AN EXPEDITIOUS SYNTHESIS OF VIBSANOL, A BENZOFURAN-TYPE LIGNAN FROM *VIBURNUM AWABUKI**

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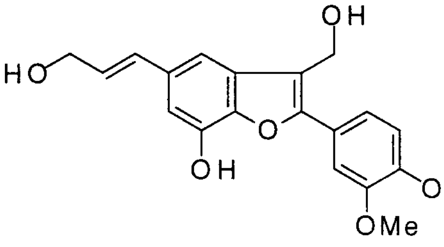
Abstract - Vibsanol (**1**), a benzofuran-type lignan isolated from the wood of *Viburnum awabuki* (Caprifoliaceae), was synthesized from the readily available vanillin; the key step is a tandem cyclization of *o*-*tert*-butyldimethylsiloxydiarylalkyne (**2**) with tetrabutylammonium fluoride and excess paraformaldehyde.

Vibsanol was isolated by Fukuyama and co-workers[1] from the wood of *Viburnum awabuki* (Caprifoliaceae), and inhibits moderately lipid peroxidation in rat brain homogenates. The structure of vibsanol was revealed to be **1**, a benzofuran-type lignan having 2-aryl and 3-hydroxymethyl substituents. We have already reported that the lithium salt of trimethylsilyldiazomethane ($Me_3SiC(Li)N_2$), a useful reagent for generating alkylidene carbenes from carbonyl compounds,[2] smoothly reacted with *o*-triisopropylsiloxyaryl ketones or aldehydes to give *o*-triisopropylsiloxyarylalkynes which were easily converted to benzofurans by treatment with tetrabutylammonium fluoride (TBAF).[3] 3-Hydroxymethylbenzofurans were also obtained when the reaction was conducted in the presence of carbonyl compounds.[3] In this paper, we describe the efficient total synthesis of vibsanol utilizing these methodology developed by our group.[4]



vibsanol (1)

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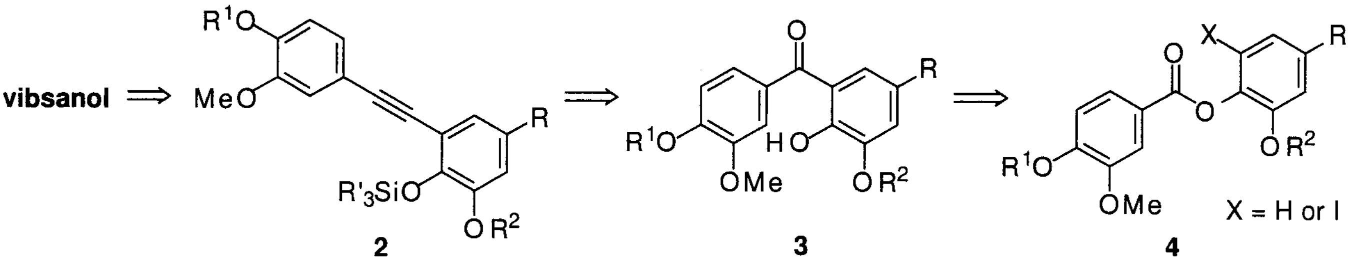
* Dedicated to Professor Teruaki Mukaiyama on the occasion of his 73rd birthday.

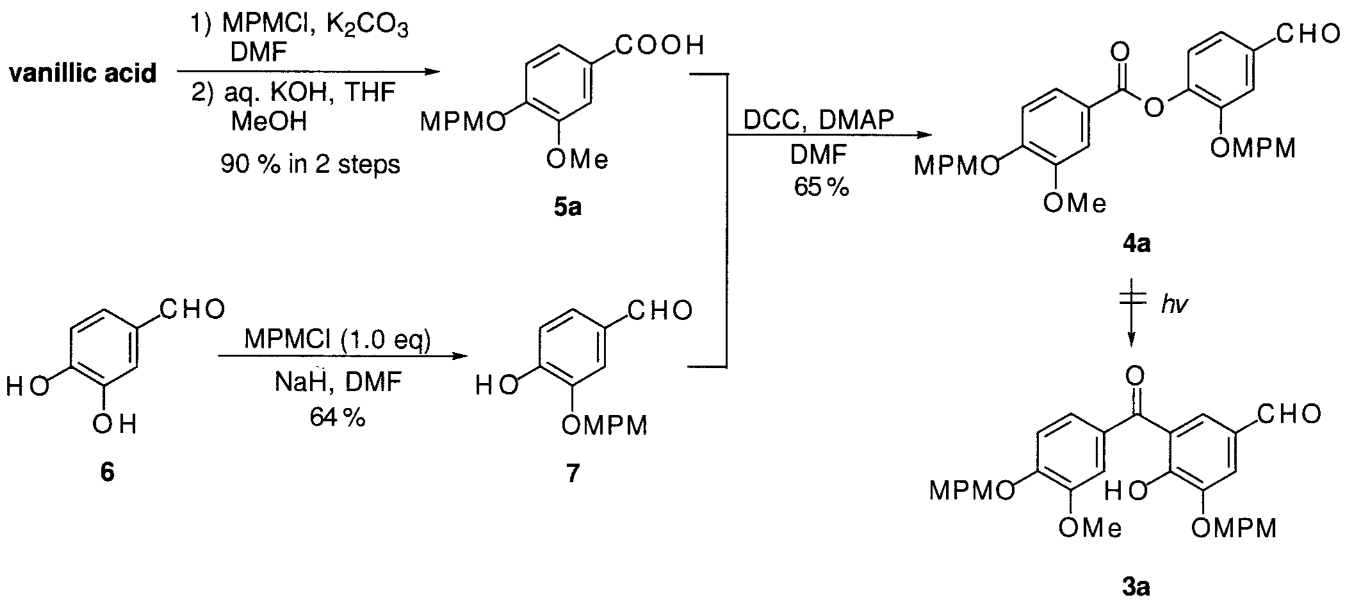
One of the important problems to synthesize vibsanol (**1**) according to the above methodology was how to construct the *o*-siloxyarylalkynes (**2**) for the formation of the benzofuran skeleton.[5] In our first approach, we adopted the *o*-hydroxybenzophenone derivatives (**3**) as a suitable precursor for **2**, which would be prepared from the benzoate derivatives (**4**) by the Fries rearrangement,[6] as shown in Scheme 1.

Scheme 1



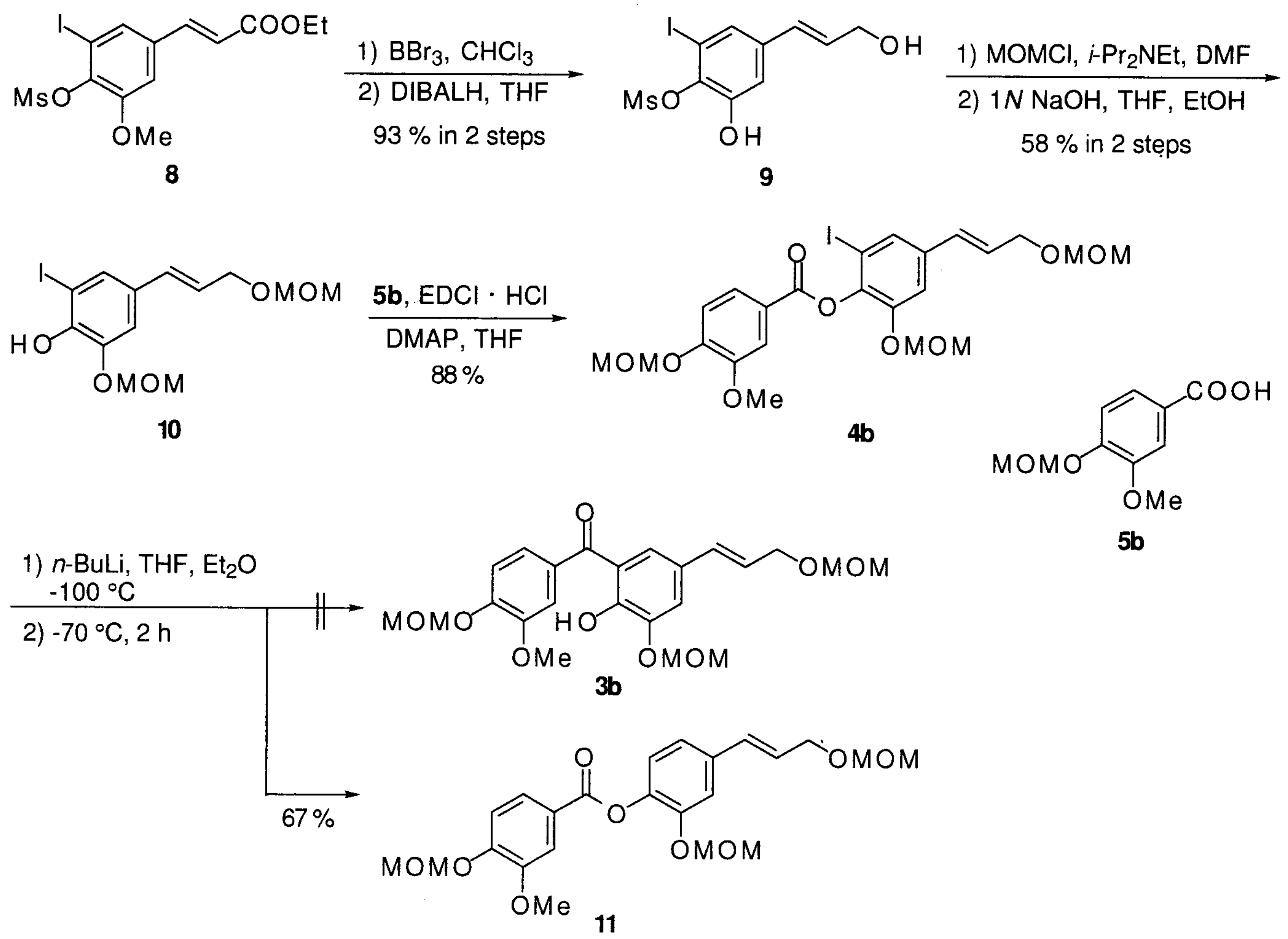
First, the photo-Fries rearrangement was investigated, as shown in Scheme 2. Vanillic acid was protected with 4-methoxybenzyl chloride (MPMCl) and then hydrolyzed the resulting ester to afford the acid (**5a**) in 90 % yield in 2 steps. The hydroxy moiety of the 3-position in 3,4-dihydroxybenzaldehyde (**6**) was regioselectively protected with MPMCl according to the literature[7] to give the phenol (**7**) in 64 % yield. The condensation of **7** with **5a** using *N*,*N'*-dicyclohexylcarbodiimide (DCC) furnished the ester (**4a**) in 65 % yield. Attempted photo-Fries rearrangement of the ester (**4a**) using a 100 W high pressure mercury lamp resulted in the decomposition in the case of the internal irradiation or the recovery of the starting material in the case of the external irradiation, and failed to produce the benzophenone derivative (**3a**).

Scheme 2



Next, we attempted the anionic Fries rearrangement of *o*-iodophenyl benzoates.[8] Horne and Rodrigo have reported that an anionic Fries rearrangement proceeded by a complex induced proximity effect in satisfactory yields only when the substrates containing a methoxy group in the appropriate positions was employed.[8] We expected that the anionic rearrangement would occur in a similar manner when a methoxymethoxy group was used instead of a methoxy group. The synthesis of *o*-iodophenyl benzoate derivatives (**4b**) was conducted as shown in Scheme 3. The methyl ether of the ferulic acid ester derivative (**8**)[5e] was deprotected with excess boron tribromide,[9] followed by reduction of the ethyl ester with diisobutylaluminum hydride (DIBALH) to give the diol (**9**) in 93 % yield in 2 steps. After the dihydroxy functions were protected with chloromethyl methyl ether (MOMCl), the mesylate was hydrolyzed with alkaline treatment to afford **10** in 58 % yield from **9**. The condensation of the phenol (**10**) with the acid (**5b**)[10] by use of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI) afforded the ester (**4b**) in 88 % yield. Although the anionic Fries rearrangement of the ester (**4b**) was conducted under the Horne and Rodrigo's conditions,[8] the *o*-hydroxybenzophenone (**3b**) was not obtained at all. Instead, the deiodinated product (**11**) was isolated in 67 % yield.

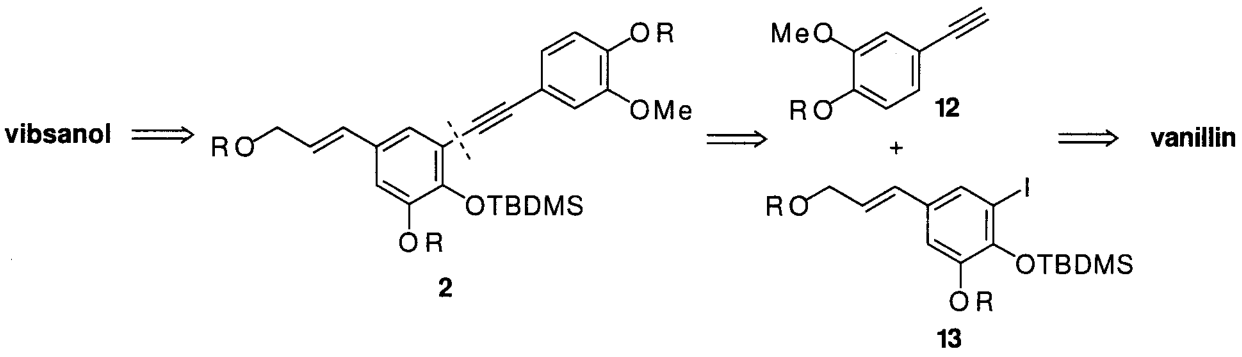
Scheme 3



In this stage, we decided to change the strategy for the synthesis of the *o*-siloxyarylalkynes (**2**), as shown in Scheme 4. The diarylalkyne moiety would be smoothly constructed from the alkyne (**12**) and the iodide

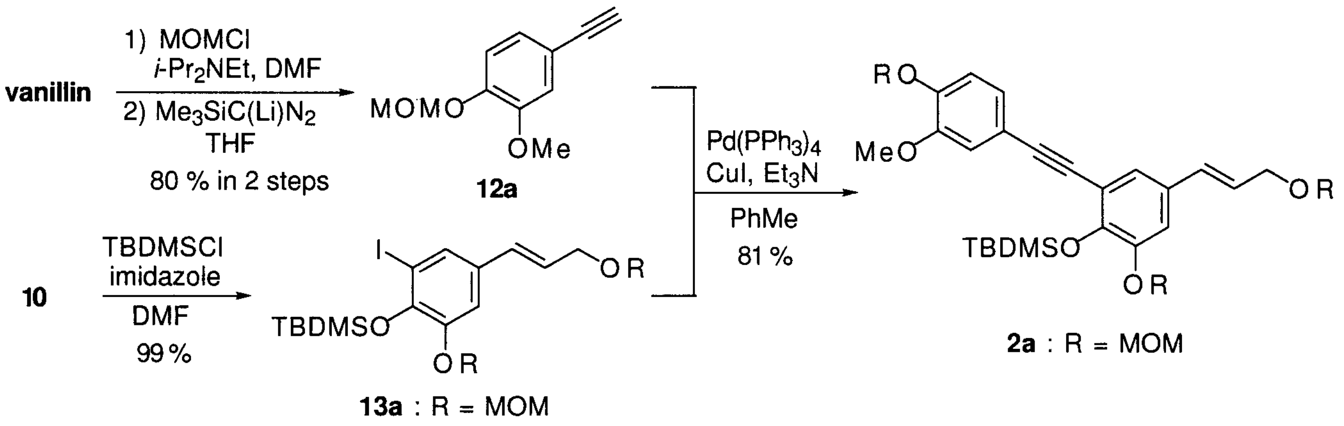
(**13**) by the palladium-copper catalyzed Sonogashira reaction.[11] In addition, the respective intermediates would be prepared from the readily available vanillin.[5e,12]

Scheme 4



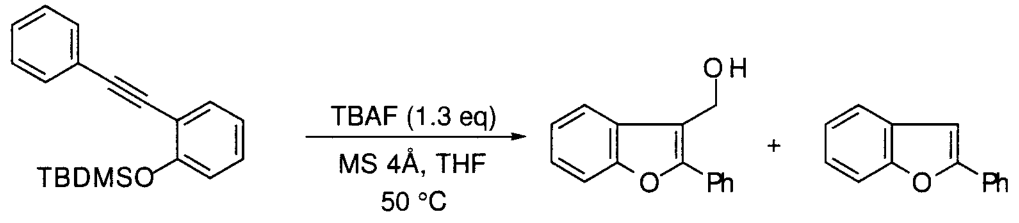
First, vanillin was efficiently converted to the alkyne (**12a**) by the sequential phenol protection with MOMCl and homologation reaction of the resulting aldehyde with $Me_3SiC(Li)N_2$[13,14] in 80 % overall yield. The phenol (**10**) was protected with the *tert*-buyldimethylsilyl (TBDMS) group to afford the iodide (**13a**) in 99 % yield. Then, the Sonogashira cross coupling reaction[11] of the iodide (**13a**) with the alkyne (**12a**) was smoothly achieved to give the benzofuran precursor (**2a**) in 81 % yield (Scheme 5).

Scheme 5



Before the tandem cyclization of **2a** was performed, we investigated the model cyclization using *o*-tert-butyldimethylsiloxydiphenylacetylene (**14**) by use of TBAF in the presence of molecular sieves 4 Å (MS 4 Å). The desired 3-benzofuranmethanol (**15**) was produced together with 2-phenylbenzofuran (**16**), as shown in Table. The yield of the 3-benzofuranmethanol (**15**) was increased by increasing the equivalents of paraformaldehyde (entries 1-4). We have found that a THF solution of TBAF should be dehydrated over molecular sieves 4 Å for 3 h, but prolongation of the dehydration as well as cyclization time did not increase the yield of **15** (entries 5, 6). Instead of paraformaldehyde, the direct introduction of formaldehyde gas was not effective (entry 7). The best result was eventually obtained by employing 15 equivalents of paraformaldehyde to give **15** in 84 % yield (entry 4).

Table : Preparation of 2-phenyl-3-benzofuranmethanol (**15**) by the tandem cyclization of **14**



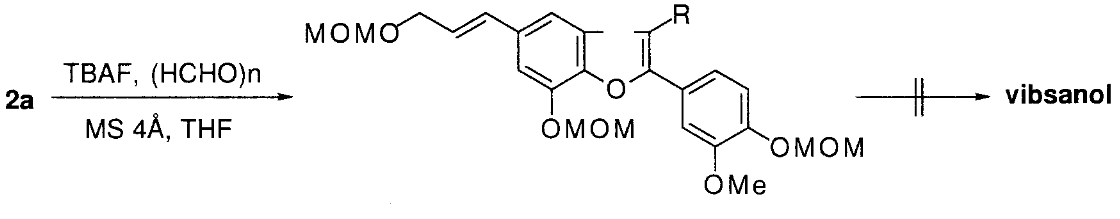
14 **15** **16**

entry	Hydroxymethylene equivalent (eq)	Time (h) Dehydration [b]	Cyclization	Yield (%) [a] **15**	**16**
1	$(HCHO)_n$ (2.5)	3	6	38	50
2	$(HCHO)_n$ (5.0)	3	6	63	37
3	$(HCHO)_n$ (10)	3	6	82	16
4	$(HCHO)_n$ (15)	3	6	84	16
5	$(HCHO)_n$ (15)	14	6	74	24
6	$(HCHO)_n$ (15)	3	13	83	16
7	HCHO (gas, excess)	3	5	59	41

a) Isolated yield. b) Time for dehydration of TBAF with MS 4Å.

Although the tandem cyclization of **2a** proceeded under the same reaction conditions, the desired benzofuran (**17a**) was obtained in poor yield. However, in this case, we found that the yield of **17a** was affected by the dehydration ability of molecular sieves 4 Å. For this purpose, molecular sieves 4 Å were dried at 180 °C for 4 h under reduced pressure just prior to use. Thus, when well fine dried molecular sieves 4 Å were used, the tandem cyclization of **2a** successfully proceeded to give the desired **17a** in 65 % yield accompanied with the benzofuran (**18a**) in 35 % yield (Scheme 6). The nucleophilicity of the anion of benzofuran in the 3-position derived from **2a** may be lower than that derived from **14** because of the steric hindrance or electronic effect by the oxygen-functionalized substitution groups. Unfortunately, the various attempts of the deprotection of the methoxymethyl function from **17a** in the final step resulted in the

Scheme 6

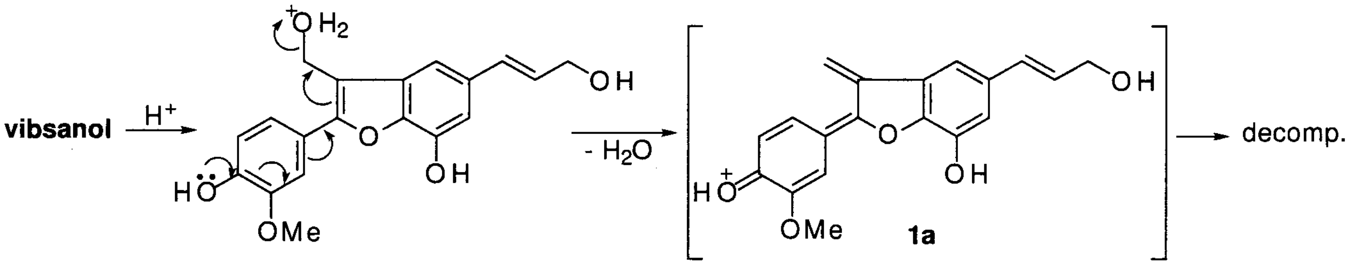


17a : R = CH_2OH 65%
18a : R = H 35%

decomposition under the normal reaction conditions (e.g., 0.1 N HCl, TFA, cat. HCl/NaI/acetone, TMSBr, *B*-bromo-catecholborone, triphenylmethyltetrafluoroborate).

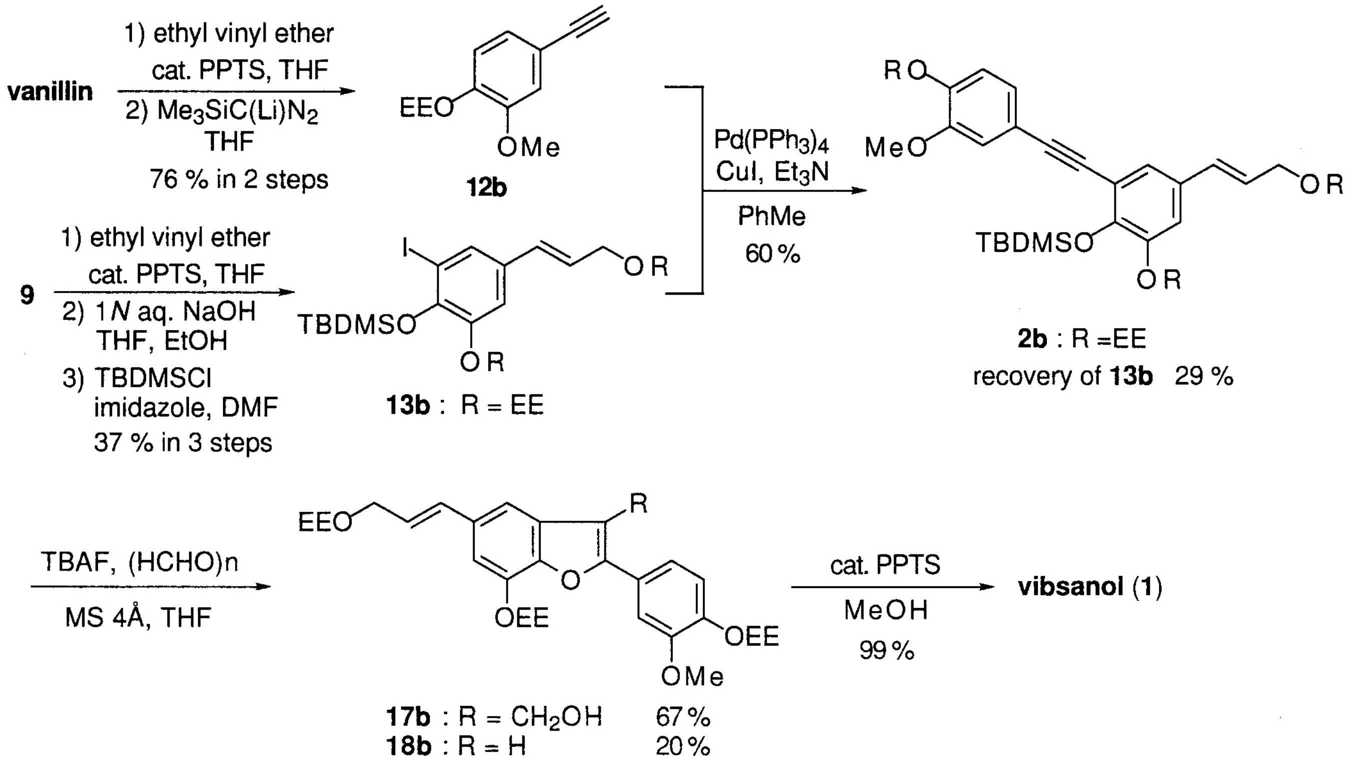
The decomposition process of vibsanol with the strong acids may be explained by assuming the dehydrated intermediate (**1a**), as shown in Scheme 7.

Scheme 7



Ultimately, the total synthesis of vibsanol was accomplished by using the 1-ethoxyethyl (EE) group readily cleaved under less acidic conditions in place of the MOM group. Vanillin was converted to the alkyne (**12b**) by the sequential hydroxy protection with ethyl vinyl ether in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS),[15] and homologation reaction of the resulting aldehyde with $Me_3SiC(Li)N_2$[13] in 76 % yield in 2 steps. Also, the diol (**9**) was protected with ethyl vinyl ether in the presence of a catalytic amount of PPTS to afford the labile mesylate. After alkaline saponification of the mesylate, resulting phenol was reprotected with TBDMSCl to give **13b** in 37 % overall yield. The cross

Scheme 8



coupling reaction of the alkyne (**12b**) with the iodide (**13b**) was achieved to provide **2b** in 60 % yield together with the recovery of **13b** in 29 % yield.[11] The tandem cyclization of **2b** afforded the desired benzofuran (**17b**) in 67 % yield together with **18b** in 20 % yield. Finally, the deprotection of **17b** smoothly occurred using a catalytic amount of PPTS in MeOH[15] to give vibsanol (**1**) in 99 % yield, as shown in Scheme 8. Synthetic vibsanol exhibited identical properties to those reported for the natural substance (IR, ^{1}H and ^{13}C NMR, MS and HRMS).

In conclusion, we have completed the convenient total synthesis of vibsanol using the tandem cyclization of *o*-siloxydiarylalkyne in the presence of paraformaldehyde. The method employed will be useful for the synthesis of other 3-hydroxymethylbenzofuran derivatives.

EXPERIMENTAL

All melting points were uncorrected. IR spectra were measured with a SHIMADZU FT IR-8100 spectrophotometer. ^{1}H NMR spectra were measured with a JEOL EX-270 (270 MHz) or GSX-400 (400 MHz) spectrometer with tetramethylsilane or $CHCl_3$ as an internal standard. ^{13}C NMR spectra were measured with a JEOL EX-270 (67.8 MHz) spectrometer with the solvent as an internal standard (deuterochloroform: δ 77.0 ppm). Analytical thin layer chromatography was carried out on a silica gel plate (Merck Art. 5715). MS spectra were obtained on a JEOL JMS-SX 102A spectrometer. Silica gel BW-820 MH (purchased from Fuji Davison Co.) was used for column chromatography. Tetrabutylammonium fluoride (TBAF) was heated at 40-45 ℃ under reduced pressure in the presence of P_2O_5 for 72 h, dissolved in THF under argon , and reserved in a freezer.

3-Methoxy-4-(4-methoxyphenylmethoxy)benzoic acid (5a)

To a solution of vanillic acid (1.68 g, 10.0 mmol) in DMF (25 mL) were added MPMCl (3.29 g, 21.0 mmol) and K_2CO_3 (2.98 g, 21.6 mmol) at rt. The reaction mixture was stirred at 65 ℃ for 37 h. After cooling to rt, the mixture was diluted with EtOAc (50 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL × 4), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give the ester (3.90 g, 95 %) as a white solid.

The resulting ester (408 mg, 1.00 mmol) was added to a solution of KOH (85 % purity, 330 mg, 5.00 mmol) in H_2O (3.3 mL), THF (3.3 mL), and MeOH (5 mL). The mixture was stirred at rt for 9 h. Then, the mixture was cooled to 0 ℃ and acidified by addition of conc. HCl to adjust pH 3-4. The aqueous layer was extracted with $CHCl_3$ (25 mL × 4), and the combined organic extracts were washed with H_2O (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was recrystallized from hexane-EtOAc to give **5a** (275 mg, 95 %) as a white solid: mp 178 ℃; IR ν_{max}^{Nujol} cm^{-1} 3100-2400, 1678, 1590, 1518, 1426, 1347, 1273, 1225, 1177, 1030, 984; ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 3.93 (3H, s), 5.16 (2H, s), 6.91 (2H, d, J = 8.9 Hz,), 6.94 (1H, d, J = 8.6 Hz), 7.37 (2H, d, J = 8.6 Hz), 7.59 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 2.0, 8.2 Hz); Anal. Calcd for $C_{16}H_{16}O_5$: C, 66.66; H, 5.59. Found: C, 66.41; H, 5.52.

4-Hydroxy-3-(4-methoxyphenylmethoxy)benzaldehyde (7)

The aldehyde (7) (6.60 g, 64 %) was prepared from vanillin (5.53 g, 40 mmol) according to the literature procedure.[7]

7: a white solid; mp 130-132 °C (MeOH-Et_2O); IR ν_{max}^{Nujol} cm^{-1} 3178, 1651, 1576, 1516, 1464, 1256, 1129, 1005, 974; ^{1}H NMR ($CDCl_3$) δ 3.84 (3H, s), 5.10 (2H, s), 6.23 (1H, s, exchangeable with D_2O), 6.95 (2H, d, J = 8.6 Hz), 7.05 (1H, d, J = 7.9 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.44 (1H, dd, J = 1.8, 8.1 Hz), 7.52 (1H, d, J = 2.0 Hz), 9.83 (1H , s); Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.48.

4-Formyl-2-(4-methoxyphenylmethoxy)phenyl 3-methoxy-4-(4-methoxyphenylmethoxy)-benzoate (4a)

To a solution of **5a** (1.27 g, 4.40 mmol) and **7** (1.03 g, 4.00 mmol) in DMF (10 mL) were successively added DCC (1.00 g, 4.84 mmol) and DMAP (161 mg, 1.32 mmol) at 0 °C under argon. After being stirred at 0 °C for 10 min, the mixture was stirred at rt for 22 h. The mixture was filtered through a pad of Celite, and the filtrate was diluted with EtOAc (50 mL) and H_2O (30 mL). The aqueous layer was extracted with EtOAc (30 mL × 2), and the combined organic extracts were washed with 1*N* aqueous KOH (30 mL × 3) and saturated brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1 → 1 : 1) to afford the ester (**4a**) (1.37 g, 65 %) as a white solid: mp 128-129 °C (hexane-EtOAc); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 1732, 1696, 1615, 1599, 1516, 1273, 1252, 1211, 1175, 1032; ^{1}H NMR ($CDCl_3$) δ 3.77 (3H, s), 3.82 (3H, s), 3.91 (3H, s), 5.10 (2H, s), 5.18 (2H, s), 6.80 (2H, d, J = 8.6 Hz), 6.92 (2H, d, J = 8.6 Hz,), 6.97 (2H, d, J = 8.3 Hz), 7.24-7.26 (2H, m), 7.38 (2H, d, J = 6.9 Hz), 7.52 (1H, d, J = 1.7 Hz), 7.57 (1H, d, J = 8.9 Hz), 7.65 (1H, d, J = 2.0 Hz), 7.79 (1H, dd, J = 2.0, 8.3 Hz), 9.95 (1H, s); Anal. Calcd for $C_{31}H_{28}O_8$: C, 70.44; H, 5.34. Found: C, 70.25; H, 5.42.

(*E*)-3-(5-Hydroxy-3-iodo-4-mesyloxyphenyl)-2-propen-1-ol (9).

To a solution of the ether (**8**)[5e] (1.47 g, 3.45 mmol) in $CHCl_3$ (30 mL) was dropwise added boron tribromide (4.32 g, 17.3 mmol) in $CHCl_3$ (10 mL) at 0 °C under argon. The reaction mixture was stirred at 0 °C for 52 h, and then quenched by the addition of cold water (30 mL). The aqueous phase was extracted with $CHCl_3$ (50 mL × 3) and the combined organic extracts were washed with H_2O (30 mL × 2) and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from hexane-EtOAc to give the phenol (1.34 g, 94 %) as a white solid: mp 170-172 °C; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3389, 1684, 1636, 1592, 1428, 1364, 1304, 1277, 1171, 1117; ^1H NMR ($CDCl_3$) δ 1.34 (3H, t, J = 7.1 Hz), 3.51 (3H, s), 4.27 (2H, q, J = 7.0 Hz), 6.38 (1H, d, J = 15.8 Hz,), 6.69 (1H, s, exchangeable with D_2O), 7.19 (1H, d, J = 2.0 Hz), 7.50 (1H, d, J = 16.2 Hz), 7.55 (1H, d, J = 2.0 Hz); EIMS *m/z*: 412 (M^+), 333 (base peak, M^+-$MeSO_2$); Anal. Calcd for $C_{12}H_{13}O_6IS$: C, 34.97; H, 3.18. Found: C, 35.37; H, 3.18.

To a solution of the resulting ester (4.49 g, 10.9 mmol) in THF (150 mL) was dropwise added DIBALH (29 mL, 1.5 M in toluene, 43.5 mmol) at -78 °C under argon. The reaction mixture was stirred at -78 °C for 4 h and the reaction was quenched by the addition of 6 *N* aqueous HCl (20 mL). The aqueous layer was extracted with EtOAc (50 mL × 3), and the combined organic extracts were washed with saturated brine (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was recrystallized from hexane-EtOAc to give the diol (**9**) (4.00 g, 99 %) as a white solid: mp 125-126 °C; IR ν_{max} ^{CHCl_3} cm^{-1} 3440, 1590, 1489, 1424, 1206, 1192, 1171, 1117, 1084; ^1H NMR (DMSO-d6) δ 3.52 (3H, s), 4.09 (2H, t, J = 4.6 Hz), 4.90 (1H, t, J = 5.4 Hz, exchangeable with D_2O), 6.28 (1H, dt, J = 4.3, 16.2 Hz), 6.41 (1H, d, J = 16.5 Hz), 6.95 (1H, d, J = 1.7 Hz), 7.35 (1H, d, J = 2.0 Hz); ^{13}C NMR (CD_3OD) δ 41.3, 63.3, 93.9, 115.5, 128.8, 129.3,132.3, 139.6 (× 2), 151.5; EIMS *m/z*: 370 (M^+), 291 (base peak, M^+-$MeSO_2$), 136; HRMS Calcd for $C_{10}H_{11}O_5IS$: 369.9331. Found: 369.9371.

(*E*)-1-(4-Hydroxy-3-iodo-5-methoxymethoxyphenyl)-3-methoxymethoxy-1-propene (10). To a solution of the diol (**9**) (320 mg, 0.865 mmol) in DMF (4 mL) were added diisopropylethylamine (671 mg, 5.19 mmol) and chloromethyl methyl ether (348 mg, 4.33 mmol) at 0 °C. After being stirred at 0 °C for 30 min, the reaction mixture was warmed to rt and was stirred at this temperature for 16.5 h. The mixture was diluted with EtOAc (50 mL), washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1) to give the mesylate (301 mg, 79 %) as a pale yellow oil: IR ν_{max}^{neat} cm^{-1} 1559, 1458, 1364, 1173, 1154, 1015; ^1H NMR ($CDCl_3$) δ 3.41 (3H, s), 3.45 (3H, s), 3.52 (3H, s), 4.22 (2H, dd, J = 1.7, 5.6 Hz), 4.69 (2H, s), 5.24 (2H, s), 6.27 (1H, dt, J = 5.6, 15.8 Hz), 6.51 (1H, d, J = 15.8 Hz), 7.22 (1H, d, J = 2.0 Hz), 7.50 (1H, d, J = 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 41.3, 55.3, 56.6, 67.2, 92.0, 95.3, 95.7, 114.2, 128.4, 129.4, 130.4, 138.0, 140.1, 150.1; EIMS *m/z* 458 (M^+), 379 (M^+-$MeSO_2$), 303 (base peak), 148; HRMS Calcd for $C_{14}H_{19}O_7IS$: 457.9855. Found: 457.9897.

To a solution of the resulting mesylate (301 mg, 0.681 mmol) in THF (1.5 mL) and EtOH (3 mL) was added 1 *N* aqueous NaOH (1.5 mL) at rt. The reaction mixture was heated at 50 °C, and stirred at this temperature for 2 h. Then the reaction mixture was cooled to 0 °C, and acidified by the addition of 1 *N* aqueous NH_4Cl to adjust pH 3-4. The aqueous layer was extracted with EtOAc (30 mL × 3), and the combined organic extracts were washed with saturated brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1) to give the phenol (**10**) (188 mg, 73 %) as a colorless oil: IR ν_{max}^{neat} cm^{-1} 3378, 1595, 1570, 1493, 1428, 1399, 1277, 1152, 1015; ^1H NMR ($CDCl_3$) δ 3.40 (3H, s), 3.52 (3H, s), 4.19 (2H, dd, J = 1.3, 5.9 Hz), 4.68 (2H, s), 5.21 (2H, s), 6.14 (1H, dt, J = 6.0, 15.8 Hz), 6.41 (1H, s, exchangeable with D_2O), 6.46 (1H, d, J = 16.2 Hz), 7.14 (1H, d, J = 2.0 Hz), 7.41 (1H, d, J = 1.7 Hz).

2-Iodo-6-methoxymethoxy-4-[3-methoxymethoxy-1-(*E*)-propenyl]phenyl 3-methoxy-4-methoxymethoxybenzoate (4b)

To a solution of **5b** (437 mg, 2.06 mmol), **10** (521 mg, 1.37 mmol), and DMAP (33 mg, 0.274 mmol) in THF (8 mL) was added EDCI·HCl (341 mg, 1.78 mmol) at 0 °C under argon. After being stirred at 0 °C for 30 min, the mixture was stirred at rt for 15.5 h. The mixture was diluted with EtOAc (150 mL), washed with saturated aqueous NH_4Cl (50 mL × 2), H_2O (30 mL), 10 % aqueous K_2CO_3 (50 mL), and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1 → 1 : 1) to give **4b** (692 mg, 88 %) as a viscous oil. The product (**4b**) was solidified in a freezer: mp 87-89 °C (hexane-EtOAc); IR ν_{max}^{neat} cm^{-1} 1738, 1599, 1592, 1510, 1289, 1271, 1215, 1200, 1175, 1157, 1130, 1080, 1017, 980; ^1H NMR ($CDCl_3$) δ 3.41 (3H, s), 3.43 (3H, s), 3.54 (3H, s), 3.98 (3H, s), 4.23 (2H, dd, J = 1.5, 5.8 Hz), 4.70 (2H, s), 5.14 (2H, s), 5.34 (2H, s), 6.27 (1H, dt, J = 5.8, 15.8 Hz), 6.55 (1H, d, J = 15.8 Hz), 7.24-7.28 (2H, m), 7.52 (1H, d, J = 1.7 Hz), 7.75 (1H, d, J = 2.0 Hz),7.89 (1H, dd, J = 2.1, 8.4 Hz); Anal. Calcd for $C_{23}H_{27}O_9I$: C, 48.10; H, 4.74. Found: C, 48.12, H, 4.73.

4-Methoxymethoxy-2-[3-methoxymethoxy-1-(*E*)-propenyl]phenyl 3-methoxy-4-methoxymethoxybenzoate (11)

To a solution of **4b** (150 mg, 0.26 mmol) in THF (1.2 mL) and Et_2O (0.3 mL) was dropwise added *n*-butyllithium (0.18 mL, 1.61 M in hexane, 0.29 mmol) at -100 °C under argon. After being stirred at -100 °C for 15 min, the mixture was stirred at -70 °C for 2 h. The mixture was quenched with saturated aqueous NH_4Cl (1 mL) and warmed to rt. EtOAc (50 mL) and saturated aqueous NH_4Cl (30 mL) were added to the mixture. The aqueous layer was extracted with EtOAc (30 mL × 2). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1) to afford **11** (78 mg, 67 %) as a yellow oil: IR

ν_{max}^{neat} cm^{-1} 1735, 1601, 1512, 1289, 1269, 1215, 1198, 1175, 1156, 1080, 1032, 997; ^{1}H NMR ($CDCl_3$) δ 3.42 (3H, s), 3.44 (3H, s), 3.54 (3H, s), 3.97 (3H, s), 4.24 (2H, dd, J = 1.5, 6.1 Hz), 4.71 (2H, s), 5.16 (2H, s), 5.33 (2H, s), 6.27 (1H, dt, J = 5.7, 15.8 Hz), 6.62 (1H, d, J = 15.8 Hz), 7.05-7.09 (2H, m), 7.20-7.29 (2H, m), 7.71 (1H, d, J = 2.0 Hz), 7.84 (1H, dd, J = 2.0, 8.6 Hz).

3-Methoxy-4-methoxymethoxyphenylacetylene (12a).

To a solution of vanillin (1.52 g, 10 mmol) in DMF (10 mL) were added diisopropylethylamine (1.55 g, 12 mmol) and chloromethyl methyl ether (970 mg, 12 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was warmed to rt and was stirred at this temperature for 12 h. The reaction mixture was diluted with EtOAc (100 mL), washed with H_2O (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give the protected vanillin (1.90 g, 97 %) as a pale yellow oil: IR ν_{max}^{neat} cm^{-1} 1682, 1590, 1507, 1266, 1156, 1130,1080, 980; ^{1}H NMR ($CDCl_3$) δ 3.53 (3H, s), 3.96 (3H, s), 5.33 (2H, s), 7.29 (1H, d, J = 2.6 Hz), 7.42-7.45 (2H, m), 9.88 (1H, s); EIMS *m/z*: 196 (M^+, base peak), 166.

n-Butyllithium (3.8 mL, 1.59 M in hexane, 6.0 mmol) was added dropwise to a solution of trimethylsilyldiazomethane[14] (3.4 mL, 1.75 M in hexane, 6.0 mmol) in THF (40 mL) at -78 °C under argon and the mixture was stirred for 30 min. The protected vanillin (980 mg, 5.0 mmol), prepared as above, in THF (10 mL) was dropwise added at -78 °C. The mixture was stirred at -78 °C for 1 h, and then heated under reflux for 3 h. After being quenched with cold water (5 mL), the mixture was diluted with EtOAc (100 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (50 mL × 2), and the combined extracts were washed with saturated brine (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 3 : 2) to afford the acetylene (**12a**) (784 mg, 82 %) as a pale yellow solid: mp 44-45 °C (hexane/EtOAc); IR ν_{max}^{neat} cm^{-1} 3285, 2107, 1599, 1580, 1510, 1264, 1154, 1130, 1078, 992; ^{1}H NMR ($CDCl_3$) δ 3.01 (1H, s), 3.51 (3H, s), 3.88 (3H, s), 5.24 (2H, s), 7.02-7.08 (3H, m); EIMS *m/z*: 192 (M^+, base peak), 162; Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.61; H, 6.31.

(*E*)-1-(4-*tert*-Butyldimethylsiloxy-3-iodo-5-methoxymethoxyphenyl)-3-methoxymethoxy-1-propene (13a).

The phenol (**10**) (133 mg, 0.35 mmol), imidazole (60 mg, 0.875 mmol), and *tert*-butylchlorodimethylsilane (79 mg, 0.525 mmol) were dissolved in DMF (2 mL) at rt, and then stirred at this temperature for 13 h. The reaction mixture was diluted with EtOAc (30 mL) and H_2O (30 mL). The aqueous layer was extracted with EtOAc (30 mL × 2), and the combined organic extracts were successively washed with saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and saturated brine (30 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 6 : 1) to give **13a** (171 mg, 99 %) as a colorless oil: IR ν_{max}^{neat} cm^{-1} 1553, 1480, 1426, 1393, 1302, 1252, 1157, 1140, 1105, 1084, 1021; ^{1}H NMR ($CDCl_3$) δ 0.27 (6H, s), 1.05 (9H, s), 3.40 (3H, s), 3.48 (3H, s), 4.19 (2H, dd, J = 1.3, 5.9 Hz), 4.68 (2H, s), 5.14 (2H, s), 6.15 (1 H, dt, J = 6.1, 15.5 Hz), 6.45 (1H, d, J = 15.8 Hz), 7.17 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 2.0 Hz); EIMS *m/z*: 494 (M^+), 331, 204 (base peak); Anal. Calcd for $C_{19}H_{31}O_5ISi$: C, 46.15; H, 6.32. Found: C, 46.44; H, 6.31.

2-*tert*-Butyldimethylsiloxy-3-methoxymethoxy-5-(*E*)-(3-methoxymethoxy-1-propenyl)-phenylethynyl 3-methoxy-4-methoxymethoxybenzene (2a).

To a mixture of the iodide (**13a**) (638 mg, 1.29 mmol), tetrakis(triphenylphosphine)palladium (149 mg, 0.129 mmol), and CuI (49 mg, 0.258 mmol) in toluene (6 mL) was added a solution of the acetylene (**12a**) (298 mg, 1.55 mmol) and triethylamine (188 mg, 1.86 mmol) in toluene (2 mL) at rt under argon. The reaction mixture was stirred in the dark at rt for 22.5 h, and then diluted with EtOAc (150 mL). The solution was washed with saturated aqueous NH_4Cl (50 mL) and saturated brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 4 : 1) to afford the desired product (**2a**) (580 mg, 81 %) as a yellow oil. The product was solidified in a freezer: mp 64-67 °C (hexane-EtOAc); IR ν_{max}^{neat} cm^{-1} 1512, 1472, 1250, 1156, 1040; ^{1}H NMR ($CDCl_3$) δ 0.25 (6H, s), 1.06 (9H, s), 3.40 (3H, s), 3.50 (3H, s), 3.52 (3H, s), 3.89 (3H, s), 4.20 (2H, d, J = 5.9 Hz), 4.69 (2H, s), 5.16 (2H, s), 5.25 (2H, s), 6.19 (1H, dt, J = 6.2, 15.8 Hz), 6.51 (1H, d, J = 16.2 Hz), 7.06-7.17 (5H, m); ^{13}C NMR ($CDCl_3$) δ -4.0 (× 2), 18.7, 25.9 (× 3), 55.3, 55.9, 56.2 (× 2), 67.7, 85.8, 92.9, 95.1, 95.3, 95.5, 113.9, 114.7, 115.9, 116.5, 117.4, 124.6, 124.7, 125.0, 130.1, 131.7, 146.1, 146.8, 148.5, 149.2; EIMS *m/z*: 558 (M^+), 395 (base peak); HRMS Calcd for $C_{30}H_{42}O_8Si$: 558.2649. Found: 558.2649.

2-Phenyl-3-benzofuranmethanol (15) and 2-phenylbenzofuran (16).

General procedure: To a suspension of powdered molecular sieves 4 Å (400 mg), paraformaldehyde (90 % purity) in THF (3 mL) was added TBAF (0.49 M in THF, 0.94 mL, 0.46 mmol) at rt under argon. The reaction mixture was stirred at rt for a period shown in Table. Then, the alkyne (**14**) (108 mg, 0.35 mmol) in THF (1 mL) was added to the mixture, which was stirred at 50 °C for a period shown in Table. After cooling to rt, the mixture was filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 2 : 1) to give the 3-hydroxymethylated **15** and the benzofuran (**16**).[16] In the case of entry 7 in Table, formaldehyde, which was generated from paraformaldehyde by heating at 150-160 °C, was employed in place of paraformaldehyde.

15: a white solid; mp 92-94 °C (hexane-Et_2O); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3351, 1593, 1570, 1478, 1456, 1443, 1343, 1264, 1240, 1200, 1125, 1069, 1007, 994; ^1H NMR ($CDCl_3$) δ 1.63 (1H, t, J = 5.6 Hz, exchangeable with D_2O), 5.01 (2H, d, J = 5.0 Hz), 7.29-7.89 (9H, m); EIMS *m/z*: 224 (M^+, base peak), 207; Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.04; H, 5.65.

16: mp 116-118 °C (hexane-Et_2O), [lit.,[16] mp 118-119 °C (Et_2O-CH_2Cl_2)].

MOM-protected vibsanol (17a) and benzofuran (18a).

To a mixture of paraformaldehyde (25 mg, 90 % purity, 0.75 mmol) and powdered molecular sieves 4 Å (400 mg, dried over at 180 °C for 4 h under reduced pressure prior to use) in THF (1 mL) was added TBAF (0.13 mL, 0.49 M in THF, 0.065 mmol) at rt under argon, and the mixture was stirred at rt for 3 h. Then the alkyne (**2a**) (29 mg, 0.052 mmol) in THF (1 mL) was added dropwise to the mixture, which was stirred at 50 °C for 3 h. After cooling to rt, 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 (BW-820MH, hexane : EtOAc = 1 : 1 → EtOAc only) to afford the benzofuran (**18a**) (8 mg, 35 %) as a yellow solid and the desired **17a** (16 mg, 65 %) as a yellow solid.

17a: mp 91-93 °C (hexane-EtOAc); IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3384, 1615, 1597, 1512, 1372, 1314, 1250, 1156, 1140, 1080, 1034; ^1H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.55 (3H, s), 3.58 (3H, s), 3.98 (3H, s), 4.26 (2H, d, J = 5.6 Hz), 4.72 (2H, s), 4.93 (2H, s), 5.30 (2H, s), 5.40 (2H, s), 6.30 (1H, dt, J = 6.2, 15.8 Hz), 6.72 (1H, d, J = 15.8 Hz), 7.17 (1H, d, J = 1.3 Hz), 7.24-7.27 (2H, m), 7.36-7.46 (2H, m); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.4, 56.0, 56.3, 56.4, 67.8, 95.3, 95.5, 95.6, 109.8, 111.0, 111.4, 114.4, 116.1, 120.5, 124.2, 124.8, 131.4, 132.8, 133.0, 142.3, 143.5, 147.3, 149.8, 154.3; EIMS *m/z*: 474 (M^+, base peak), 429; HRMS Calcd for $C_{25}H_{30}O_9$: 474.1889. Found: 474.1891.

18a: 74-76 °C (hexane-EtOAc); IR $\nu_{max}^{CHCl_3}$ cm^{-1}1597, 1512, 1339, 1277, 1159, 1134, 1071, 1001; ^1H NMR ($CDCl_3$) δ 3.43 (3H, s), 3.54 (3H, s), 3.60 (3H, s), 3.99 (3H, s), 4.25 (2H, d, J = 5.4 Hz), 4.72 (2H, s), 5.28 (2H, s), 5.41 (2H, s), 6.27 (1H, dt, J = 6.2, 15.8 Hz), 6.69 (1H, d, J = 15.8 Hz), 6.89 (1H, s), 7.14 (1H, d, J = 1.3 Hz), 7.20-7.23 (2H, m), 7.38 (1H, d, J = 2.0 Hz), 7.42 (1H, dd, J = 2.1, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 55.3, 56.0, 56.3, 56.4, 67.8, 95.3, 95.5, 95.7, 100.8, 108.5, 109.4, 112.9, 116.2, 118.1, 124.6, 124.7, 131.4, 132.9 (× 2), 142.3, 144.5, 147.1, 149.8, 156.5; EIMS *m/z*: 444 (M^+, base peak), 399; HRMS Calcd for $C_{24}H_{28}O_8$: 444.1784. Found: 444.1805.

4-(1-Ethoxyethoxy)-3-methoxyphenylacetylene (12b).

To a solution of vanillin (1.52 g, 10 mmol) in THF (5 mL) at rt were added ethyl vinyl ether (5 mL, 52 mmol) and PPTS (50 mg, 0.20 mmol). After the mixture was stirred at rt for 30 h, the mixture was diluted with EtOAc (150 mL), washed with saturated aqueous $NaHCO_3$ (50 mL) and saturated brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the protected vanillin (2.24 g, 100 %) as a pale yellow oil: IR ν_{max}^{neat} cm^{-1} 1684, 1596, 1586, 1507, 1466, 1424, 1395, 1385, 1267, 1154, 1123,1032; ^1H NMR ($CDCl_3$) δ 1.21 (3H, t, J = 6.9 Hz), 1.58 (3H, d, J = 5.3 Hz), 3.52-3.88 (2H, m), 3.93 (3H, s), 5.54 (1H, q, J = 5.3 Hz), 7.23 (1H, d, J = 8.6 Hz), 7.40-7.43 (2H, m), 9.87 (1H, s); EIMS *m/z*: 224 (M^+), 152 (base peak), 151, 73.

The protected vanillin (1.10 g, 5.0 mmol) was converted as described for **12a** to give the acetylene (**12b**) (833 mg, 76 %) as a pale yellow oil: IR ν_{max}^{neat} cm^{-1} 3287, 2107, 1599, 1576, 1507, 1264, 1121, 1036; ^1H NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7.1 Hz), 1.51 (3H, d, J = 5.6 Hz), 3.02 (1H, s), 3.53-3.88 (2H, m), 3.85 (3H, s), 5.39 (1H, q, J = 5.4 Hz), 7.01-7.04 (3H, m); ^{13}C NMR ($CDCl_3$) δ 15.1, 20.2, 55.8, 61.9, 76.0, 83.6, 101.0, 115.5, 116.0, 118.5, 125.2, 146.8, 150.3; EIMS *m/z*: 220 (M^+), 148 (base peak), 73; HRMS Calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1088.

(*E*)-3-(1-Ethoxyethoxy)-1-[4-*tert*-butyldimethylsiloxy-5-(1-ethoxyethoxy)-3-iodophenyl]-1-propene (13b).

To a solution of the diol (**9**) (1.48 g, 4.0 mmol) in THF (3 mL) were added ethyl vinyl ether (3 mL) and PPTS (50 mg, 0.20 mmol) at 0 °C. After being stirred at 0 °C for 13 h, the reaction mixture was diluted with EtOAc (100 mL), washed with saturated brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 6 : 1 → 3 : 1) to give the mesylate (1.52 g, 74 %) as a pale orange oil: IR ν_{max}^{neat} cm^{-1} 1586, 1563, 1456, 1418, 1374, 1300, 1277, 1175, 1111; ^1H NMR ($CDCl_3$) δ 1.14-1.29 (6H, m), 1.36 (3H, d, J = 5.3 Hz), 1.55 (3H, d, J = 5.3 Hz), 3.45 (3H, s), 3.40-3.82 (4H, m), 4.15 (1H, dd, J = 6.4, 13.7 Hz), 4.27 (1H, dd, J = 5.3, 13.2 Hz), 4.79 (1H, q, J = 5.3 Hz), 5.48 (1H, q, J = 5.4 Hz), 6.25 (1H, dt, J = 5.4, 15.8 Hz), 6.49 (1H, d, J = 15.8 Hz), 7.17 (1H, d, J = 2.0 Hz), 7.48 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.3, 19.8, 19.9, 41.2, 60.7, 61.5, 65.0, 92.5, 99.2, 100.7, 115.0, 128.9, 129.0, 130.1, 138.0, 140.6, 149.5; EIMS *m/z* 514 (M^+), 147, 73 (base peak). The product was very labile and immediately used for the next reaction.

To a solution of the mesylate (874 mg, 1.70 mmol) in THF (5.2 mL) and MeOH (2.6 mL) was added 1 *N* aqueous NaOH (2.6 mL) at rt. The reaction mixture was heated at 50 °C, and stirred at 50 °C for 3 h. Then the reaction mixture was cooled to 0 °C, and acidified by the addition of 50 % aqueous NH_4Cl to adjust pH 5-6. The aqueous layer was extracted with EtOAc (40 mL × 3) , and the combined organic extracts were washed with saturated brine (50 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 5 : 1 → 3 : 1) to give the phenol as a reddish orange oil.

The resulting phenol, imidazole (289 mg, 4.25 mmol) and *tert*-butylchlorodimethylsilane (384 mg, 2.55 mmol) were dissolved in DMF (2 mL) at rt, and then stirred at rt for 3 h. The reaction mixture was diluted with EtOAc (100 mL), washed with saturated brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chromatography (BW-820MH, hexane : EtOAc = 12 : 1) to give **13b** (465 mg, 50 % in 2 steps) as a pale yellow oil: IR ν_{max}^{neat} cm^{-1} 1551, 1507, 1418, 1381, 1306, 1252, 1129, 1102, 1044; ^{1}H NMR ($CDCl_3$) δ 0.26 (3H, s), 0.30 (3H, s), 1.05 (9H, s), 1.17-1.28 (6H, m) 1.35 (3H, d, J = 5.3 Hz), 1.50 (3H, d, J = 5.3 Hz), 3.44-3.84 (4H, m), 4.12 (1H, dd, J = 6.1, 13.0 Hz), 4.24 (1H, dd, J = 5.8, 12.7 Hz), 4.78 (1H, q, J = 5.4 Hz), 5.38 (1H, q, J = 5.4 Hz), 6.13 (1 H, dt, J = 5.9, 15.8 Hz), 6.43 (1H, d, J = 15.8 Hz), 7.07 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ -3.1, -2.9, 15.1, 15.3, 18.9, 19.9, 20.1, 26.2 (× 3), 60.5, 61.8, 65.6, 91.1, 99.1, 100.2, 114.5, 125.4, 130.3 (× 2), 131.8, 145.9, 146.9; EIMS *m/z*: 550 (M$^+$), 478, 421, 204, 73 (base peak); HRMS Calcd for $C_{23}H_{39}O_5ISi$: 550.1612. Found: 550.1661.

2-*tert*-Butyldimethylsiloxy-3-(1-ethoxyethoxy)-5-(*E*)-[3-(1-ethoxyethoxy)-1-propenyl]-phenylethynyl 4-(1-ethoxyethoxy)-3-methoxybenzene (2b).

The acetylene (**12b**) (209 mg, 0.95 mmol) and the iodide (**13b**) (437 mg, 0.79 mmol) were converted as described for **2a** to give the alkyne (**2b**) (306 mg, 60 %) as a viscous yellow oil together with recovery of **13b** (129 mg, 29 %): IR ν_{max}^{neat} cm^{-1} 1599, 1568, 1510, 1474, 1269, 1132, 1076, 1040; ^{1}H NMR ($CDCl_3$) δ 0.24 (3H, s), 0.28 (3H, s), 1.06 (9H, s), 1.17-1.28 (9H, m), 1.36 (3H, d, J = 5.3 Hz), 1.51 (3H, d, J = 5.3 Hz), 1.52 (3H, d, J = 5.3 Hz), 3.45-3.90 (6H, m), 3.86 (3H, s), 4.14 (1H, dd, J = 6.4, 11.7 Hz), 4.25 (1H, dd, J = 5.8, 12.7 Hz), 4.80 (1H, q, J = 5.4 Hz), 5.35-5.42 (2H, m), 6.17 (1H, dt, J = 5.9, 15.8 Hz), 6.49 (1H, d, J = 15.8 Hz), 7.02-7.05 (3H, m), 7.08 (1H, J = 2.0 Hz), 7.15 (1H, d, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$) δ -3.7, -3.5, 15.4 (× 2), 15.7, 19.1, 20.2, 20.5, 20.6, 26.2 (× 3), 56.1, 60.8, 61.9, 62.3, 66.0, 86.4, 93.2, 99.4, 100.4, 101.3, 115.3, 117.0, 118.0, 118.9, 124.8 (× 2), 125.1, 125.3, 130.4, 131.5, 146.5, 146.9, 148.3, 150.6; EIMS *m/z*: 642 (M$^+$), 570, 498, 369, 351 (base peak), 204, 73; Anal. Calcd for $C_{36}H_{54}O_8Si$: C, 67.26; H, 8.47. Found: C, 67.08; H, 8.50.

EE-protected vibsanol (17b) and benzofuran (18b).

The alkyne (**2b**) (43 mg, 0.067 mmol) was converted as described for **17a** and **18a** to give the desired **17b** (25 mg, 67 %) as a colorless oil and the benzofuran (**18b**) (7 mg, 20 %) as a yellow oil.

17b: IR ν_{max}^{neat} cm^{-1} 3459, 1597, 1510, 1470, 1381, 1262, 1223, 1125, 1040; ^{1}H NMR ($CDCl_3$) δ 1.11-1.32 (9H, m), 1.38 (3H, d, J = 5.3 Hz), 1.55 (3H, d, J =5.3 Hz), 1.61 (3H, d, J = 5.3 Hz), 1.85 (1H, brs, exchangeable with D_2O), 3.49-4.01 (6H, m), 3.94 (3H, s), 4.18 (1H, dd, J = 5.8,13.0 Hz), 4.29 (1H, dd, J = 5.3, 13.2 Hz), 4.82 (1H, q, J = 5.4 Hz), 4.93 (2H, s), 5.45 (1H, q, J = 5.3 Hz), 5.64

(1H, q, J = 5.6 Hz), 6.29 (1H, dt, J = 5.9, 15.8 Hz), 6.68 (1H, d, J = 15.8 Hz), 7.09 (1H, d, J = 1.0 Hz), 7.20 (1H, d, J = 8.6 Hz), 7.35 (1H, d, J = 1.0 Hz), 7.39 (1H, dd, J = 2.0, 8.2 Hz), 7.45 (1H, d, J = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.2, 15.3, 19.9, 20.2, 20.7, 55.5, 56.0, 60.6, 62.0, 62.7, 65.8, 99.1, 101.0, 101.7, 111.2, 111.5, 112.3, 114.3, 118.8, 120.3, 124.5, 125.4, 131.6, 132.2, 133.2, 141.8, 144.2, 146.8, 150.8, 154.3; EIMS *m/z*: 558 (M^+), 486, 73 (base peak); Anal. Calcd for $C_{31}H_{42}O_9$: C, 66.65; H, 7.58. Found: C, 66.43; H, 7.64.

18b: IR ν_{max}^{neat} cm^{-1}1595, 1507, 1472, 1456, 1381, 1339, 1271, 1246, 1125, 1040; ^{1}H NMR ($CDCl_3$) δ 1.17-1.29 (9H, m), 1.38 (3H, d, J = 5.6 Hz), 1.55 (3H, d, J =5.3 Hz), 1.63 (3H, d, J = 5.2 Hz), 3.49-4.04 (6H, m), 3.95 (3H, s), 4.18 (1H, dd, J = 5.8, 13.4 Hz), 4.29 (1H, dd, J = 5.1, 13.4 Hz), 4.82 (1H, q, J = 5.8 Hz), 5.43 (1H, q, J = 5.3 Hz), 5.65 (1H, q, J = 5.2 Hz), 6.25 (1H, dt, J = 6.1, 15.8 Hz), 6.66 (1H, d, J = 15.8 Hz), 6.89 (1H, s), 7.06 (1H, d, J = 1.7 Hz), 7.17 (1H, d, J = 7.9 Hz), 7.22 (1H, s), 7.37-7.41 (2H, m); ^{13}C NMR ($CDCl_3$) δ 15.1, 15.2, 15.3, 19.9, 20.3, 20.8, 56.0, 60.6, 62.0, 62.8, 65.8, 99.1, 100.8, 101.1, 101.8, 108.8, 112.0, 113.1, 118.0, 119.1, 124.9, 125.2, 131.6, 132.3, 133.0, 141.7, 145.2, 146.5, 150.9, 156.4; EIMS *m/z*: 528 (M^+), 456, 384 (base peak), 296, 73; Anal. Calcd for $C_{30}H_{40}O_8$: C, 68.16; H, 7.63. Found: C, 67.91; H, 7.75.

Vibsanol (1).

PPTS (0.27 mL, 2.5 mg/mL in MeOH, 0.0027 mmol) was added to **17b** (11 mg, 0.020 mmol) at rt and the whole was stirred for 32 h. The reaction mixture was directly purified by silica gel chromatography (BW-820MH, $CHCl_3$: MeOH = 12 : 1) to afford the desired product (**1**) (6.8 mg, 99 %) as a viscous colorless oil: IR $\nu_{max}^{CHCl_3}$ cm^{-1} 3409, 1601, 1516; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.85 (3H, s), 4.11 (2H, dd, J = 4.0, 5.2 Hz), 4.66 (2H, d, J = 5.2 Hz), 4.80 (1H, t, J = 5.3 Hz, exchangeable with D_2O), 5.20 (1H, t, J = 5.2 Hz, exchangeable with D_2O), 6.22 (1H, dt, J = 5.3, 15.9 Hz), 6.54 (1H, d, J = 15.9 Hz), 6.81 (1H, d, J = 1.2 Hz), 6.92 (1H, d, J = 8.2 Hz), 7.16 (1H, d, J =1.2 Hz), 7.29 (1H, dd, J = 2.1, 8.2 Hz), 7.41 (1H, d, J = 2.1 Hz), 9.43 (1H, s, exchangeable with D_2O), 9.96 (1H, s, exchangeable with D_2O); ^{13}C NMR (DMSO-d_6) δ. 53.6, 55.7, 61.6, 108.3, 108.6, 111.0, 114.7, 115.8, 120.3, 121.3, 129.0, 129.4, 131.8, 132.6, 141.4, 142.1, 147.6, 147.8, 153.0; EIMS *m/z*: 342 (M^+, base peak), 151; HRMS Calcd for $C_{19}H_{18}O_6$: 342.1103. Found: 342.1105.

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