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The First and Facile Synthesis of (±) Syringaresinol

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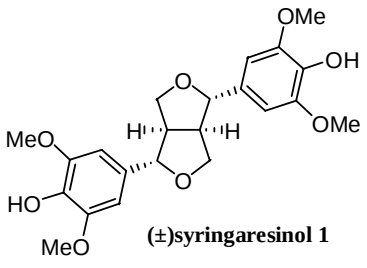
Abstract: The first and facile synthesis of (±)syringaresinol was described.

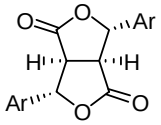
Keywords: Lignans, (±)syringaresinol, synthesis.

Lignans have drawn enormous attention of the chemists throughout the world in recent years because of their wide abundance in nature and broad range of biological activities[1]. Syringaresinol **1** and other furofuran lignans have also been reported to exhibit various biological activities, including antifungal[2], anti-inflammatory[3], antimalarial activities[4], inhibition of cyclic AMP phosphodiesterase[5], inhibiton of platelet aggregation[6], antileukemic[7], antioxidation[8] and cytotoxic activities[9], DNA cleavage effect[10], *etc*. Although a number of synthesis of lignans have been reported, there is no report on the synthesis of syringaresinol yet. Herein we like to report the first and facile synthesis of (±)syringaresinol.

For the synthesis of furofuran lignans, usually the 4,8-bislactone **2** was the common intermediate. The general methods so far available for the synthesis of **2** involved the $TiCl_4$-catalyzed condensation of 2,5-bis(trimethylsiloxy)furan with aromatic aldehydes[11] or oxidative coupling of cinnamic acid derivatives with thallium trifluoroacetate[12](TTFA) (**Scheme 1**). However, the former method was not practical, and the latter one needed highly toxic reagent TTFA. The conversion of **2** to furofuran lignans **6** was achieved in low to moderate yield by two approaches, which are illustrated in **Scheme 2**.



(±)syringaresinol 1



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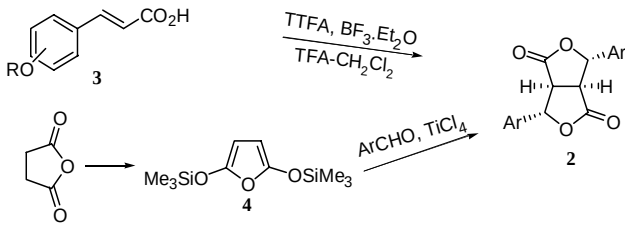
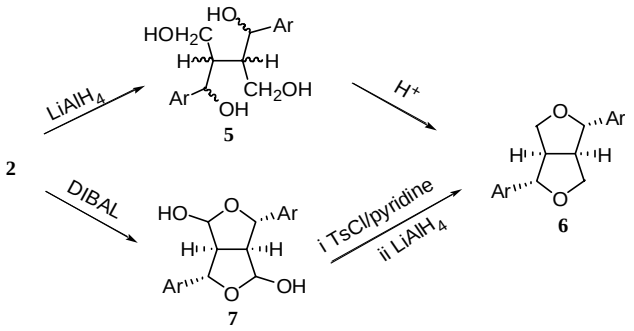
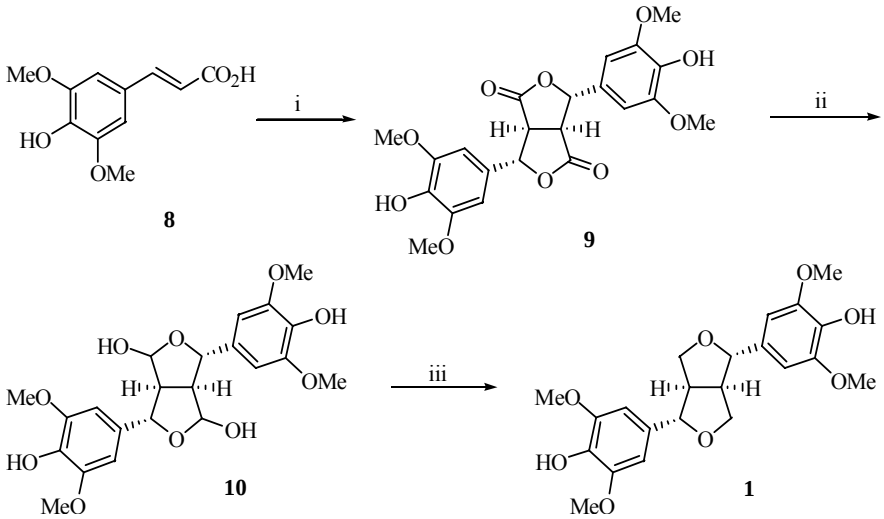
Scheme 1



Scheme 2



Scheme 3



Reagents and conditions: i. $FeCl_3$, O_2, EtOH-H_2O, rt., 54% yield; ii. 1.5eq. DIBAL, THF, -78°C, 90% yield; iii. 1.5eq. Et_3SiH, 1.1eq. $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C, 88% yield.

Our strategy is to find one straightforward method to produce the target molecule (±)syringaresinol. Thus, oxidative coupling of 4-hydroxy-3, 5-dimethoxycinnamic acid with $FeCl_3$ and O_2 directly gave the bislactone **9**[13], stereochemistry of which was assigned to be all-*cis* from the small H_A-H_B coupling constant in the proton *NMR*. Reduction of **9** with DIBAL readily afforded the lactol **10**, and subsequently deoxygenation of **10** with Et_3SiH[14] in the presence of $BF_3{\cdot}Et_2O$ produced the target molecule (±) syringaresinol[15] in high yield (**Scheme 3**). The spectral data of the synthetic sample are in agreement with those reported for (+)- and (±) syringaresinol[16, 17]

In conclusion, we have described here the first total synthesis of (±) syringaresinol, and developed a facile method to produce the (±) syringaresinol straightforwardly.

References and Notes

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15. The data of synthetic sample **1**: mp. 173-5^{o}C. HREI-MS *m/z*: 418.1620[M^{+}($C_{21}H_{26}O_8$), 100%]. ^{1}HNMR($CDCl_3$, 400MHz δppm) 6.60 (s, 4H), 5.48(br s, 2H), 4.70(d, 2H, *J*= 4Hz), 4.2-4.4(m , 2H), 3.88(s, 12H), 3.8-4.0(m, 2H), 3.08(m, 2H). ^{13}CNMR($CDCl_3$, 90MHz δppm) 147.26, 134.46, 132.16, 102.86, 86.11, 71.84, 56.42, 54.40.
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