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Facile Total Synthesis of Benzo[*b*]furan Natural Product XH-14

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Abstract: An efficient and practical total synthesis of benzo[*b*]furan natural product XH-14 is demonstrated in nine steps from vanillin. Introduction of iodide substituents in the reaction including optimization of the reaction sequences is essential for the successful synthesis of XH-14. Sonogashira coupling with iodobenzene, iodine-induced cyclization, Wittig reaction, and formylation are critical in the high-yield total synthesis of XH-14.

Keywords: Benzofuran, danshen, lignan, Sonogashira coupling, XH-14

2-(4-Hydroxy-3-methoxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran-3-carbaldehyde (XH-14, **1**, Fig. 1) is a benzo[*b*]furan lignan natural product and was isolated from *Salvia miltiorrhiza* Bunge (Chinese name ''Danshen''), which has been widely used in China for the treatment of cardiovascular diseases such as acute myocardial infarction and angina pectoris.[1] It was the first reported nonnucleoside-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] However, the limited supply (approximately 0.1 ppm) of XH-14 from Danshen has prevented the diverse characterization of its biological activities.[3] Since the initial total synthesis of **1** by Yang et al. in 1991,[3] several syntheses have been reported by Yang et al.,[4] Luetjens[4] and Scammells,[5] and, Kao and Chern[6] using Sonogashira coupling reactions.[7] However, the synthetic

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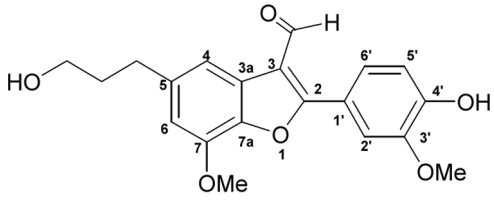

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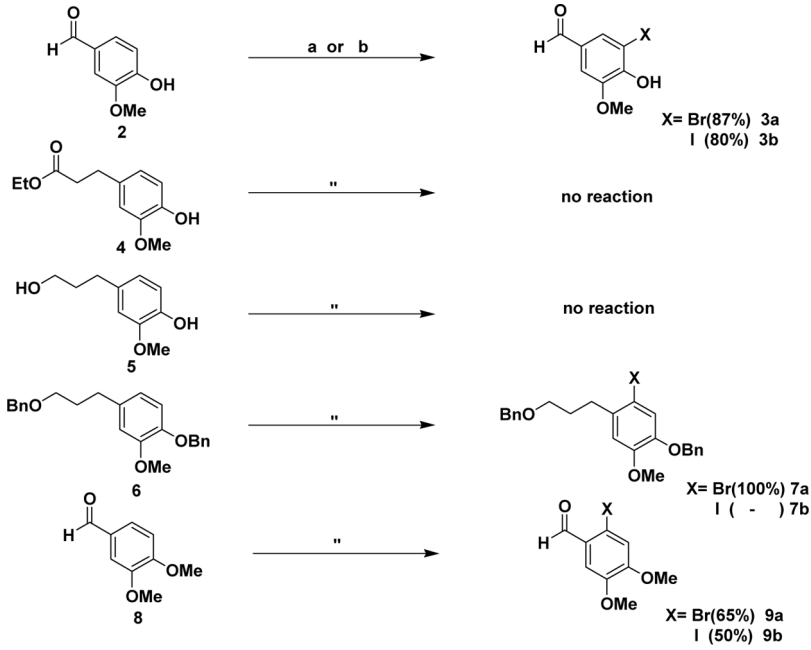
Figure 1. Structure of XH-14.

yields and steps are not optimized. We report herein the convenient and practical total synthesis of XH-14 (**1**) in nine steps from vanillin by using Sonogashira coupling reactions with iodine-induced cyclization.

In the present work, a key feature is the introduction of iodine substituents in the reaction including optimization of the synthetic sequences as part of a convenient route for the synthesis of XH-14.

To find the optimized reaction sequences, we investigated regioselective halogenations, Sonogashira couplings, and halogen-induced cyclizations in different substituents. The halogenation was quite sensitive, depending on substituents as shown in Scheme 1.[8] Vanillin **2** reacted with Br_2 in AcOH at rt, to give *o*-bromophenol **3a** in 87% yield and with I_2 and Ag_2SO_4 in EtOH at rt, yielding *o*-iodophenol **3b** in 80% yield. However, substituents **4** and **5** showed no reactions both in bromination and iodination. Bromination of **6** gave quantitative yield of *m*-benzyloxybromobenzene **7a** without any *o*-bromo-product, but iodination gave no result. Methoxyvanillin **8** gave *m*-bromo **9a** (65%) and *m*-iodo **9b** (50%)[8b] products regioselectively compare to *o*-haloproduct **3**. To obtain the regioselective *o*-haloproduct for Sonogashira coupling to give benzofuran structure, the hydroxyl functional group should be maintained before halogenation reaction.

Sonogashira coupling reactions were also sensitive to the haloaryl substituents as shown in Scheme 2. Bromomethoxyvanillin **10a** was not reacted with acetylene **11**, which is easily prepared from benzylated vanillin by Colvin rearrangement,[9] by using $PdCl_2(PPh_3)_2$/CuI/triethylamine (TEA)/N,N-dimethylformamide (DMF) to give coupled product, but iodo-derivative **10b** gave the expected coupled diarylyne **12** in 89% yield. Also, iodophenol **13b** showed much higher yield in Sonogashira coupling reaction than bromophenol **13a** to give benzofuran **14**. Benzofuran structure **14** was formed during the Sonogashira coupling reaction after formation of the coupled diarylyne, which reacted with an intrahydroxyl group to form benzofuran ring in oneflask. The regioselective formylation of benzofuran sometimes showed difficulties using Gattermann–Adams or Vilsmeier–Haack reactions.[4]

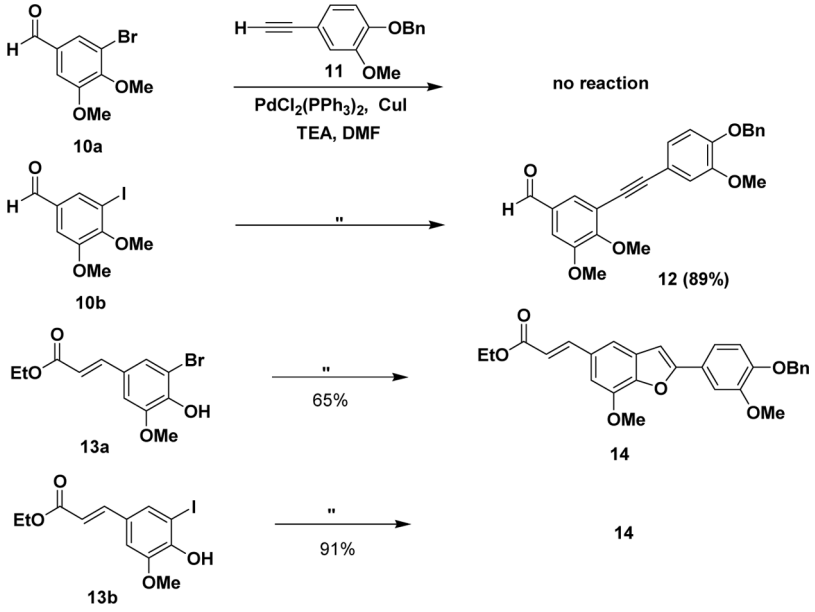


Scheme 1. Reagents and conditions: (a) Br_2, AcOH rt, (b) I_2, Ag_2SO_4, EtOH, rt.

To avoid this formylation problem, we should protect the further reaction of diarylyne to benzofuran ring cyclization during Sonogashira coupling reaction. Protection of the free hydroxyl group of **3** by methylation with tetrabutylammonium iodide (TBAI)/NaOH/MeI, producing **10** in 97% yield, will prohibit insitu benzofuran ring cyclization during coupling reaction. The halogen-induced cyclization of coupled diarylyne **12** yielded 3-halobenzofuran **15** as shown in Scheme 3.[6] Iodine (2 equiv)–induced benzofuran ring formation showed much higher yield (**15b**, 95%) than bromobenzofuran **15a** (30%) through a cyclic halonium intermediate.

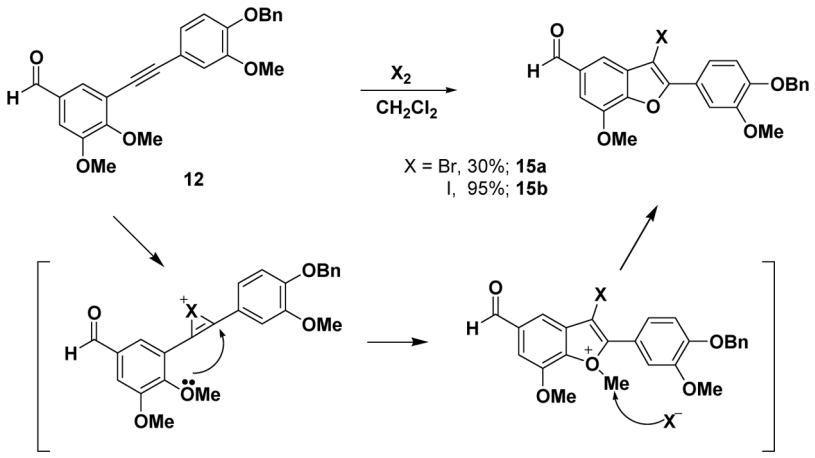
The Wittig reaction of iodobenzofuranaldehyde (**15b**) in methylene chloride at reflux with (carbethoxymethylene)triphenylphosphorane produced 93% yield of only (*E*)-**16**, which was then reduced to **17** (70%) by $LiBH_4$ reduction (Scheme 4). Benzylation of **17** with BnBr/NaH yielded **18** (85%) and following formylation with *n*-BuLi/*N*-formylpiperidine gave **19** in 70% yield. Finally, debenzylation of **19** with H_2/Pd-C caused deformylation; however, debenzylation with BCl_3 gave XH-14 (**1**) in 90% yield, and the spectroscopic data were confirmed by literature.[6]

In conclusion, the most practical and optimized nine step reaction procedures including regioselective iodination, methylation, Sonogashira

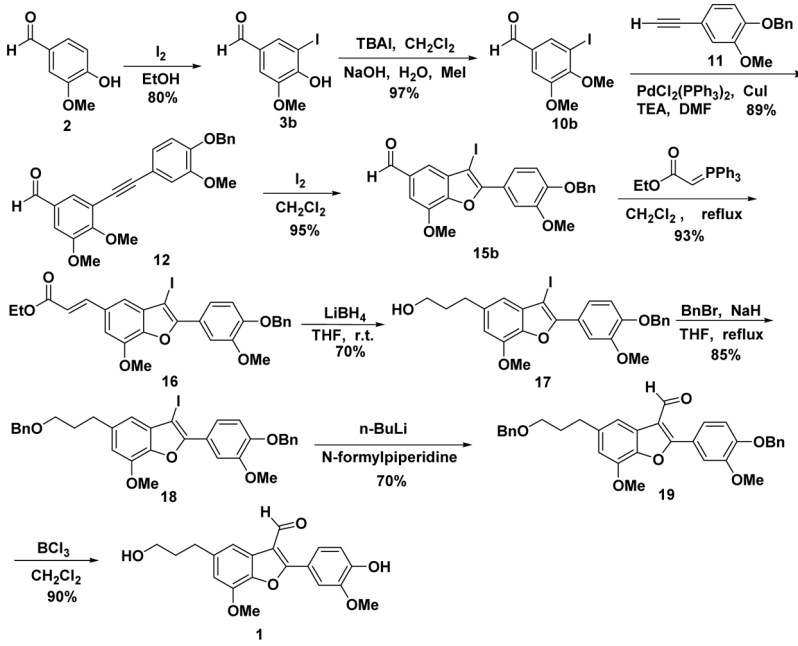


Scheme 2. Sonogashira coupling reactions.

coupling, iodine-induced cyclization, Wittig reaction, reduction, benzylation, formylation, and debenzylation gave XH-14 (**1**) in 23% overall yield from vanillin. XH-14 is now under investigation for biological activities.



Scheme 3. Halogen-induced cyclization.



Scheme 4. Total synthesis of XH-14 from vanillin.

EXPERIMENTAL

All chemicals used were purchased from commercial sources and used as received unless otherwise stated. NMR spectra were recorded at 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 hertz. $CDCl_3$ was used as a solvent and an internal standard. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Gas chromatography-mass spectrometer (GC-MS) analyses were performed using a HP-5890/JMS-AM 150, Jeol. 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 (3b)

To a solution of vanillin (**2**) (1.00 g, 6.57 mmol) in EtOH (50 mL) under nitrogen atmosphere, I_2 (2.08 g, 7.89 mmol) and silver sulfate (2.46 g,

7.89 mmol) were added 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 **3b** (1.47 g, 80%). R_f 0.34 (EtOAc–Hexane = 1:3); mp 179–181 °C [lit.[8b] mp 180 °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).

3-Iodo-4,5-dimethoxybenzaldehyde (10b)

To a solution of **3b** (1.05 g, 3.78 mmol) in CH_2Cl_2 (50 mL), aqueous NaOH solution (1.93 g in 30 mL of water) and TBAI (2.09 g, 5.66 mmol) mmol) were added and stirred until clear. Methyl iodide (2.8 mL, 45.8 mmol) was added to the reaction mixture and stirred for 12 h at rt. The reaction was quenched with 6N HCl, 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 = 1:4) to give the white solid **10b** (1.07 g, 97%). R_f 0.78 (EtOAc–Hexane = 1:3); 1:3); mp 58–60 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s, OMe), 3.92 (3H, s, OMe), 7.39 (1H, d, J = 1.8 Hz, C6-H), 7.83 (1H, d, J = 1.5 Hz, C2-H), 9.81 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.4 (OMe), 61.0 (OMe), 92.4 (C3-I), 111.3 (C6), 134.1 (C1), 134.9 (C2), 153.1 (C5), 154.3 (C4), 189.8 (C = O).

3-(4-Benzyloxy-3-methoxyphenylethynyl)-4,5-dimethoxybenzaldehyde (12)

To a solution of **10b** (0.59 g, 2.03 mmol), $PdCl_2(PPh_3)_2$ (0.014 g, 0.02 mmol), 4-benzyloxy-3-methoxyphenylacethylene **(11,** 0.72 g, 3.04 mmol), and CuI (0.008 g, 0.04 mmol) in DMF (10 mL) under nitrogen atmosphere, Et_3N (0.56 mL, 4.05 mmol) was added and stirred for 15 h at rt. 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 = 1:4) to give the yellow solid **12** (0.72 g, 89%). R_f 0.38 (EtOAc–hexane = 1:3); mp 110–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (3H, s, OMe), 3.93 (3H, s, OMe), 4.10 (3H, s, OMe), 5.18 (2H, s, OCH_2Ph), 6.85 (1H, d, J = 8.1 Hz, C5′-H), 7.06 (1H, s, C2′-H), 7.02 (1H, dd, J = 1.2 8.4 Hz, C6′-H), 7.24–7.44 (6H, m), 7.57 (1H, d, J = 1.5 Hz, C2-H), 9.85 (1H, s, CHO). ^{13}C NMR(75 MHz,

$CDCl_3$) δ 56.3 (OMe), 56.4 (OMe), 61.5 (OMe), 71.2 (OCH_2Ph), 83.3 (acethylene C), 95.1 (acethylene C), 110.2 (C3), 113.8 (C6), 114.9 (C5′), 115.7 (C1′), 118.1 (C2′), 125.1 (C6′), 127.4 (×2), 128.2 (benzyl-C4), 128.8 (×2), 130.0 (C1), 132.2 (C2), 136.8 (benzyl-C1), 149.1 (C4′), 149.5 (C3′), 153.3 (C5), 155.4 (C4), 190.7 (CHO).

2-(4-Benzyloxy-3-methoxyphenyl)-3-iodo-7-methoxybenzofuran-5-carbaldehyde (15b)

To a solution of **12** (0.030 g, 0.074 mmol) in CH_2Cl_2 (3 mL), I_2 (0.038 g, 0.149 mmol) was added and stirred for 2 h at rt. 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) 1:3) to give the white solid **15b** (0.036 g, 95%). R_f 0.43 (EtOAc–hexane = 1:3); mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (3H, s), 4.07 (3H, s), 5.22 (2H, s), 6.98 (1H, d, J = 8.1 Hz, C5′-H), 7.28–7.46 (6H, m), 7.55 (1H, d, J = 1.2 Hz, C6′-H), 7.70 (1H, dd, J = 1.8 Hz, 8.1 Hz, C6′-H), 7.72 (1H, d, J = 2.1 Hz, C4-H), 10.03 (1H, s). ^{13}C NMR(75 MHz, $CDCl_3$) δ 56.6, 56.7, 60.1 (C3-I), 71.2 (OCH_2), 105.6 (C6), 111.4 (C2′), 113.7 (C4), 119.8 (C5′), 121.1 (C6′), 122.4 (C1′), 127.5 (×2), 128.2 (benzyl-C4), 128.8 (×2), 133.7 (C5), 134.7 (C3a), 136.8 (benzyl-C1), 145.9 (C4′), 146.9 (C3′), 149.6 (C7), 149.7 (C7a), 155.1 (C2), 191.5 (C = O).

(*E*)-2-(4-Benzyloxy-3-methoxyphenyl)-3-iodo-7-methoxy-5-carbethoxy Ethenylbenzofuran (16)

To a solution of **15b** (0.064 g, 0.12 mmol) in CH_2Cl_2 (10 mL) under nitrogen atmosphere, (carbethoxymethylene)triphenylphosphorane (0.068 g, 0.19 mmol) was added and refluxed for 6 h. 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 = 1:4) to give the white solid **16** (0.067 g, 93%). R_f 0.44 (EtOAc–hexane = 1:3); 1:3); mp 165–167 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (3H, t, J = 7.2 Hz, CH_3), 3.99 (3H, s), 4.04 (3H, s), 4.28 (2H, q, J = 7.2 Hz, OCH_2), 5.22 (2H, s), 6.45 (1H, d, J = 15.9 Hz, trans ethenyl C1-H), 6.96 (1H, d, J = 8.7 Hz), 7.01 (1H, d, J = 1 Hz), 7.19 (1H, d, J = 1 Hz), 7.28–7.46 (5H, m) 7.68 (1H, dd, J = 1.8 Hz 8.1 Hz), 7.71 (1H, d, J = 1.8 Hz), 7.77 (1H, d, J = 15.6 Hz trans ethenyl C2-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7 (CH_3), 56.5 (OCH_3), 56.6 (OCH_3), 60.0 (C3-I), 60.8 (OCH_2), 71.2 (OCH_2), 106.9, 111.4, 113.7, 115.0, 117.9 (trans

ethenyl-C1), 121.1, 122.8, 127.5 (×2), 128.2, 128.8 (×2), 131.2, 134.7, 136.9, 144.5 (trans ethenyl-C2), 145.0, 145.3, 149.5, 154.4, 167.1 (C = O).

2-(4-Benzyloxy-3-methoxyphenyl)-3-iodo-5-(3-hydroxypropyl)-7-methoxybenzofuran (17)

$LiBH_4$ (2.0M, 0.38 mL) was added to a solution of **16** (0.089 g, 0.15 mmol) in THF (10 mL) under nitrogen atmosphere and stirred for 24 h at rt. 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 = 1:1) to give the white solid **17** (0.057 g, 70%). R_f 0.45 (EtOAc–hexane = 1:1); mp 112–115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (2H, m, propyl C2-H), 2.81 (2H, t, J = 6.9 Hz, propyl C1-H), 3.71 (2H, t, J = 6.3 Hz, propyl C3-H), 3.98 (3H, s), 4.01 (3H, s), 5.20 (2H, s), 6.70 (1H, s), 6.83 (1H, s), 6.95 (1H, d, J = 8.4 Hz), 7.28–7.45 (5H, m) 7.67 (1H, dd, J = 1.8 Hz, 8.1 Hz), 7.71 (1H, d, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8 (propyl C2-H), 35.0 (propyl C1-H), 56.5 (OCH_3), 56.6 (OCH_3), 60.3 (C3-I), 62.6 (OCH_2), 71.2 (OCH_2Ph), 108.8, 111.5, 113.2, 113.7, 120.9, 123.3, 127.5 (×2), 128.1, 128.3, 128.8 (×2), 134.3, 137.0, 138.3, 144.8, 149.2, 149.5, 153.6.

2-(4-Benzyloxy-3-methoxyphenyl)-3-iodo-5-(3-benzyloxypropyl)-7-methoxybenzofuran (18)

To a solution of **17** (0.023 g, 0.04 mmol) in THF (5 mL) under nitrogen atmosphere, NaH (0.005 g, 0.13 mmol) and BnBr (0.01 mL, 0.06 mmol) were added and refluxed for 7 h. After the solution was filtered using 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 the solid. The solid was chromatographed (EtOAc–hexane = 1:3) to give the white solid **18** (0.022 g, 85%). R_f 0.76 (EtOAc–hexane = 1:2); mp 100–102 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (2H, m), 2.84 (2H, t, J = 7.5 Hz), 3.54 (2H, t, J = 6.3 Hz), 3.99 (3H, s), 4.00 (3H, s), 4.54 (2H, s, benzyl-CH_2), 5.23 (2H, s, benzyl-CH_2), 6.70 (1H, s), 6.85 (1H, s), 6.96 (1H, d, J = 8.4 Hz), 7.28–7.45 (10H, m), 7.69 (1H, dd, J = 1.8 Hz, 8.1 Hz), 7.72 (1H, d, J = 1.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3, 33.2, 56.5 (OCH_3), 56.6 (OCH_3), 60.3 (C3-I), 69.8 (OCH_2), 71.2 (OCH_2Ph), 73.3 (OCH_2Ph), 108.7, 111.3, 113.3, 113.6, 120.9, 123.3, 127.5 (×2), 127.8, 127.9 (×2), 128.0, 128.2, 128.6 (×2), 128.7, 128.8 (×2), 134.2, 136.9, 138.4, 144.7, 149.1, 149.4, 153.5.

2-(4-Benzyloxy-3-methoxyphenyl)-5-(3-benzyloxypropyl)-7-Methoxybenzofuran-3-carbaldehyde (19)

To a solution of **18** (0.05 g, 0.08 mmol) in toluene (5 mL) under a nitrogen atmosphere, *N*-formylpiperidine (0.09 mL, 0.79 mmol) and *n*-BuLi (0.5 mL, 1.6 M in hexane) were added and stirred for 0.5 h at 0 °C. After the solution was neutralized with 1 N HCl, the organic product was extracted with diethyl ether, washed with brine, dried, and concentrated to give the solid. The solid was chromatographed (EtOAc–hexane = 1:4) to give the white solid **19** (0.03 g, 70%). R_f 0.47 (EtOAc–hexane = 1:2); mp 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (2H, m), 2.83 (2H, t, $J = 8.1$ Hz), 3.52 (2H, t, $J = 6.3$ Hz), 3.98 (3H, s), 3.99 (3H, s), 4.52 (2H, s), 5.24 (2H, s), 6.72 (1H, d, $J = 1.2$ Hz), 7.00 (1H, d, $J = 8.4$ Hz), 7.25–7.47 (12H, m), 7.65 (1H, s), 10.26 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3, 33.3, 56.4 (OCH_3), 56.6 (OCH_3), 69.9 (OCH_2), 71.2, 73.3, 109.1, 112.1, 113.7, 113.8, 117.1, 121.7, 123.0, 127.4, 127.5 (×2), 127.7, 127.9 (×2), 128.3, 128.6 (×2), 128.9 (×2), 136.5, 138.7, 140.3, 141.8, 144.7, 150.0, 150.9, 165.9, 186.9 (CHO).

XH-14 (1)

BCl_3 (0.11 mL, 1.0 M in CH_2Cl_2) was added to a solution of **19** (0.03 g, 0.06 mmol) in CH_2Cl_2 (5 mL) under nitrogen atmosphere and stirred for 1 h at −78 °C. 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** (0.017 g, 90%). R_f 0.31 (MeOH–$CHCl_3$ = 1:15); mp 77–79 °C (lit.[6] mp 77–79 °C); ^{1}H NMR(300 MHz, CD_3OD) δ 1.89 (2H, m, propyl C2-H), 2.75 (2H, t, $J = 8.4$ Hz, propyl C1-H), 3.59 (2H, t, $J = 6.6$ Hz, CH_2OH), 3.95 (3H, s, C3′-OCH_3), 3.97 (3H, s, C7-OCH_3), 6.79 (1H, d, $J = 1.2$ Hz, C6-H), 6.94 (1H, d, $J = 8.1$ Hz C5′-H), 7.33 (1H, dd, $J = 1.8$ Hz 8.4 Hz, C6′-H), 7.41 (1H, d, $J = 2.1$ Hz, C2′-H), 7.50 (1H, d, $J = 1.2$ Hz, C4-H), 10.16 (1H, s, CHO). ^{13}C NMR(75 MHz, CD_3OD) δ 32.5 (propyl C2), 34.8 (propyl C1), 55.4 (C3′-OCH_3), 55.5 (C5-OCH_3), 61.1 (CH_2OH), 108.7 (C6), 111.7 (C4), 113.0 (C2′), 115.6 (C5′), 116.1 (C3a), 120.0 (C6′), 123.2 (C1′), 127.2 (C5), 140.2 (C3), 141.5 (C7a), 144.7 (C7), 148.2 (C4′), 150.0 (C3′), 166.3 (C2), 187.0 (CHO).

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