A Short and Convergent Synthesis of the Phytoalexins Vignafuran, 6-Demethylvignafuran, and Moracin M *via* Directed Lithiation Reaction

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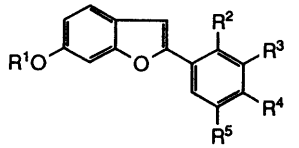
Received July 30, 1990

2-Methyl-5-(*tert*-butyldimethylsilyloxy)phenyl *N,N,N',N'*-tetramethylphosphorodiamidate was lithiated with *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine at −105 °C to generate the corresponding benzylic anion. This benzylic anion was reacted with various methyl benzoates to provide deoxybenzoin derivatives which, without purification, were treated with formic acid to give 2-aryl-6-hydroxybenzo[*b*]furans. The utility of this strategy has been demonstrated by its application to the short synthesis of phytoalexins, such as vignafuran, 6-demethylvignafuran, and moracin M.

Keywords lithiation; bis(dimethylamino)phosphoryl group; 2-arylbenzo[*b*]furan; phytoalexin; vignafuran; 6-demethylvignafuran; moracin M

In our previous papers, we reported a new and general synthetic method of 2-arylbenzo[*b*]furans, including naturally occurring neolignans, *via* regioselective lithiation of *ortho*-cresols using the bis(dimethylamino)phosphoryl group as a directing group.[1)] We report here the application of the above methodology to the total synthesis of several phytoalexins, including vignafuran (**1**), 6-demethylvignafuran (**2**), and moracin M (**3**) (Chart 1).

Recently, much attention has been given to antifungal compounds (phytoalexins) which are produced in plants after exposure to micro-organisms.[2)] These compounds include a series of 2-aryl-6-hydroxy- (or methoxy-)benzo[*b*]furan derivatives. Vignafuran (**1**) was isolated from the leaves of cowpea, *Vigna unguiculata* (L.) WALP., infected with *Colletotrichum lindemuthianum* and was identified as 6-methoxy-2-(2'-methoxy-4'-hydroxyphenyl)benzo[*b*]furan in 1975.[3)] Two total syntheses of **1** have been reported using two types of key reactions: i) the Hoesch reaction of 2-benzyloxy-4-methoxyphenylacetonitrile with 3-methoxyphenol in the presence of $ZnCl_2$ and $AlCl_3$ in low overall yield[3)]; ii) the reaction of copper(I) 4-benzyloxy-2-methoxyphenylacetylide with 2-bromo-5-methoxyphenol in 7.1% overall yield, starting from 4-benzyloxy-2-hydroxyphenyl methyl ketone.[4)] 6-Demethylvignafuran (**2**) was isolated from the leaves of *Tetragonolobus maritimus* (L.) ROTH inoculated with *Helminthosporium carbonum* ULLSTRUP. It was synthesized *via* deoxybenzoin derived from basic hydrolysis of 2'-benzyloxyisoflavone in 2.8% overall yield, the latter compound having been obtained from 4-benzyloxy-2-hydroxyphenyl methyl ketone.[5)] Moracin M (**3**) was isolated from the heartwood of *Morus laevigata* in 1975.[6)] The structure of **3** was elucidated as 2-(3',5'-dihydroxyphenyl)-6-hydroxybenzo[*b*]furan by Rama Rao *et al.* through synthesis starting from 2,4,3',5'-tetraacetoxystilbene, although in very poor overall yield.[6)] Recently, Widdowson *et al.* reported an attractive strategy for the synthesis of **3** which involved the palladium-catalyzed cross-coupling of 6-(*tert*-butyldiphenylsilyloxy)-2-trimethylstannylbenzo[*b*]-furan with 5-iodoresorcinolbis(triisopropylsilyl)ether as the key step, in 55.7% overall yield, starting from 6-methoxybenzo[*b*]furan.[7)] However, these total syntheses suffer from the disadvantages of lengthy synthetic routes and poor overall yields, except for the last one. We report here a new, convergent, and expeditious synthesis of vignafuran (**1**), 6-demethylvignafuran (**2**), moracin M (**3**), and related compounds from a common starting material, 2-methyl-5-(*tert*-butyldimethylsilyloxy)phenyl *N,N,N',N'*-tetramethylphosphorodiamidate (**4**).[1c)]



	R^1	R^2	R^3	R^4	R^5
vignafuran (**1**):	Me	OMe	H	OH	H
6-demethylvignafuran (**2**):	H	OMe	H	OH	H
moracin M (**3**):	H	H	OH	H	OH

Chart 1

The requisite phosphorodiamidate **4** was regioselectively synthesized by the lithiation of 3-(*tert*-butyldimethylsilyloxy)phenyl tetramethyl phosphorodiamidate with *sec*-BuLi followed by reaction with MeI in 65% yield, as has been reported by us.[1c)] Compound **4** was converted to the methyl ether **5** (64% yield) in a one-step procedure according to Borchardt *et al.*[8)] First, we examined the lithiation behavior from the viewpoint of the regioselectivity of aromatic *vs. ortho*-methyl deprotonation in **4** and **5** (Chart 2).[1d)] Lithiation of **5** with 1.2 eq of *sec*-BuLi in tetrahydrofuran (THF) at −105 °C for 1 h followed by addition of MeI gave **6** in 61% yield, resulting from ring deprotonation; no product derived from the tolyl anion was isolated. In contrast, when **4** was lithiated under the same conditions described above and subsequently reacted with MeI, the ethyl compound **7** resulting from the benzylic anion was obtained in 51.8% yield. The significant difference in lithiation behavior between **4** and **5** may be attributed to the dual directing ability of the methoxy and the phosphorodiamidate groups, which direct the lithiation to the position between the two groups (for **5**), and to the steric hindrance of the bulky *tert*-butyldimethylsilyloxy and the phosphorodiamidate groups, which inhibit *ortho*-lithiation and thus generate the benzylic anion (for **4**).[1c,d,8,9)]

On the basis of the above results, lithiated **4** was reacted with methyl benzoates (**8a, b**) as model compounds (Chart 2). Lithiation of **4** with 1.2 eq of *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in THF at −105 °C for 1 h resulted in the formation of the

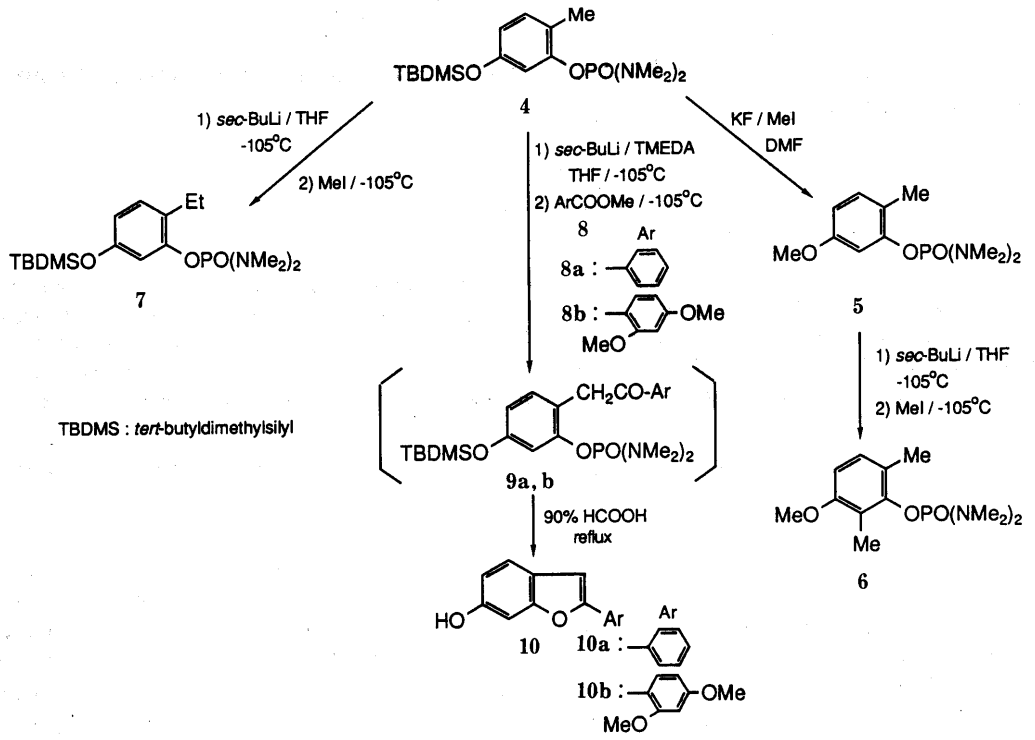


Chart 2

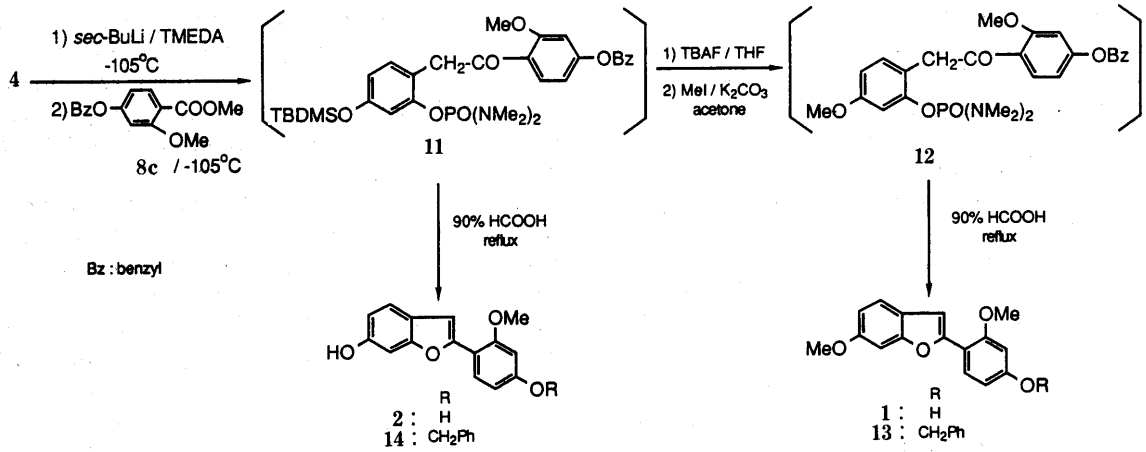


Chart 3

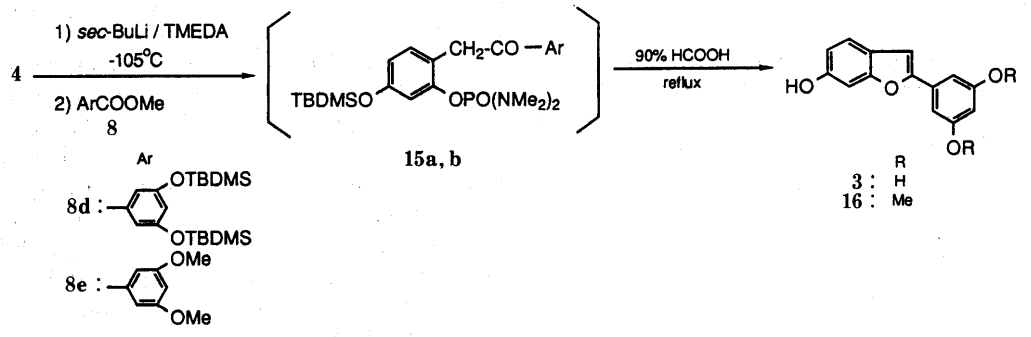


Chart 4

yellow benzylic anion, which, upon treatment with 2.0 eq of methyl benzoate (**8a**) at −105 °C and quenching with saturated NH_4Cl solution at −80 °C gave the deoxybenzoin derivative **9a** as a viscous oil in 63% yield after column chromatography. Although the structure of **9a** was confirmed by its proton nuclear magnetic resonance (^{1}H-NMR) spectrum, an analytically pure sample could not be obtained due to contamination by the starting material **4**. So, without

further purification, **9a** was treated with refluxing 90% formic acid[1b,d] for 1 h to give 6-hydroxy-2-phenylbenzo[*b*]-furan (**10a**)[2a] in 23.3% overall yield *via* dephosphorylation, desilylation, and subsequent cyclodehydration. Similarly, using methyl 2,4-dimethoxybenzoate (**8b**),[10] the corresponding product 2-(2′,4′-dimethoxyphenyl)-6-hydroxybenzo[*b*]-furan (**10b**) was obtained in 59% overall yield. The structures of **10a** and **10b** were established by infrared (IR), ultraviolet (UV), ^{1}H-NMR, mass spectral (MS) data and elemental analyses (see Experimental).

Encouraged by these model studies, we turned our attention to the total synthesis of vignafuran (**1**) and 6-demethylvignafuran (**2**) along the lines shown in Chart 3. Compound **4** was lithiated and the benzylic anion was subsequently reacted with methyl 4-benzyloxy-2-methoxybenzoate (**8c**)[11] to give the deoxybenzoin derivative **11** in 75% yield after column chromatography. Without further purification, **11** was converted into the methoxy compound (**12**) *via* desilylation with tetrabutylammonium fluoride (TBAF) in THF followed by methylation with MeI in the presence of K_2CO_3 in refluxing acetone. Compound **12**, without isolation, was then treated with 90% formic acid at reflux for 4 h to give **1** and 2-(4′-benzyloxy-2′-methoxyphenyl)-6-methoxybenzo[*b*]furan (**13**)[4] in 22.5% and 6.5% overall yields, respectively, after standard work-up and chromatographic purification. Compound **13** had previously been converted into vignafuran (**1**).[4] Synthetic **1** and **13** were shown to be identical with vignafuran and benzylvignafuran on the basis of spectroscopic comparisons with reported data.[3,4] On the other hand, when **11** was refluxed in 90% formic acid for 4 h, compound **2**, which was identical with 6-demethylvignafuran by spectroscopic comparisons,[5] was directly obtained in 6% overall yield. When refluxing was stopped after 1 h, **2** and 2(4′-benzyloxy-2′-methoxyphenyl)-6-hydroxybenzo[*b*]furan (**14**) were obtained in 2% and 8% overall yields, respectively. The protecting benzyl group in **11** was removed during prolonged reaction under the above conditions. Alternatively, acidic treatment of **11** in refluxing 90% acetic acid for 11 h gave **14** in 22% yield (14% overall yield from **4**). For the synthesis of moracin M (**3**), lithiation of **4** followed by reaction with methyl 3,5-bis(*tert*-butyldimethylsilyloxy)benzoate (**8d**) gave the deoxybenzoin derivative **15a** in 57% yield after column chromatography. Without further purification, **15a** was treated with refluxing 90% formic acid for 1 h, affording moracin M (**3**) in 7% overall yield after chromatographic purification (Chart 4). When methyl 3,5-dimethoxybenzoate (**8e**)[12] was employed in the above reaction, similar treatment gave 2-(3′,5′-dimethoxyphenyl)-6-hydroxybenzo-[*b*]furan (**16**) *via* **15b**, in 45% overall yield. Demethylation of **16** with an excess of boron tribromide (BBr_3) at room temperature for 20 d gave a mixture of **3** and 6-hydroxy-2-(3′- or 5′-hydroxy-5′-or 3′-methoxyphenyl)benzo[*b*]furan in 18% and 22% yields, respectively, after chromatographic purification. Complete demethylation was difficult to achieve under these conditions. The structure of **3** was established by the comparison of its spectral data with those of moracin M[6] and through conversion to moracin M trimethyl ether.[6]

In conclusion, the phytoalexins vignafuran (**1**), 6-demethylvignafuran (**2**), moracin M (**3**) and related compounds (**10a, b, 13, 14, 16**) were synthesized through lithiation of 2-methyl-5-(*tert*-butyldimethylsilyloxy)phenyl *N,N,N′,N′*-tetramethylphosphorodiamidate (**4**) as a common starting compound followed by reaction with benzoates and subsequent acidic treatment. Although some of the steps are low-yielding, the poor yield may be compensated for by the easy accessibility of the starting material, the small number of steps, and the high degree of convergence.

Experimental

All melting points are uncorrected. The IR spectra were measured directly on an NaCl plate or in a KBr disk with a JASCO 810 spectrophotometer. The UV spectra were recorded in 95% ethanol on a Hitachi 323 spectrophotometer. The ^{1}H-NMR spectra were obtained with Hitachi R 600 (60 MHz) and JEOL JNM GX-400 (400 MHz) spectrometers using $CDCl_3$ or $(CD_3)_2CO$ as a solvent and tetramethylsilane as an internal reference. The MS and high-resolution MS (HRMS) were determined on a JEOL-DX 303 mass spectrometer. Elemental analyses were performed at the Microanalytical Laboratory of the Center for Instrumental Analysis in Nagasaki University. All solvents used for lithiation reaction were freshly distilled from sodium benzophenone ketyl before use. Flash chromatography was carried out on a column of Kieselgel 60 (230—400 mesh).

5-Methoxy-2-methylphenyl *N,N,N′,N′*-Tetramethylphosphorodiamidate (5) This was prepared in 64% yield according to a literature procedure.[8] A colorless oil, bp 130 °C (0.5 mmHg). MS *m/z*: 272 (M^+). IR (neat): 2925, 1620, 1595, 1510, 1460, 1310, 1225, 1155, 1120, 1040, 990 cm^{-1}. UV nm (log ε): 221 (3.92), 279 (3.41), 284 (s) (3.35). ^{1}H-NMR δ: 2.22 (3H, s), 2.74 (12H, d, *J* = 10.3 Hz), 3.77 (3H, s), 6.57 (1H, dd, *J* = 8.2, 2.4 Hz), 6.88 (1H, br s), 7.05 (1H, d, *J* = 8.2 Hz). *Anal.* Calcd for $C_{12}H_{21}N_2O_3P$: C, 52.93; H, 7.77; N, 10.28. Found: C, 52.53; H, 7.71; N, 10.22.

2,6-Dimethyl-5-methoxyphenyl *N,N,N′,N′*-Tetramethylphosphorodiamidate (6) A solution of *sec*-BuLi (0.95 M in cyclohexane, 2.5 ml, 2.4 mmol) was injected into a stirred solution of **5** (0.52 g, 1.9 mmol) in THF (50 ml) at −105 °C (liquid nitrogen–ethanol bath) under a nitrogen atmosphere. After stirring at −105 °C for 30 min, a solution of MeI (0.58 g, 2.4 mmol) in THF (10 ml) was injected to the yellow lithiated solution at −105 °C. Stirring was continued for an additional 1 h at −105 °C. The reaction mixture was quenched with saturated NH_4Cl solution at −90 °C and the solution was allowed to warm to room temperature. THF was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and the organic layer was washed with 5% $Na_2S_2O_3$ solution, dried over Na_2SO_4, and then evaporated to give an oil, which was distilled to give **6** (0.33 g, 61%) as an oil, bp 125 °C (0.5 mmHg). MS *m/z*: 286 (M^+). IR (neat): 3450, 2925, 1615, 1590, 1490, 1460, 1305, 1260, 1225, 1160, 1110, 1100, 1000, 920 cm^{-1}. UV nm (log ε): 219 (4.00), 278 (3.36), 282 (s) (3.32). ^{1}H-NMR δ: 2.20 (3H, s), 2.30 (3H, s), 2.73 (12H, d, *J* = 9.6 Hz), 3.76 (3H, s), 6.55 (1H, d, *J* = 8.1 Hz), 6.94 (1H, d, *J* = 8.1 Hz). *Anal.* Calcd for $C_{13}H_{23}N_2O_3P \cdot 2/3H_2O$: C, 52.34; H, 8.22; N, 9.38. Found: C, 52.27; H, 7.90; N, 9.23.

2-Ethyl-5-(*tert*-butyldimethylsilyloxy)phenyl *N,N,N′,N′*-Tetramethylphosphorodiamidate (7) This was prepared in 51.8% (0.26 g) yield by the lithiation of **4** (0.48 g, 1.3 mmol) with *sec*-BuLi (0.95 M in cyclohexane, 1.8 ml, 1.7 mmol) at −105 °C, followed by treatment with MeI (0.37 g, 2.6 mmol) according to a literature procedure.[1d] A colorless oil, bp 150 °C (0.6 mmHg). MS *m/z*: 386 (M^+). IR (neat): 3440, 2925, 2850, 1610, 1580, 1500, 1460, 1290, 1235, 1155, 1115, 990, 910 cm^{-1}. UV nm (log ε): 218 (3.97), 274.5 (s) (3.32), 279 (s) (3.28). ^{1}H-NMR δ: 0.20 (6H, s), 0.98 (9H, s), 1.19 (3H, t, *J* = 7.5 Hz), 2.22—2.57 (2H, m), 2.73 (12H, d, *J* = 9.6 Hz), 6.54 (1H, dd, *J* = 8.2, 2.1 Hz), 6.87—7.10 (2H, m). *Anal.* Calcd for $C_{18}H_{35}N_2O_3PSi \cdot 1/3H_2O$: C, 55.07; H, 9.15; N, 7.13. Found: C, 55.19; H, 9.12; N, 7.26.

General Procedure for the Synthesis of 2-Aryl-6-hydroxy-(or 6-methoxy)-benzo[*b*]furan Derivatives (10a, b, 1, 13, 2, 14, and 16) The following procedure for the synthesis of 6-hydroxy-2-phenylbenzo[*b*]furan (**10a**) is representative; the other arylbenzo[*b*]furans (**10b, 1, 13, 2, 14, 3,** and **16**) were obtained similarly.

1) 6-Hydroxy-2-phenylbenzo[*b*]furan (10a) A solution of *sec*-BuLi (0.95 M in cyclohexane, 3.8 ml, 3.6 mmol) was injected into a stirred solution of **4** (1.1 g, 3.0 mmol) and TMEDA (0.54 ml, 3.6 mmol) in THF (50 ml) at −105 °C under a nitrogen atmosphere. Stirring was continued at −105 °C for 20 min, then a solution of **8a** (0.82 g, 6.0 mmol) in THF (10 ml) was injected into the lithiated solution at −105 °C. The stirring was continued for an additional 1 h at −105 °C. The reaction mixture was quenched with

saturated NH_4Cl solution at −80 °C and the whole was allowed to warm to room temperature. Usual work-up and chromatographic purification using CH_2Cl_2–acetone (9 : 1) as an eluent gave crude 2-phenacyl-5-(*tert*-butyldimethylsilyloxy)phenyl *N,N,N',N'*-tetramethylphosphorodiamidate (**9a**, 0.9 g, 63%). ^{1}H-NMR: δ 0.21 (6H, s), 0.98 (9H, s), 2.62 (12H, d, J=10.2 Hz), 4.27 (2H, s), 6.47—6.67 (1H, m), 6.83—6.97 (2H, m), 7.27—7.50 (3H, m), 7.90—8.10 (2H, m). An analytically pure sample was not obtained owing to difficulty of separation of the product from the starting material **4**. Without further purification, the above crude material was used in the next step. A solution of this crude **9a** (0.68 g, 1.43 mmol) in 90% HCOOH (15 ml) was refluxed for 1 h. After removal of HCOOH under reduced pressure, the residue was washed with 5% $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and evaporated to give the residue, which was chromatographed using benzene as an eluent and purified by recrystallization from ether–pentane to give **10a** as colorless crystals, mp 177—179 °C, 0.11 g, 37% yield, 23.3% overall yield from **4** (lit.[2a] mp 170—173 °C). MS *m/z*: 210 (M^+). IR (KBr): 3480, 3420, 1620, 1490, 1450, 1435, 1360, 1295, 1190, 1150, 1115, 1020, 915 cm^{-1}. UV nm (log ε): 222 (s) (4.11). 236 (s) (4.06), 287 (s) (4.06), 318 (4.48), 328 (4.42). ^{1}H-NMR ($(CD_3)_2CO$) δ: 6.89 (1H, d, J=9.0 Hz), 7.11 (2H, br s), 7.33—7.50 (4H, m), 7.75—7.88 (2H, m), 8.63 (1H, br s). *Anal.* Calcd for $C_{14}H_{10}O_2$: C, 79.98; H, 4.79. Found: C, 79.72; H, 4.98.

2) 2-(2',4'-Dimethoxyphenyl)-6-hydroxybenzo[*b*]furan (10b) The reaction of **4** (1.5 g, 4.0 mmol) with **8b** (1.6 g, 8.0 mmol) under the conditions described above gave crude **9b** (1.54 g, 72%). ^{1}H-NMR δ: 0.20 (6H, s), 0.96 (9H, s), 2.63 (12H, d, J=10.2 Hz), 3.81 (3H, s), 3.85 (3H, s), 4.24 (2H, s), 6.44—6.57 (3H, m), 6.90—7.06 (2H, m), 7.73—7.88 (1H, m). A solution of this crude **9b** (1.54 g, 2.87 mmol) in 90% HCOOH (20 ml) was refluxed for 1 h. Standard work-up and purification by chromatography using CH_2Cl_2–acetone (9 : 1) as an eluent gave **10b** as colorless crystals (ether), mp 113—116 °C (0.64 g, 82% yield, 59% overall yield from **4**). MS *m/z*: 270 (M^+). IR (KBr): 3290, 1620, 1585, 1500, 1480, 1285, 1210, 1155, 1140, 1105, 1045 cm^{-1}. UV nm (log ε): 225 (s) (4.14), 240 (s) (4.01), 249 (s) (3.91), 284 (4.13), 311 (s) (4.37), 322.5 (4.59), 337.5 (4.57). ^{1}H-NMR ($(CD_3)_2CO$) δ: 3.75 (3H, s), 3.89 (3H, s), 6.49—6.64 (2H, m), 6.91 (1H, dd, J=8.4, 2.4 Hz), 7.16—7.19 (2H, m), 7.47 (1H, d, J=9.0 Hz), 7.91 (1H, d, J=9.0 Hz), 8.49 (1H, br s). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.96; H, 5.30.

3) 2-(4'-Hydroxy-2'-methoxyphenyl)-6-methoxybenzo[*b*]furan; Vignafuran (1) and 2-(4'-Benzyloxy-2'-methoxyphenyl)-6-methoxybenzo[*b*]furan (13) The reaction of **4** (1.12 g, 3.0 mmol) with **8c**[11] (1.36 g, 5.0 mmol) under the conditions described above gave the crude deoxybenzoin derivative **11** (1.38 g, 75%). ^{1}H-NMR δ: 0.20 (6H, s), 0.98 (9H, s), 2.63 (12H, d, J=9.6 Hz), 3.85 (3H, s), 4.25 (2H, s), 5.10 (2H, s), 6.52—6.66 (3H, m), 6.93—7.06 (2H, m), 7.39 (5H, s), 7.80 (1H, d, J=8.4 Hz). This crude **11** was used, without further purification, in the next step. A solution of TBAF (1.0 M in THF, 2.3 ml, 2.3 mmol) was added to a stirred solution of crude **11** (1.38 g, 2.25 mmol) in THF (20 ml) at room temperature. Stirring was continued for 10 min, then the THF was removed under reduced pressure to give a residue. A mixture of the residue, K_2CO_3 (0.69 g, 5.0 mmol), and MeI (0.71 g, 5.0 mmol) in acetone (100 ml) was refluxed for 4 h. After cooling to room temperature, the precipitated solid was filtered off. The filtrate was concentrated and usual work-up and chromatographic purification using CH_2Cl_2–acetone (9 : 1) as an eluent gave the crude deoxybenzoin derivative **12** (1.32 g). ^{1}H-NMR δ: 2.63 (12H, d, J=9.6 Hz), 3.77 (3H, s), 3.86 (3H, s), 4.25 (2H, s), 5.10 (2H, s), 6.52—6.64 (3H, m), 6.97—7.13 (2H, m), 7.39 (5H, s), 7.80 (1H, d, J=8.4 Hz). A solution of crude **12** (0.8 g, 1.6 mmol) in 90% HCOOH (10 ml) was refluxed for 4 h. Standard work-up gave a mixture of **1** and **13** which was chromatographed on silica gel. 2-(4'-Benzyloxy-2'-methoxyphenyl)-6-methoxybenzo[*b*]furan (**13**) was eluted faster than vignafuran (**1**) with CH_2Cl_2 as an eluent. 2-(4'-Benzyloxy-2'-methoxyphenyl)-6-methoxybenzo-[*b*]furan (**13**; 0.05 g, 8.7% yield, 6.5% overall yield from **4**). A colorless oil (lit.[4] mp 111—116 °C). IR (neat): 2940, 2840, 1620, 1585, 1500, 1450, 1290, 1260, 1200, 1155, 1030, 1010 cm^{-1}. UV nm (log ε): 228 (s) (4.21), 248 (s) (3.91), 284 (4.15), 310 (s) (4.37), 322 (4.59), 337.5 (4.56). ^{1}H-NMR δ: 3.81 (3H, s), 3.89 (3H, s), 5.05 (2H, s), 6.61—7.22 (6H, m), 7.39 (5H, s), 7.92 (1H, d, J=9.6 Hz). Vignafuran (**1**; 0.13 g, 30% yield, 22.5% overall yields from **4**). Oil (lit.[3,4] oil). MS *m/z*: 270 (M^+). IR ($CHCl_3$): 3600, 3320, 3020, 1620, 1595, 1510, 1495, 1470, 1310, 1155, 1110, 1035 cm^{-1}. UV nm (log ε): 224 (s) (4.17), 247 (s), (3.70), 283 (3.91), 309 (s) (3.99), 321 (4.17), 336.5 (4.11). ^{1}H-NMR (400 MHz) δ: 3.86 (3H, s), 3.91 (3H, s), 6.50 (2H, m), 6.84 (1H, dd, J=8.4, 2.2 Hz), 7.03 (2H, m), 7.41 (1H, d, J=8.4 Hz), 7.84 (1H, d, J=9.2 Hz).

4) 6-Hydroxy-2-(4'-hydroxy-2'-methoxyphenyl)benzo[*b*]furan; 6-Demethylvignafuran (2) and 2-(4'-Benzyloxy-2'-methoxyphenyl)-6-hydroxybenzo[*b*]furan (14) A solution of crude **11** (1.53 g, 2.5 mmol) obtained above was refluxed for 1 h in 90% HCOOH (20 ml). Standard work-up and chromatographic purification gave **14** (CH_2Cl_2 as an eluent) and **2** (CH_2Cl_2–acetone = 9 : 1 as an eluent). 2-(4'-Benzyloxy-2'-methoxyphenyl)-6-hydroxybenzo[*b*]furan (**14**; 0.09 g, 10.6% yield, 8.0% overall yield from **4**) was obtained as colorless crystals (from CH_2Cl_2/pentane), mp 107—110 °C. MS *m/z*: 346 (M^+). IR (KBr): 3250, 1610, 1580, 1495, 1420, 1285, 1195, 1150, 1110, 1025, 950 cm^{-1}. UV nm (log ε): 241.5 (s) (3.97), 249 (s) (3.88), 285 (4.10), 312 (s) (4.38), 323 (4.61), 338.5 (4.59). ^{1}H-NMR δ: 3.89 (3H, s), 5.09 (2H, s), 6.62—6.81 (3H, m), 6.98—7.03 (4H, m), 7.41 (5H, s), 7.91 (1H, d, J=9.6 Hz). HRMS *m/z* M^+ Calcd for $C_{22}H_{18}O_4$: 346.1205. Found: 346.1203. 6-Demethylvignafuran (**2**; 0.017 g, 2.7% yield, 2.0% overall yield from **4**). An oil (lit.[5] oil). MS *m/z*: 256 (M^+). IR ($CHCl_3$): 3600, 3300, 1620, 1595, 1505, 1450, 1475, 1445, 1305, 1255, 1150, 1115, 1060 cm^{-1}. UV nm (log ε): 225 (s) (4.07), 248.5 (s) (3.78), 284 (3.94), 309.5 (s) (4.14), 321.5 (4.34), 337 (4.29). ^{1}H-NMR δ: 3.93 (3H, s), 6.48—6.87 (2H, m), 7.01—7.43 (4H, m), 7.59 (1H, br s), 7.83 (1H, d, J=9.0 Hz), 7.86 (1H, br s). When a solution of crude **11** (0.38 g, 0.62 mmol) in 90% CH_3COOH (20 ml) was refluxed for 11 h, compound **14** (0.047 g, 22%) was obtained (14% overall yield from **4**). When a solution of crude **11** (1.08 g, 1.7 mmol) in 90% HCOOH (20 ml) was refluxed for 4 h, compound **2** (0.035 g, 8.0%) was obtained (6.0% overall yield from **4**).

5) Methyl 3,5-Bis(*tert*-butyldimethylsilyloxy)benzoate (8d) *tert*-Butyldimethylsilyl chloride (8.25 g, 55 mmol) was added to a stirred solution of imidazole (3.7 g, 55 mmol) and methyl 3,5-dihydroxybenzoate (4.2 g, 25 mmol) in *N,N*-dimethylformamide (20 ml) at room temperature. The reaction mixture was stirred at room temperature for 24 h. Water and *n*-hexane were added to the reaction mixture. The organic layer was separated, washed with 5% $NaHCO_3$ solution, and dried over Na_2SO_4. The solvent was removed to give a residue, which was distilled to give **8d** (8.09 g, 82%) as an oil, bp 160 °C (1.5 mmHg). IR (neat): 2955, 2940, 2860, 1730, 1590, 1450, 1340, 1255, 1170, 1030, 1015, 730, 835 cm^{-1}. UV nm (log ε): 247 (3.81), 303 (3.42). ^{1}H-NMR δ: 0.26 (12H, s), 1.04 (18H, s), 3.93 (3H, s), 6.55—6.63 (1H, m), 7.18—7.21 (2H, m). HRMS *m/z* M^+ Calcd for $C_{20}H_{36}O_4Si_2$: 396.2152. Found: 396.2152.

6) 2-(3',5'-Dihydroxyphenyl)-6-hydroxybenzo[*b*]furan; Moracin M (3) The reaction of **4** (1.1 g, 3.0 mmol) with **8d** (1.8 g, 4.5 mmol) under the conditions described above gave the crude deoxybenzoin **15a** (1.25 g, 57%). ^{1}H-NMR δ: 0.20 (18H, s), 0.98 (27H, s), 2.64 (12H, d, J=9.6 Hz), 4.21 (2H, s), 6.52—6.66 (2H, m), 6.95—7.13 (4H, m). A solution of this crude **15a** (1.25 g, 1.7 mmol) in 90% HCOOH (20 ml) was refluxed for 1 h. Standard work-up and purification by chromatography using CH_2Cl_2–acetone (4 : 1) as an eluent gave moracin M (**3**; 0.05 g, 12.3%, 7.0% overall yield from **4**) as crystals, mp 263—270 °C (acetone/ether) (lit.[6] mp 259—262 °C; lit.[7] mp 260—262 °C). MS *m/z*: 242 (M^+). IR (KBr): 3520, 3275, 1610, 1580, 1435, 1295, 1140, 1120, 1000, 965 cm^{-1}. UV nm (log ε): 218 (4.43), 251.5 (s) (3.74), 286 (s) (4.05), 296 (s) (4.13), 317.5 (4.46), 331 (4.39). ^{1}H-NMR ($(CD_3)_2CO$) δ: 6.38 (1H, t, J=3.0), 6.73—6.76 (1H, m), 6.89 (2H, d, J=1.8 Hz), 7.03 (2H, br s), 7.41 (1H, d, J=7.8 Hz), 8.41 (2H, br s). Moracin M trimethyl ether was obtained in 78% yield by the reaction of **3** with MeI in the presence of K_2CO_3 in refluxing acetone.

Moracin M Trimethyl Ether: Crystals, mp 70—72 °C (lit.[6] mp 80 °C). MS *m/z*: 284 (M^+). IR (KBr): 2960, 2940, 2835, 1600, 1570, 1490, 1450, 1415, 1360, 1275, 1205, 1150, 1110, 1065, 1025, 820 cm^{-1}. UV nm (log ε): 218 (4.47), 295 (s) (4.17), 317 (4.49), 330 (4.41), ^{1}H-NMR δ: 3.78 (6H, s), 3.86 (3H, s), 6.44 (1H, t, J=2.1 Hz), 6.85—7.04 (5H, m), 7.43 (1H, d, J=8.4 Hz).

7) 2-(3',5'-Dimethoxyphenyl)-6-hydroxybenzo[*b*]furan (16) The reaction of **4** (1.49 g, 4.0 mmol) with **8e** (1.57 g, 8.0 mmol) under the conditions described above gave the crude deoxybenzoin derivative **15b** (1.87 g, 87%). ^{1}H-NMR δ: 0.23 (6H, s), 0.90 (9H, s), 2.62 (12H, d, J=10.2 Hz), 3.70 (3H, s), 3.77 (3H, s), 4.23 (2H, s), 6.33—6.68 (4H, m), 6.93—7.20 (2H, m). A solution of this crude **15b** (1.87 g, 3.5 mmol) in 90% HCOOH (20 ml) was refluxed for 1 h. Standard work-up and purification by chromatography using CH_2Cl_2–acetone (9 : 1) as an eluent gave 2-(3',5'-dimethoxyphenyl)-6-hydroxybenzo[*b*]furan (**16**: 0.49 g, 52%, 45% overall yield from **4**) as colorless crystals (ether/pentane), mp 112—115 °C. MS *m/z*: 270 (M^+). IR (KBr): 3425, 1620, 1605, 1570, 1460, 1450, 1425, 1360, 1310, 1210, 1155, 1115, 1065, 1035, 960, 920 cm^{-1}. UV nm (log ε): 218 (4.49), 319 (4.53), 329 (s) (4.47). ^{1}H-NMR δ: 3.78 (6H, s), 6.40—6.48 (1H, m), 6.87—7.08 (5H, m), 7.36 (1H, d, J=8.4 Hz). *Anal.* Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 70.94; H, 5.38.

Demethylation of 16 Using BBr_3 A solution of BBr_3 (1 ml, 10.6 mmol)

in CH_2Cl_2 (5 ml) was injected into a solution of **16** (0.22 g, 0.81 mmol) in dry CH_2Cl_2 (50 ml) at −78 °C under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature, stirred for 20 d, and then treated with 5% $NaHCO_3$ solution. The organic layer was separated, dried over Na_2SO_4 and evaporated to dryness. The residue was purified by chromatography to afford 6-hydroxy-2-(3′- or 5′-hydroxy-5′- or 3′-methoxyphenyl)benzo[*b*]furan (0.046 g, 22%) and moracin M (**3**; 0.035 g, 18%) using benzene–acetone (9 : 1) as an eluent.

6-Hydroxy-2-(3′- or 5′-hydroxy-5′- or 3′-methoxyphenyl)benzo[*b*]furan: Colorless crystals, mp 130—139 °C (acetone–ether). IR (KBr): 3290, 1620, 1580, 1440, 1425, 1380, 1320, 1295, 1190, 1155, 1140, 1120, 1050, 960 cm^{-1}. UV nm (log ε): 217.5 (4.43), 251 (s) (3.79), 286 (s) (4.05), 295 (s) (4.14), 317.5 (4.47), 330 (4.40). ^{1}H-NMR δ: 3.76 (3H, s), 6.41 (1H, t, J=4.2 Hz), 6.98—7.10 (4H, m), 7.34—7.50 (3H, m). HRMS m/z M^+ Calcd for $C_{15}H_{12}O_4$: 256.0736. Found: 256.0736.

Acknowledgement We are indebted to the staff of the Center for Instrumental Analysis in Nagasaki University for IR, UV, MS, HRMS, and NMR measurements and elemental analysis.

References and Notes

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