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Total Synthesis of Vibsanol, a Benzofuran-Type Lignan

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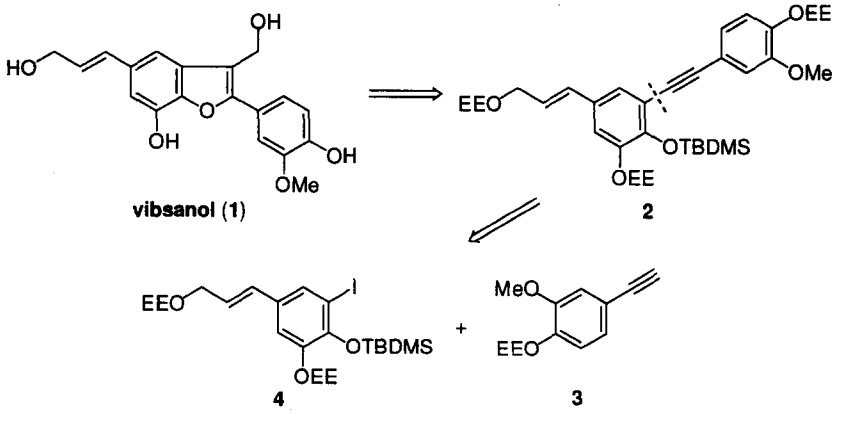
Abstract Vibsanol (**1**), a benzofuran-type lignan isolated from the wood of *Viburnum awabuki* (Caprifoliaceae), was synthesized by the tandem cyclization of *o-tert*-butyldimethylsiloxydiarylalkyne with tetrabutylammonium fluoride and excess paraformaldehyde as the key step.

The leaves of *Viburnum awabuki* (Caprifoliaceae) are known to have been used as a fish poison for the purpose of catching fish around the Okinawa Islands. Vibsanine A, an unprecedented humulene-type diterpene, was isolated from these leaves as a piscicidal compound.[1] Recently, vibsanol (**1**), a natural occurring benzofuran-type lignan, was isolated by Fukuyama *et al.* from the wood of *V. awabuki* (Caprifoliaceae) and showed moderate inhibitory activity toward lipid peroxidation in rat brain homogenates.[2] The structure of **1** was mainly established on the basis of spectroscopic methods and composed of 2-aryl and 3-hydroxymethyl substituents. It is well known that 2-substituted benzofurans are readily prepared from the

Scheme 1



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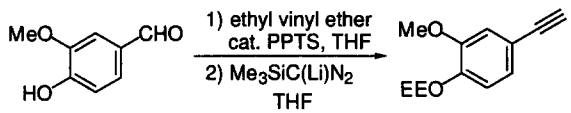
o-hydroxyarylalkynes under basic conditions.[3] We have recently described a new approach to the synthesis of benzofurans and 3-hydroxymethylbenzofurans from *o*-triisopropylsiloxyarylalkynes by treatment with tetrabutylammonium fluoride (TBAF) under mild neutral conditions, and in the latter case, in the presence of carbonyl compounds.[4] We now wish to report the total synthesis of vibsanol from readily available vanillin as the starting material using the above method.

Strategically, the key features of our synthesis are (1) Colvin rearrangement[5] of the vanillin derivative with lithium trimethylsilyldiazomethane ($Me_3SiC(Li)N_2$)[6] via the alkylidene carbene, (2) Sonogashira cross coupling of the terminal alkyne **3** with the aryl iodide **4**,[7] and (3) the tandem cyclization reaction of *o-tert*-butyldimethylsiloxydiarylalkyne **2**, as shown in Scheme 1.

Our synthesis started from the terminal alkyne **3**, as shown in Scheme 2. Thus vanillin was efficiently converted by the sequential phenol protection with ethyl vinyl ether in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS),[8] homologation reaction of the resulting aldehyde with $Me_3SiC(Li)N_2$ to afford the alkyne **3** in 76 % overall yield.

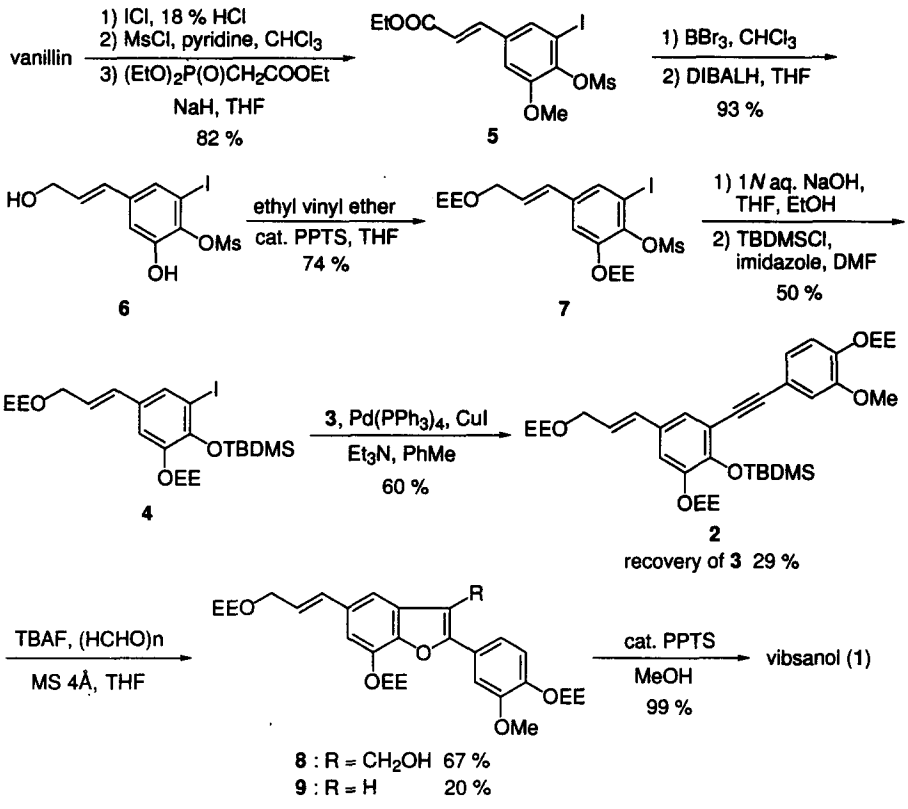
Scheme 2



vanillin — 76 % — **3**

Vanillin was also converted to the ferulic acid derivative **5** in three steps according to the literature.[3e,9] Removal of the methyl ether function with excess boron tribromide[10] followed by reduction of the ethyl ester with diisobutylaluminum hydride (DIBALH) gave the diol **6** in 93 % overall yield. The diol **6** was protected with ethyl vinyl ether in the presence of a catalytic amount of PPTS to afford the labile mesylate **7** in 74 % yield. After alkaline saponification of the mesylate **7** upon heating at 50 ℃, the resulting phenol was reprotected with TBDMSCl to give **4** in 50 % overall yield. The palladium-copper catalyzed Sonogashira cross coupling reaction of the alkyne **3** with the iodide **4** was then achieved to provide the benzofuran precursor **2** in 60 % yield with the recovery of **4** in 29 % yield.[11] 3-Hydroxymethylation of the benzofurans by the tandem cyclization of *o*-siloxyarylalkynes requires the total removal of any proton sources since the basicity of the anion of the benzofurans in the 3-position is very strong.[12] For this purpose, 4Å molecular sieves were dried at 180 ℃ for 4 h under reduced pressure just prior to use and the TBAF solution was dehydrated with 4Å molecular sieves by stirring for 3 h. Also, the equivalents of paraformaldehyde were crucial to the yield of the 3-benzofuranmethanols. In a model study using *o-tert*-butyldimethylsiloxydiphenylacetylene, the best result was obtained by employing 15 equivalents of paraformaldehyde to give 2-phenyl-3-benzofuranmethanol in 84 % yield.[13] The tandem cyclization of **2** afforded the desired benzofuran **8** in 67 % yield and the protonated one **9** in 20 % yield using the above reaction conditions.[14] Finally, the deprotection of **8** smoothly occurred using a catalytic amount of PPTS in MeOH to give vibsanol (**1**) in 99 % yield (Scheme 3).[15] Synthetic vibsanol exhibited identical properties to those reported for the natural substance (IR, ^1H and ^{13}C NMR, MS and HRMS).

Scheme 3



In summary, we have completed the convenient total synthesis of vibsanol from readily available vanillin as the starting material. The synthesis hinges on the tandem cyclization of the *o*-siloxyarylalkyne as the key step. The method employed will be useful for the synthesis of other 3-hydroxymethylbenzofuran derivatives.

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11. To a mixture of tetrakis(triphenylphosphine)palladium (0) (91 mg, 0.079 mmol) and CuI (30 mg, 0.16 mmol) were successively added a solution of the iodide **4** (437 mg, 0.79 mmol) in toluene (4 ml) and a solution of the acetylene **3** (209 mg, 0.95 mmol) and triethylamine (121 mg, 1.2 mmol) in toluene (2 ml) at room temperature under argon. The reaction mixture was stirred in the dark at this temperature for 20 h, and then diluted with EtOAc (100 ml). The solution was washed with 10 % aqueous NH_4Cl (30 ml) and saturated brine (30 ml), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane : EtOAc = 6 : 1 → 4 :1) to afford the recovered **4** (129 mg, 29 %) and the desired **2** (306 mg, 60 %) as a viscous yellow oil.
12. The use of acetonitrile instead of THF gave only the protonated benzofurans and no hydroxymethylation products were obtained. See ref. 4.
13. *Cf.* ref. 4. 2-Phenylbenzofuran was also obtained in 16 % yield.
14. To a stirred mixture of paraformaldehyde (34 mg, 90 % purity, 1.0 mmol) and powdered 4 Å molecular sieves (400 mg, dried over at 180 ℃ for 4 h under reduced pressure prior to use) in THF (1 ml) was added TBAF (0.18 ml, 0.49 M in THF, 0.087 mmol) at room temperature under argon, and the mixture was stirred at this temperature for 3 h. Then the alkyne **2** (43 mg, 0.067 mmol) in THF (1 ml) was added dropwise to the mixture, which was stirred at 50 ℃ for 3 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite to remove the molecular sieves. The filtrate was concentrated *in vacuo*, and the residue was purified by silica gel chromatography (hexane : EtOAc = 4 : 1 → 2 :1) to afford the protonated **9** (7 mg, 20 %) as a yellow oil and the desired **8** (25 mg, 67 %) as a colorless oil.
15. Unfortunately, when *O*-methoxymethyl groups were employed instead of *O*-1-ethoxyethyl groups, the deprotection of the final step was unsuccessful for decomposition under the normal reaction conditions (e.g., 0.1*N* HCl, TFA, cat.HCl/NaI/acetone, TMSBr, *B*-bromocatecholborone, triphenylmethyl tetrafluoroborate).