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Total synthesis of lespedezavirgatol

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Lespedezavirgatol, a novel 2-phenylbenzofuran compound which was isolated from *Lespedeza virgata*, was firstly synthesized from pyrogallic acid and 3,4-dimethoxyphenol as starting materials with 8 steps. The key steps for the total synthesis were the selective iodination at 3-position of 1,2-dimethoxy-4-methoxymethoxybenzene and the Sonogashira cross-coupling reaction between 4-iodo-2-methoxybenzene-1,3-diol and 2-ethynyl-3,4-dimethoxy-1-(methoxy-methoxy)-benzene.

2-phenylbenzofuran, lespedezavirgatol, Sonogashira cross-coupling reaction

1 Introduction

Many 2-phenylbenzofuran derivatives are biologically active components isolated from plants or Chinese herbal medicines. 2-Arylbenzo[b]furans with hydroxyl and methoxyl groups usually have good physiological activities [1–4], such as anti-tumor [5], anti-virus [6–9], anti-oxidative activity [10, 11], antifungal [12], anti-radicals activities [13] and as immunosuppressive agents [14]. The discovery and synthesis of new benzo[b]furan compounds have attracted much attention. In 2008, Chen *et al.* [15] isolated a new 2-phenylbenzofuran derivative named lespedezavirgatol **1** (2-(6-hydroxy-2,3-dimethoxyphenyl)-7-methoxybenzofuran-6-ol) from the aerial parts of *Lespedeza virgata* (Figure 1). They made an oxygen radical absorbance capacity (ORAC) fluorescein assay of **1** and further evaluated its inhibitory activity against lipid peroxidation in rat kidney homogenate and plasma using a thiobarbituric acid reactive substances (TBARS) assay. The results showed that **1** had good oxygen radical eliminating activities. However, its isolation process from the herb was very complex and difficult, what's more, the yield was intolerably low. In this paper, we first report the total synthesis of **1** with a satisfactory yield of 6.9% in total eight steps.

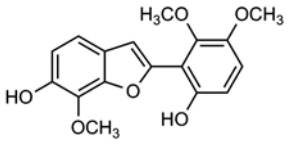

Figure 1 Structure of lespedezavirgatol **1**.

2 Experimental

2.1 Materials and measurements

Melting points were measured with a Tektronix X4 apparatus and were uncorrected. NMR spectra were obtained on a Bruker DRX 400 spectrometer with tetramethylsilane as the internal standard. Pyrogallic acid and 3,4-dimethoxyphenol were commercially available. Ethyl ether was freshly distilled from sodium/benzophenone and dichloromethane was distilled from calcium hydride. All yields refer to isolated products.

2.2 Synthesis

*Synthesis of 2-methoxybenzene-1,3-diol (**3**)*

3 was prepared as white needles (yield 35%) according to

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the ref. [16], mp 81–83 °C (ref. [16] 82–84 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H, OCH_3), 5.27 (brs, 2H, OH), 6.48 (d, ^3J = 8.0 Hz, 2H, Ar-H), 6.86 (t, ^3J = 8.0 Hz, 1H, Ar-H).

*Synthesis of 4-iodo-2-methoxyresorcinol (**4**)*

To a stirred solution of **3** (700 mg, 5 mmol) and I_2 (305 mg, 6 mmol) in 10 mL of CH_3CN, ammonium ceric nitrate (CAN) (10 mol%) was added. After 10 h, the reaction was completed. The mixture was diluted with saturated aqueous sodium bisulfite (5 mL), followed by extraction with ethyl acetate (3×20 mL). The combined organic layer was washed with saturated brine, and then dried with anhydrous $MgSO_4$. The solvent was removed under vacuum and the residue was purified by column chromatography (petroleum ether: ethyl acetate, 5:1) to give **4** (1.197 g, 90%) as white solid, mp 111–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.89 (s, 3H, OCH_3), 5.49 (s, 1H, OH), 5.55 (s, 1H, OH), 6.38 (d, 1H, ^3J = 8.8 Hz, Ar-H), 7.25 (d, 1H, ^3J = 8.8 Hz, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.9, 151.5, 133.5, 110.8, 108.1, 71.3, 60.7. MS (APCI): *m/z* 264.1 (M^+-2H). Anal. calcd for $C_7H_7O_3I$: C, 31.60; H, 2.65. Found: C, 32.58; H, 2.63.

*Synthesis of 1,2-dimethoxy-4-(methoxymethoxy)benzene (**6**)*

Bromomethyl methyl ether (MOMBr) (0.11 mL, 1.5 mmol) was added dropwise to a stirred solution of **3**, 4-dimethoxyphenol **5** (155 mg, 1 mmol) and *N*,*N*-diisopropylethylamine (0.35 ml, 2 mmol) in dry CH_2Cl_2 (3 mL) at 0 °C under argon. After stirring at room temperature for 17 h, the reaction was quenched with 1% aqueous HCl (0.20 mL), and the organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by column chromatography (petroleum ether:ethyl acetate, 5:1) to give **6** (148 mg, 75%) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 5.09 (s, 2H, CH_2), 6.56 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.4 Hz, Ar-H), 6.62 (d, ^4J = 2.4 Hz, Ar-H), 6.75 (d, 1H, ^3J = 8.8 Hz, Ar-H).

*Synthesis of 2-iodo-3,4-dimethoxy-1-(methoxy-methoxy) benzene (**8**)*

n-BuLi in *n*-hexane (2.5 M, 0.6 mL, 1.5 mmol) was added dropwise to a stirred solution of **6** (198 mg, 1 mmol) and 5 mL dry ether at room temperature under argon. After 1 h, I_2 (0.307 g, 1.2 mmol) dissolved in 3 mL of dry ether was added dropwise to the solution during 20 min. In the end a distinct orange color due to excess I_2 was noted and the white, insoluble organolithium compound disappeared, resulting in a clear solution. The ether solution was washed with sodium thiosulfate aqueous solution (5 mL, 20%) to remove I_2 and LiI. After drying over anhydrous $CaCl_2$, the ether was evaporated in vacuum and the residue was purified by column chromatography (petroleum ether:ethyl acetate, 10:1) to give **8** (233 mg, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.52 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 5.17 (s, 2H, CH_2), 6.80 (d, 1H, ^3J = 8.8 Hz, Ar-H), 6.85 (d, 1H, ^3J = 8.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.4, 56.5, 60.3, 87.3, 95.7, 110.6, 113.1, 148.1, 150.0, 150.9. MS (APCI): *m/z* 324.1 (M^+). Anal. calcd for $C_{10}H_{13}O_4I$: C, 37.06 ; H, 4.04. Found: C, 37.13; H, 4.48.

*Synthesis of 4-(2,3-dimethoxy-6-(methoxymethoxy)phenyl)-2-methylbut-3-yn-2-ol (**9**)*

8 (1.1 g, 3.4 mmol) and 3-methyl-3-hydroxy-1-butyne (350 mg, 1.2 equiv) were dissolved in 30 mL of *N*,*N*-diisopropylamine. A gentle stream of nitrogen was bubbled into the mixture for 20 min. After addition of $Pd(PPh_3)_2Cl_2$ (119.2 mg, 5 mol%) and CuI (32.5 mg, 5 mol%), the mixture was heated to 50 °C. The mixture immediately turned dark and a white solid precipitated. After 4 h, the reaction was completed, and then the mixture was cooled to room temperature. The solvent was removed by filtration under a reduced pressure to yield a residue as a yellow oil. The residue was diluted with ethyl acetate and washed with saturated brine twice. The organic phase was dried over anhydrous Na_2SO_4 and the residue was purified by column chromatography (petroleum ether:ethyl acetate, 5:1) to give **9** (799 mg, 84%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 2.93 (s, 1H, OH), 3.48 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.12 (s, 2H, CH_2), 6.73 (d, 1H, ^3J = 8.8 Hz, Ar-H), 6.76 (d, 1H, ^3J = 8.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 31.3, 56.2, 56.5, 60.8, 65.5, 74.1, 95.8, 102.4, 109.6, 111.4, 113.2, 148.0, 151.1, 152.0. MS (APCI): *m/z* 280.2 (M^+).

*Synthesis of 2-ethynyl-3,4-dimethoxy-1-(methoxymethoxy) benzene (**10**)*

A mixture of **9** (448 mg, 1.6 mmol) and pulverized KOH (448 mg, 5.0 eq) in 20 mL of *iso*-propanol was refluxed under N_2 with vigorous stirring for 2 h. The solution was washed with water (2×20 mL) and brine, dried over anhydrous Na_2SO_4. The solvent was removed in vacuum, and the residue was purified by column chromatography (petroleum ether:ethyl acetate, 10:1) to give **10** (301 mg, 85%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.46 (s, 1H, acetylenic H), 3.48 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 5.16 (s, 2H, CH_2), 6.78 (d, 1H, ^3J = 8.8 Hz, Ar-H), 6.81 (d, 1H, ^3J = 8.8 Hz, Ar-H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 56.1, 56.4, 60.9, 75.8, 85.2, 95.5, 108.5, 110.6, 113.8, 147.7, 151.9, 152.8. MS (APCI): *m/z* 222.3 (M^+).

*Synthesis of benzo[b] furan (**11**)*

10 was added to a stirred mixture of **4** (266 mg, 1 mmol), $Pd(Ph_3P)_2Cl_2$ (35 mg, 5 mol%), CuI (19 mg, 10 mol%) in Et_3N/DMF (1:5, 10 mL) under N_2. The mixture was stirred at 80 °C for 18 h. The solution was washed with water (2× 20 mL) and brine, dried over anhydrous Na_2SO_4. Then the mixture was filtered and evaporated under vacuum, The

residue was purified through silica-gel column chromatography (petroleum ether:ethyl acetate, 10:1) to afford **11** as a yellow oil with yield of 60%.

*Synthesis of lespedezavirgatol **1***

HCl (12 M, 4 mL) was added to a stirred solution of **11** (82 mg, 0.23 mmol) in methanol (2 mL) at room temperature, and the mixture was then heated at 40 °C for 4 h. After cooling, the mixture was diluted with ethyl acetate and the water layer was extracted with ethyl acetate (2 × 10 mL). The combined organic phase was washed with saturated $NaHCO_3$ aqueous solution and brine, then dried over Na_2SO_4. The solvent was evaporated to afford **1** (68 mg, 95%) as light yellow solid, mp 109–111 °C. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 6.66 (d, 1H, ^3J = 8.8 Hz, Ar-H), 6.78 (d, 1H, ^3J = 8.0 Hz, Ar-H), 6.85 (s, 1H, furan-H), 6.96 (d, 1H, ^3J = 8.8 Hz, Ar-H), 7.09 (d, 1H, ^3J = 8.0 Hz, Ar-H), 9.13 (brs, 1H, OH), 9.40 (brs, 1H, OH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 56.5, 60.2, 60.6, 107.3, 110.5, 113.2, 113.1, 114.5, 114.9, 122.6, 132.4, 145.6, 146.1, 146.7, 147.8, 148.6, 149.8. HRESIMS: found $[M+H]^+$ 317.1019 ; $C_{17}H_{17}O_6$ requires M 317.1021.

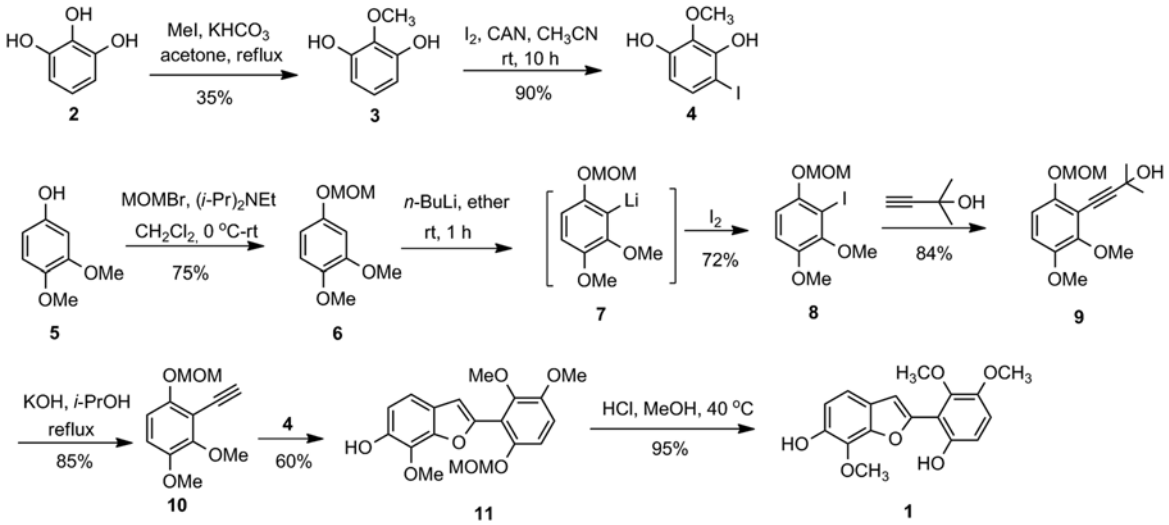
3 Results and discussion

There are many methods to form the benzo[b]furan skeleton [17–19]. We designed the synthetic plan by utilizing the protocol of Sonogashira cross-coupling cyclization reaction of 2-halophenols with terminal alkynes in the presence of catalyst as the key step (Scheme 1). As shown in Scheme 1, the selective reaction for the intermediates **4** and **8** was important since the structures of the two intermediates were both *ortho*-tetrasubstituted benzene rings. Because of the existence of steric hindrance the preparation of **8** is difficult. Normally the iodination of **6** occurred easier on the 6-position than on the 2-position. We tried many methods for the iodination of **5**, but failed. We adopted Gilman's method [20], used a protocol of directly metallation with *n*-BuLi in the 2-position, then iodination for the synthesis of **8**. In the literature, the reaction of the iodination via *n*-BuLi was conducted under reflux and N_2. Herein we improved the procedure: the reaction was carried out at room temperature, which greatly simplified the operation. The metallation-iodination of 1,2,4-trimethoxy benzene was achieved by the same method. In the synthesis of **10**, the phenolic hydroxyl of **5** should be protected with MOMBr (CH_3OCH_2Br), and the MOM group was deprived in the final step. Otherwise, the self-cyclization of 2-ethynyl-3,4-dimethoxy-phenol was occurred.

For the synthesis of benzo[b]furan **11**, we tried three different conditions to explore the effect of solvent and catalyst on the yields. When $Pd(PPh_3)Cl_2$-CuI was used as catalyst and Et_3N/DMF (1/5, *v*/*v*) as solvent [21], the yield of **11** was high (60%), and the by-products were much less than Et_3N–dioxane system [22]. When $[Cu(phen)(PPh_3)_2]NO_3$-Cs_2CO_3 was used as catalyst [23], most starting materials didn't react even after 48 h, and the desired product was trace.

4 Conclusion

A new natural product with 2-phenylbenzo[b]furan skeleton, lespedezavirgatol was firstly total synthesized by 8 steps with Sonogashira cross-coupling reaction as the key step. Gilman's metalation-iodination method showed highly regioselective iodination for alkoxy benzene at big steric hindrance position. The further biological activity study of the lespedezavirgatol is going on.



Scheme 1 Synthesis of lespedezavirgatol **1**.

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