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A convenient synthesis of naturally occurring benzofuran ailanthoidol

Chai-Lin Kao and Ji-Wang Chern*

School of Pharmacy, College of Medicine, National Taiwan University No. 1, Section 1, Jen-Ai Road, Taipei 100, Taiwan

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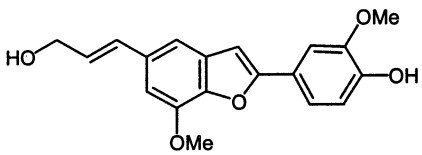
Abstract—A convenient method for the synthesis of ailanthoidol starting from vanillin is provided using trimethylsilyldiazomethane lithium salt to generate a diphenylacetylene and subsequent oxymercuration cyclization of the resulting alkyne with mercury acetate in acetic acid as key steps.

Ailanthoidol **1**, a neolignan with a 2-arylbenzofuran skeleton, was isolated from the Chinese herbal medicine *Zanthoxylum ailanthoides*. It has been reported that neolignans and lignans possess a variety of biological activities, such as anticancer,[1] antiviral,[2] immunosuppressive,[3] antioxidant,[4] antifungal[5] and antifeedant activities.[6] However, due to the limited amounts of compound **1**, its biological activity has not yet been established.



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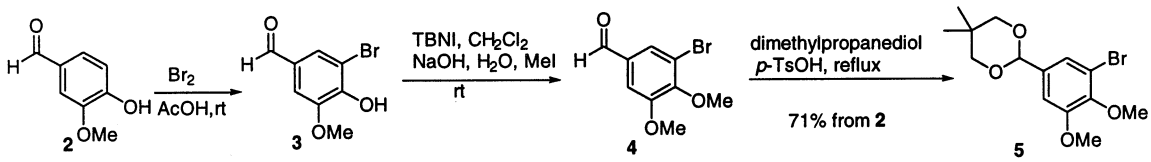
Although there are several approaches available in the literature[7] for the preparation of compound **1**, most involve the coupling of *ortho*-halophenols with alkynes via an organometallic reaction with concomitant cyclization of the resulting diphenylacetylene skeleton. However, to explore the structure–activity relationship, a variety of analogs are required and a wide diversity of available starting materials is critical to synthesize analogs for biological studies. Therefore, an efficient and practical approach for the synthesis of versatile analogs is needed. We reasoned that the diphenylacetylene skeleton would be suitable by coupling the appropriate diphenyl ketone with the lithium salt of trimethylsilyldiazomethane.[8] Subsequently, the resulting diphenylacetylene would undergo facile intramolecular solvomercuration with mercury acetate to afford the corresponding benzofuran skeleton.[9] Herein, we develop a convenient approach for the synthesis of ailanthoidol starting from vanillin.

Our strategy starts with the bromination of vanillin with bromine in acetic acid to give 3-bromo-4-hydroxy-



Scheme 1.

Keywords: ailanthoidol; benzofuran; trimethylsilyldiazomethane lithium salt; oxymercuration.

* Corresponding author. Fax: 886-2-23934221; e-mail: chern@jwc.mc.ntu.edu.tw

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5-methylbenzaldehyde **3**. Methylation of compound **3** with methyl iodide in the presence of tetrabutylammonium iodide (TBNI) as catalyst[10] produces the 3-bromo-4,5-dimethoxybenzaldehyde **4**, which was treated with 2,2-dimethyl-1,3-propanediol to afford 1-bromo-2,3-dimethoxy-5-(5′,5′-dimethyl-1′,3′-dioxan-2′-yl)benzene **5** in 58% yield (Scheme 1). However, direct methylation of **3** with methyl iodide under various conditions, such as K_2CO_3/MeI in ethanol, KOH/MeI in methanol, KOH/MeI in DMF, or NaH/MeI in DMF, was unsuccessful.

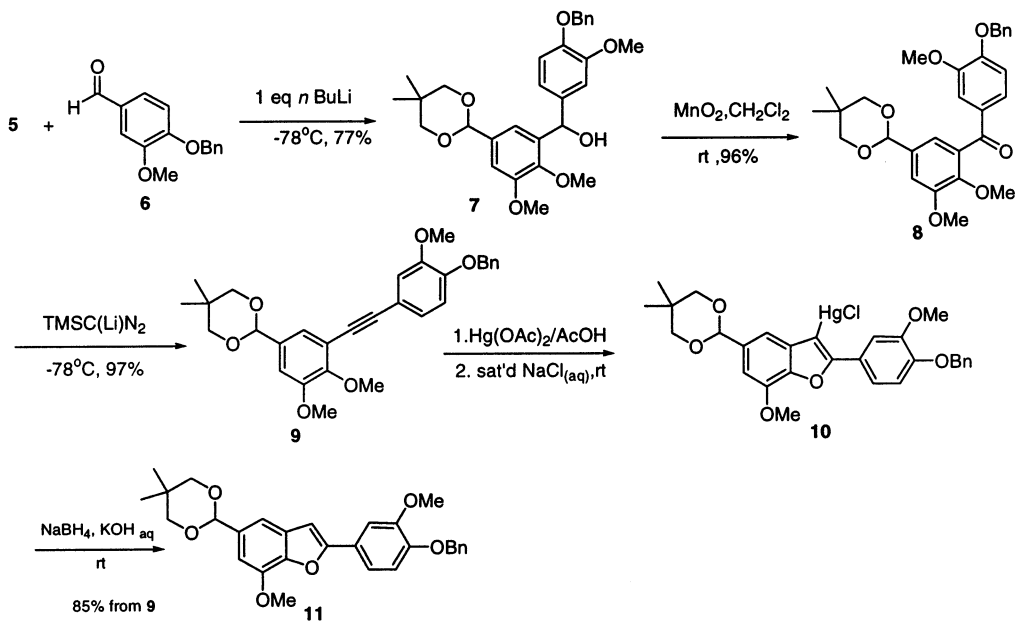
Nevertheless, compound **5** was obtained in 71% yield starting from **2** without any further purification of the intermediates. Compound **5** was then treated with *n*-butyl lithium and coupled with 4-benzyloxy-3-methoxybenzaldehyde **6** to give 1-(*p*-benzyloxy-*m*-methoxyphenyl)-1-(2,3-dimethoxy-5-(5′,5′-dimethyl-1′,3′-dioxan-2′-yl)phenyl carbinol **7** in 77% yield accompanied with a trace amount of the debrominated product of compound **5** (Scheme 2).

Subsequent oxidation of the resulting carbinol **7** with manganese oxide furnished the corresponding ketone **8** in 96% yield. Compound **8** was then treated with trimethylsilyl diazomethane lithium salt to give the corresponding alkyne **9** via a Covlin rearrangement[11] in 97% yield. Compound **9** was treated with mercury acetate in acetic acid and then quenched with saturated sodium chloride solution to yield 2-(*p*-benzyloxy-*m*-methoxyphenyl)-3-chloromercurio-5-(5′,5′-dimethyl-1′,3′-dioxan-2′-yl)-7-methoxybenzofuran **10**. The chloromercurial intermediate **10** was isolated without further purification and treated with $NaBH_4$ in THF to afford compound **11**[12] in 85% yield.

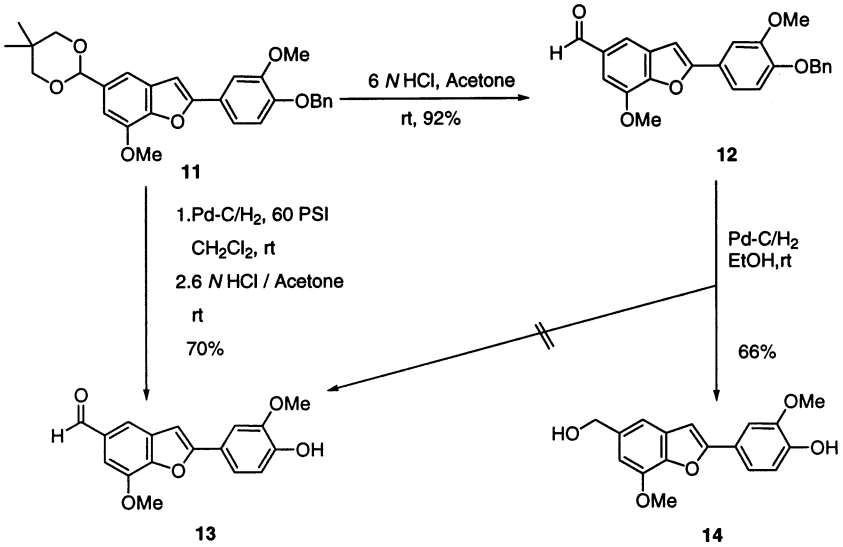
The dioxane moiety of **11** was deprotected in a mixture of acetone and hydrochloric acid to furnish 2-(4-benzyloxy-3-methoxyphenyl)-7-methoxybenzo[*b*]furan-5-carboxaldehyde **12** in 92% yield. Unfortunately, hydrogenation of **12** with Pd–C/H_2 gave an unexpected compound **14** by reduction of the aldehyde group instead of the desired product **13** (Scheme 3). Alternatively, compound **11** was debenzylated with Pd–C/H_2 and subsequently deacetylated in a mixture of acetone and 6N HCl to afford the desired product **13** in 70% yield.

Finally, elongation of the side chain at the 5-position of **13** via a Wittig reaction gave 2-(*p*-hydroxy-*m*-methoxyphenyl)-7-methoxy-5-(carbethoxy-1-propen-1-yl)-benzo[*b*]furan **15**[13] which was treated with DIBAL-H to afford the target compound **1** in 77% yield (Scheme 4).

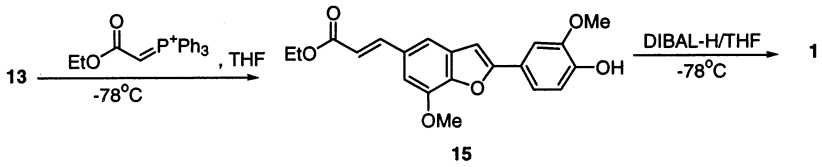
In summary, a total synthesis of ailanthoidol was achieved in 12 steps with a 17% overall yield from vanillin **2**. This investigation provides a practical approach toward the synthesis of ailanthoidol. Its analogs can also be simply synthesized either by functionalization at the 5-position of **13** or by using a variety of vanillin analogs as starting material. The mercurial intermediate **10** is considered to be a very useful intermediate for the preparation of analogs by the direct replacement of the mercurial moiety with different functional groups. Using this strategy, the synthesis of other neolignans and lignans is currently under active investigation in our laboratory.



Scheme 2.



Scheme 3.



Scheme 4.

Acknowledgements

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12. Compound **11**: mp 160–162°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 3 H), 1.33 (s, 3 H), 3.67 (d, $J=11$ Hz, 2 H), 3.79 (d, $J=11$ Hz, 2 H), 3.97 (s, 3 H), 4.05 (s, 3 H), 5.17 (s, 2 H), 5.44 (s, 1 H), 6.85 (s, 1 H), 6.91 (d, $J=8$ Hz, 1 H), 6.98 (s, 1 H), 7.30 (s, 2 H), 7.34–7.39 (m, 4 H), 7.44 (d, $J=8$ Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.4, 23.6, 30.7, 56.5, 56.7, 71.5, 78.2, 101.2, 102.6, 104.9, 109.2, 111.6, 114.5, 118.5, 124.3, 127.8, 128.4, 129.0, 131.3, 134.9, 137.3, 144.6, 145.5, 149.2, 150.3, 157.0. Anal. calcd for $C_{29}H_{30}O_6$: C, 73.40; H, 6.37. Found: C, 73.37; H, 6.37.
13. The *E*-olefin geometry was confirmed by the coupling constant ($J=16$ Hz) of two vinylic protons. Compound **15**: mp 149–151°C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (t, $J=7$ Hz, 3 H), 3.95 (s, 3 H), 4.03 (s, 3 H), 4.26 (q, $J=7$ Hz, 2 H), 5.90 (s, 1 H, exchangeable), 6.38 (d, $J=16$ Hz, 1 H), 6.81 (s, 1 H), 6.92 (s, 1 H), 6.96 (d, $J=8$ Hz, 1 H), 7.27 (s, 1 H), 7.32 (d, $J=2$ Hz, 1 H), 7.37 (dd, $J=2$, 8 Hz, 1 H), 7.72 (d, $J=16$ Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.8, 56.5, 56.6, 60.9, 100.6, 105.6, 108.1, 114.9, 115.3, 117.3, 117.4, 119.5, 122.9, 131.0, 131.9, 145.6, 145.9, 147.1, 147.3, 157.8, 167.7. Anal. calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.63; H, 5.52.