.1 ($CH_2OH$), 95.1 (C7), 112.6 (C2'), 116.1 (C5'), 116.7 (C5), 118.1 (C4), 119.8 (C6'), 121.9 (C3a), 123.2 (C1'), 128.6 (C3), 148.7 (C4'), 150.3 (C3'), 153.4 (C6), 156.9 (C7a), 164.8 (C2), 187.4 (CHO). Anal. Calcd for $C_{20}H_{20}O_6$ (356.37): C, 67.41; H, 5.66%. Found: C, 67.05; H, 5.52%

**1-(2-Carbethoxyethenyl)-2,5-dimethoxybenzene (15).** To a solution of 2,5-dimethoxybenzaldehyde (**14**) (1.00 g, 6.02 mmol) in $CH_2Cl_2$ (100 mL) under a nitrogen atmosphere was added (carbethoxymethylene)triphenylphosphorane (3.31 g, 9.03 mmol) and the mixture heated at reflux for 3 days. Solvent was removed by evaporation and the organic product was extracted into $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give an oil which was purified by chromatography (EtOAc:hexane=1:4) to give the yellow oil **15** (1.40 g, 99%, *E:Z*=24:1). ***E*-15:** $R_f$ 0.58 (EtOAc:hexane=1:2); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.34 (3H, t, *J*=7.2 Hz), 3.78 (3H, s, OMe), 3.84 (3H, s, OMe), 4.26 (2H, q, *J*=7.2 Hz, $OCH_2$), 6.48 (1H, d, *J*=15.9 Hz, *trans* ethenyl C1-H), 6.82-6.92 (2H, m), 7.03 (1H, d, *J*=3.0 Hz), 7.95 (1H, d, *J*=16.2 Hz, *trans* ethenyl C2-H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.8 ($CH_3$), 56.1 (OMe), 56.4 (OMe), 60.7 ($OCH_2$), 112.6 (C4), 113.4 (C3), 117.2 (C6), 119.2 (*trans* ethenyl C2), 124.1 (C1), 139.9 (*trans* ethenyl C1), 152.9 (C2), 153.6 (C5), 167.5 (C=O); Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83% Found: C, 65.97, H, 6.51% ***Z*-15:** $R_f$ 0.64 (EtOAc:hexane=1:2); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.21 (3H, t, *J*=7.2 Hz), 3.81 (3H, s, OMe), 3.78 (3H, s, OMe), 4.14 (2H, q, *J*=7.2 Hz, $OCH_2$), 5.96 (1H, d, *J*=12.6 Hz, *cis* ethenyl C1-H), 6.77-6.82 (2H, m), 7.11 (1H, d, *J*=12.6 Hz, *cis* ethenyl C2-H), 7.20 (1H, d, *J*=3.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.5, 56.1, 56.4,

60.5, 111.6, 115.8, 116.2, 120.5, 124.9, 138.6, 151.7, 152.9, 166.4; Anal. Calcd for $C_{13}H_{16}O_4$ (236.26): C, 66.09; H, 6.83% Found: C, 65.89, H, 6.57%

**1-(2-Carbethoxyethyl)-2,5-dimethoxybenzene (16).** To a solution **15** (1.61 g, 6.80 mmol) in THF (50 mL) was added Pd/C (0.51 g, 10 wt% dry basis on activated carbon) with a hydrogen balloon and the mixture stirred 10 h at rt. After the solution was filtered using Celite, the solvent was removed by evaporation and the organic product was extracted with $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give a liquid. The liquid was purified by chromatography (EtOAc:hexane=1:4) to give **16** as a colorless oil (1.55 g, 96%). $R_f$ 0.72 (EtOAc:hexane=1:2); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.25 (3H, t, *J*=7.2 Hz), 2.59 (2H, t, *J*=8.1 Hz, ethyl C1-H), 2.90 (2H, t, *J*=8.1 Hz, ethyl C2-H), 3.75 (3H, s, OMe), 3.77 (3H, s, OMe), 4.12 (2H, q, *J*=7.2 Hz, $OCH_2$), 6.67-6.77 (3H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 14.7 ($CH_3$), 26.6 (ethyl C1), 34.6 (ethyl C-2), 56.0 (OMe), 56.1 (OMe), 60.6 ($OCH_2$), 111.2 (C4), 111.6 (C3), 116.5 (C6), 130.2 (C1), 151.9 (C2), 153.5 (C5), 173.5 (C=O); Anal. Calcd for $C_{13}H_{18}O_4$ (238.28): C, 65.53; H, 7.61% Found: C, 65.33, H, 7.35%

**1-(3-Hydroxypropyl)-2,5 dimethoxybenzene (17)**. To a solution of $LiAlH_4$ (0.51 g, 12.8 mmol) in THF (20 mL) under nitrogen was slowly added **16** (2.04 g, 8.56 mmol) and the resulting mixture stirred for 30 min at 0 ˚C. The reaction was quenched by addition of 1 N NaOH solution and filtered using Celite filter. The solvent was removed by evaporation and the organic product was extracted using EtOAc, the extract washed with brine, dried and concentrated to give a liquid, which was purified by chromatography (EtOAc:hexane=1:2) to give the colorless oil **17** (1.66 g, 99%). $R_f$ 0.22 (EtOAc:hexane=1:3; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.84 (2H, m, propyl C2-H), 2.70 (2H, t, *J*=7.2 Hz, propyl C1-H), 3.57 (2H, t, *J*=6.3 Hz, propyl C3-H), 3.76 (3H, s), 3.79 (3H, s), 6.67-6.79 (3H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.3 (propyl C2), 33.3 (propyl C1), 56.0 ($OCH_3$), 56.4 ($OCH_3$), 62.0 ($HOCH_2$), 111.3 (C4), 111.5 (C3), 116.6 (C6), 131.3 (C1), 151.8 (C2), 153.8 (C5); Anal. Calcd for $C_{11}H_{16}O_3$ (196.24): C, 67.32; H, 8.22% Found: C, 67.21, H, 8.13%

**1-(3-Benzyloxypropyl)-2,4-dimethoxybenzene (18).** To a solution of **17** (1.67 g, 8.49 mmol) in THF (25 mL) under a nitrogen atmosphere was added NaH (1.02 g, 25.5 mmol) with BnBr (1.50 mL, 12.7 mmol) and the mixture heated at reflux for 10 h. After the solution was filtered through Celite, the solvent was removed by evaporation and the residue was extracted with $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give a crude oil, which was purified by chromatography (EtOAc:hexane=1:7) to give **18** as a colorless oil (2.43 g, 99%). $R_f$ 0.63 (EtOAc:hexane=1:3); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.91 (2H, m), 2.68 (2H, t, *J*=7.5 Hz), 3.50 (2H, t, *J*=6.6 Hz), 3.74 (3H, s), 3.76 (3H, s), 4.51 (2H, s, benzyl-$CH_2$), 6.65-6.76 (3H, m), 7.24-7.34 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.4 (propyl C2), 30.1 (propyl C1), 56.0 ($OCH_3$), 56.2 ($OCH_3$), 70.3 ($OCH_2$), 73.1 ($OCH_2Ph$), 111.1 (C4), 111.3 (C3), 116.5 (C6), 127.7 (benzyl C4), 127.8 (x2), 128.5 (x2), 131.8 (C1), 138.9 (benzyl C1), 152.0 (C2), 153.5 (C5); Anal. Calcd for $C_{18}H_{22}O_3$ (286.37): C, 75.50; H, 7.74% Found: C, 75.35, H, 7.62%

**1-(3-Benzyloxypropyl)-4-iodo-2,5-dimethoxybenzene (19).** To a solution of **18** (4.44 g, 15.5 mmol) in EtOH (150 mL) under nitrogen atmosphere was added $I_2$ (4.72 g, 18.6 mmol) with

silver sulfate (5.80 g, 18.6 mmol) and stirred for 2 h at rt. Solvent was removed by evaporation and the residue was extracted into $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give a solid. The solid was purified by chromatography (EtOAc:hexane=1:7) to give **19** as a white solid (6.18 g, 97%). $R_f$ 0.72 (EtOAc:hexane=1:2); mp 52-54 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.88 (2H, m), 2.67 (2H, t, *J*=7.5 Hz), 3.48 (2H, t, *J*=6.3 Hz), 3.74 (3H, s), 3.77 (3H, s), 4.50 (2H, s), 6.64 (1H, s, C6-H), 7.17 (1H, s, C3-H), 7.23-7.34 (5H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.7, 30.0, 56.4, 57.4, 70.1, 73.2, 82.1 (C4-I), 113.6 (C3), 121.6 (C6), 127.7, 127.8 (x2), 128.6 (x2), 132.0 (C1), 138.8, 152.5 (x2); Anal. Calcd for $C_{18}H_{21}IO_3$ (412.26): C, 52.44; H, 5.13; I, 30.78% Found: C, 52.28, H, 5.05; I, 30.75%

**1-(4-Benzyloxy-3-methoxyphenyl)-2-[4-(3-benzyloxypropyl)-2,5-dimethoxyphenyl]acetylene (20).** To a solution of **19** (0.41 g, 1.00 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol), 4-benzyloxy-3-methoxyphenylacetylene **(10,** 0.36 g, 1.50 mmol) and CuI (0.005 g, 0.03 mmol) in DMF (7 mL) under nitrogen was added $Et_3N$ (0.28 mL, 2.00 mmol) and stirred for 48 h at rt. The reaction mixture was extracted with $CHCl_3$, the extract washed with brine, dried and concentrated to give a solid which was purified by chromatography (EtOAc:hexane=1:3) to give **20** as a yellow solid (0.49 g, 93%). $R_f$ 0.40 (EtOAc:hexane=1:3); mp 90-92 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.91 (2H, m), 2.71 (2H, t, *J*=8.4 Hz), 3.50 (2H, t, *J*=6.3 Hz), 3.78 (3H, s), 3.83 (3H, s), 3.89 (3H, s), 4.51 (2H, s), 5.16 (2H, s), 6.70 (1H, s, C3'-H), 6.82 (1H, d, *J*=8.7 Hz, C5-H), 6.93 (1H, s, C6'-H), 7.05-7.09 (2H, m), 7.27-7.43 (10H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.8, 30.0, 56.2, 56.3, 56.8, 70.1, 71.2, 73.2, 84.8 (acetylene), 93.1 (acetylene), 113.7, 113.8, 115.1, 115.2, 116.5, 125.0, 127.5 (x2), 127.7, 127.8 (x2), 128.1, 128.6 (x2), 128.7 (x2), 128.8, 132.6, 137.0, 138.8, 148.6, 149.3, 151.3, 154.2; Anal. Calcd for $C_{34}H_{34}O_5$ (522.63): C, 78.14; H, 6.56% Found: C, 78.05, H, 6.39%

**2-(4-Benzyloxy-3-methoxyphenyl)-6-(3-benzyloxypropyl)-3-iodo-5-methoxybenzofuran (21).** To a solution of **20** (0.49 g, 0.93 mmol) in $CHCl_3$ (20 mL) was slowly added $I_2$ (0.47 g, 1.86 mmol) at -20 ˚C and the mixture stirred for 5 h at rt. After addition of aqueous $NaHCO_3$, the mixture was extracted with $CHCl_3$, washed with brine, dried and concentrated to give the solid. The solid was purified by chromatography (EtOAc:hexane=1:3) to give **21** as a yellow solid (0.48 g, 82%). $R_f$ 0.60 (EtOAc:hexane=1:3); mp 82-84 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.95 (2H, m), 2.81 (2H, t, *J*=7.5 Hz), 3.51 (2H, t, *J*=6.3 Hz), 3.90 (3H, s), 3.99 (3H, s), 4.51 (2H, s), 5.21 (2H, s), 6.76 (1H, s), 6.96 (1H, d, *J*=8.1 Hz, C4'-H), 7.21 (1H, s), 7.23-7.39 (8H, m), 7.44 (1H, s), 7.45 (1H, d, *J*=7.2 Hz, C5'-H), 7.65-7.70 (2H, m); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 27.9, 30.1, 56.2, 56.5, 60.0, 70.1, 71.2, 73.1, 101.9, 111.0, 112.2, 113.6, 120.4, 123.7, 127.4 (x2), 127.7, 127.9 (x2), 128.1, 128.5 (x2), 128.8 (x2), 129.7, 131.0, 137.0, 138.8, 148.3, 149.0, 149.5, 152.9, 155.0; Anal. Calcd for $C_{33}H_{31}IO_5$ (634.50): C, 62.47; H, 4.92; I, 20.00% Found: C, 62.25, H, 4.75; I, 20.09%

**2-(4-Benzyloxy-3-methoxyphenyl)-6-(3-benzyloxypropyl)-5-methoxybenzofuran-3-carbaldehyde (22)**. To a solution of **21** (0.10 g, 0.16 mmol) in toluene (7 mL) under a nitrogen atmosphere was added *N*-formylpiperidine (0.17 mL, 1.56 mmol) with *n*-BuLi (0.92 mL, 1.6 M in hexane) and the whole stirred for 1 h at 0 ˚C. After the solution was neutralized with 1 N HCl,

the organic product was extracted with diethyl ether, the extract washed with brine, dried and concentrated to give a solid which was purified by chromatography (EtOAc:hexane=1:4) to give **22** as a yellow solid (0.073 g, 87%). $R_f$ 0.41 (EtOAc:hexane=1:3); mp 76-78 ˚C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.96 (2H, m), 2.82 (2H, t, *J*=7.5 Hz), 3.52 (2H, t, *J*= 6.3 Hz), 3.90 (3H, s), 3.99 (3H, s), 4.52 (2H, s), 5.25 (2H, s), 7.01 (1H, d, *J*= 8.4 Hz, C5'-H), 7.24-7.47 (13H, m), 7.64 (1H, s, C7-H), 10.27 (1H, s, CHO); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.0, 30.0, 56.2, 56.6, 70.1, 71.2, 73.1, 102.7, 111.8, 112.0, 113.8, 117.3, 122.0, 122.7, 124.1, 127.4 (x2), 127.7, 127.9 (x2), 128.3, 128.5 (x2), 128.9 (x2), 130.0, 136.5, 138.8, 148.6, 150.1, 150.8, 155.8, 165.4, 186.9 (CHO); Anal. Calcd for $C_{34}H_{32}O_6$ (536.61): C, 76.10; H, 6.01% Found: C, 75.93, H, 5.97%

**2-(4-Hydroxy-3-methoxyphenyl)-6-(3-hydroxypropyl)-5-methoxybenzofuran-3-carbaldehyde (3).** To a solution of **22** (0.02 g, 0.04 mmol) in $CH_2Cl_2$ (5 mL) was added $BBr_3$ (0.07 mL, 1.0 M in $CH_2Cl_2$) and the reaction mixture stirred for 1 h at -78 ˚C. The mixture was extracted with $CH_2Cl_2$, the extract washed with brine, dried and concentrated to give a solid which was purified by chromatography (MeOH:$CHCl_3$=1:15) to give **3** as a yellow solid (0.012 g, 92%). $R_f$ 0.54 (MeOH:$CHCl_3$=1:15); mp 134-136 $^o$C; $^1$H NMR (300 MHz, $CD_3OD$) δ (2H, m, propyl C2-H), 2.76 (2H, t, *J*=7.8 Hz, propyl C1-H), 3.58 (2H, t, *J*=6.6 Hz, $CH_2OH$), 3.87 (3H, s, C3'-$OCH_3$), 3.95 (3H, s, C5-$OCH_3$), 6.95 (1H, d, *J*=8.4 Hz, C5'-H), 7.32 (1H, s, C4-H), 7.38 (1H, dd. *J*=1.8, 15.6 Hz, C6'-H), 7.40 (1H, br s, C2'-H), 7.58 (1H, s, C7-H), 10.18 (1H, s, CHO); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 27.5 (propyl C2), 33.3 (propyl C1), 56.5 (C3'-$OCH_3$), 56.6 (C5-$OCH_3$), 61.1 ($CH_2OH$), 102.5 (C4), 112.4 (C2'), 112.9 (C5'), 116.3 (C6), 116.7 (C7), 119.8 (C6'), 123.4 (C3a), 124.2 (C1'), 130.0 (C3), 148.2 (C4'), 148.7 (C3'), 150.5 (C5), 155.6 (C7a), 165.6 (C2), 187.3 (CHO). Anal. Calcd for $C_{20}H_{20}O_6$ (356.37): C, 67.41; H, 5.66%. Found: C, 67.13; H, 5.55%.

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## References

1. Chang, H. M.; Cheng, K. P.; Choang, T. F.; Chow, H. F.; Chui, K. Y.; Hon, P. M.; Tan, F. W. L.; Yang, Y.; Zhong, Z. P.; Lee, C. M.; Sham, H. L.; Chan, C. F.; Cui, Y. X.; Wong, H. N. C. *J. Org. Chem.* **1990**, *55*, 3537.
2. Cheung, W. T.; Shi, M.-M.; Young, J. D.; Lee, C. M. *Biochem. Pharmacol.* **1987**, *36*, 2183.
3. Yang, Z.; Hon, P. M.; Chui, K. Y.; Xu, Z. L.; Chang, H. M.; Lee, C. M.; Cui, Y. X.; Wong, H. N. C.; Poon, C. D.; Fung, B. M. *Tetrahedron Lett.* **1991**, *32*, 2061.
4. (a) Dean, F. M. *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; Wiley: New

York, 1973; Vol. 1, pp 467-562. (b) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon Press: Oxford, UK, 1996; Vol. 2, pp 259-321. (c) Park, S. Y.; Lee, H.-J.; Lee, O.-K.; Kang, H.-Y.; Choi, D.-H.; Paik, K.-H.; Khan, M. *Bull. Korean Chem. Soc.* **2007**, *28*, 1874.

5. (a) Yang, Z.; Liu, H. B.; Lee, C. M.; Chang, H. M.; Wong, H. N. C. *J. Org. Chem.* **1992**, *57*, 7248. (b) Kuo, Y.-H.; Wu, C.-H. *J. Nat. Prod.* **1996**, *59*, 625. (c) Luetjens, H.; Scammells, P. J. *Tetrahedron Lett.* **1998**, *39*, 6581. (d) Hutchinson, S. A.; Luetjens, H.; Scammells, P. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3081. (e) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772. (f) Bang, H. B.; Han S. Y.; Choi, D. H.; Yang D. M.; Hwang, J. W.; Lee, H. S.; Jun, J.-G. *Synth. Commun.* **2009**, *39*, 506.
6. Jacobson, K. A.; van Galen, P. J. M.; Williams, M. *J. Med. Chem.* **1992**, *35*, 407.
7. (a) Yue, D.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 10292. (b) Hathaway, B. A.; White, K. L.; McGill, M. E. *Synth. Commun*. **2007**, *37*, 3855.
8. Leadbeater, N. E.; Tominack, B. J. *Tetrahedron Lett.* **2003**, *44*, 8653.
9. Colvin, E. W.; Hamill, B. J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 869.
10. (a) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46. (b) Choi, D. H.; Hwang, J. W.; Lee, H. S.; Yang D. M.; Jun, J.-G. *Bull. Korean Chem. Soc.* **2008**, *29*, 1594.