[Chem. Pharm. Bull. 34(8)3175—3182(1986)]

Cyanophthalide Annulation with 4-(5-Alkoxy-2-furyl)-3-buten-2-one. Application to the Synthesis of a (Naphtho)pyrano-γ-lactone

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(Received January 30, 1986)

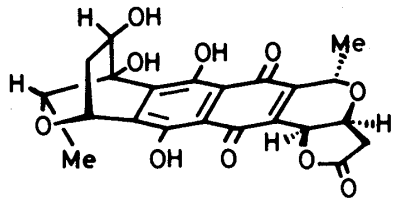
Reaction of lithiated 3-cyano-1(3*H*)-isobenzofuranone (**7**) with 5-substituted 2-furfuralacetones **6a**—**c** and subsequent *O*-methylation of the resulting naphthohydroquinones afforded 2-acetyl-3-furylnaphthalenes **8a**—**c** in good yields. Annulation of the dialkoxyphthalides **12a**, **b** with **6a** could also be carried out to give **13a**, **b**. The 5-*tert*-butoxy-2-furyl compounds were stereoselectively transformed into (1*R**,3*R**,4*R**)-pyrano-γ-lactones **16a**, **18a**, **b** in high yields by a modification of the Kraus method ($LiAlH_4$ reduction followed by treatment of the product carbinol with *p*-toluenesulfonic acid (TsOH) in acetonitrile and then with 1,8-diazabicyclo[5.4.0]undec-7-ene in toluene at low temperatures). The 5-methoxy-2-furyl compound **9b** also afforded **16a** stereoselectively in one step (treatment with TsOH), but this compound was less effective as a substrate of the pyrano-γ-lactone annulation since a side reaction leading to the spiro-γ-lactone **17** became significant. The 5-phenylthio compound **9c** failed to give **16a** under a variety of conditions.

Keywords——cyanophthalide; annulation; 5-alkoxy-2-furaldehyde; naphthopyran; naphthoquinone; antibiotic; synthesis

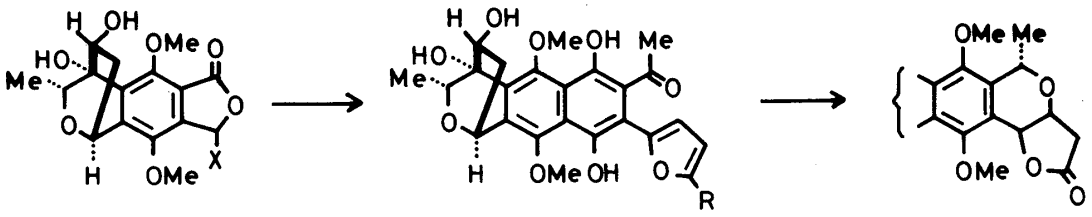
Phthalide annulation, which involves the reaction of 3-phenylsulfonyl- or 3-cyanophthalide anion and an appropriate Michael acceptor,[1,2] has been employed as a convergent method for the construction of functionalized 1,4-dihydroxynaphthalene derivatives leading to a wide range of naphthoquinone and anthraquinone antibiotics. In our studies directed at the total synthesis of granaticin (**1**),[3] attention was focussed on this technique for attachment of the (benzo)pyrano-γ-lactone moiety **4** to the preformed oxabicycle **2**[4] *via* the 2-acetyl-3-furylnaphthalene intermediate **3** as outlined in Chart 1. Here, cyanophthalide annulation introduced by the Kraus group[2] would be preferable simply because the cyano compound **2** (X=CN) could be accessible under milder conditions *via* directed *ortho* metallation-formylation of the corresponding *N*,*N*-diethylcarboxamide precursor.[5] With this idea, we commenced investigations on the annulation of 3-cyanophthalide **7** with 5-alkoxy and 5-phenylthio derivatives of 2-furfuralacetone. Stereoselective transformation of the products to the (naphtho)pyrano-γ-lactone **16a** was also a subject of concurrent interest, although a precedent exists for the 5-*tert*-butoxy-2-furyl derivative **8a**, which had been prepared from 2-acetyl-1,4-naphthoquinone *via* nucleophilic addition of 2-*tert*-butoxyfuran.[6]

5-Methoxy- and 5-*tert*-butoxy-2-furfuralacetones (**6a**, **b**) were obtained by reaction of the corresponding 5-alkoxy-2-furaldehyde (**5a**, **b**) with (acetonylidene)triphenylphosphorane[7] in refluxing benzene. The 5-phenylthio analog **6c** was prepared from 5-phenylthio-2-furaldehyde diethylacetal[8] by deacetalization followed by aldol condensation with acetone.[9]

Reaction of these potential Michael acceptors with 3-cyano-1(3*H*)-isobenzofuranone (**7**) was best carried out by treatment of **7** with dimsyllithium (CH_3SOCH_2Li) in dimethyl sulfoxide (DMSO)–tetrahydrofuran (THF) solvent[2f,5b] followed by addition of the enones **6**. The resulting hydroquinones were, without purification, subjected to *O*-methylation with

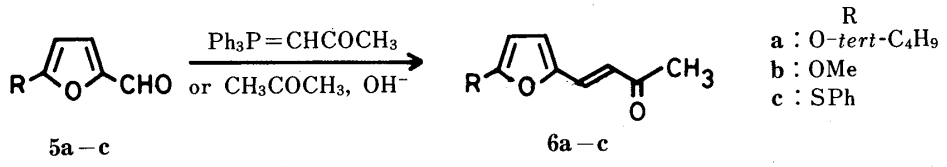


granaticin (1)



2 (X = CN, $PhSO_2$) 3 4

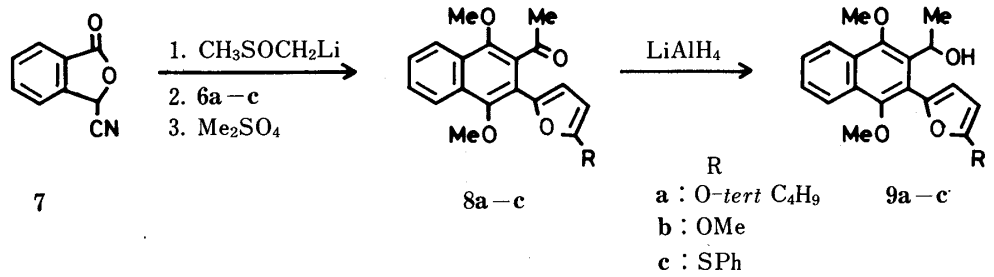
Chart 1



5a–c 6a–c

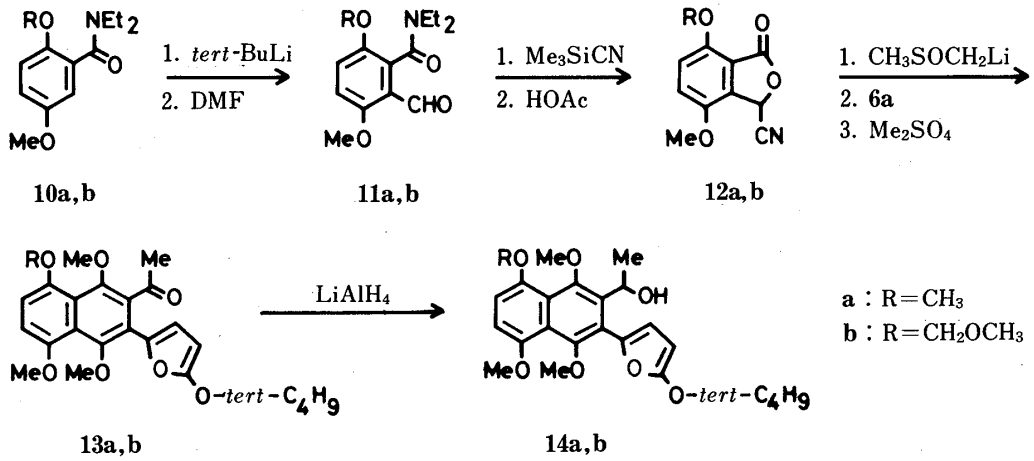
R
a : O-*tert*-C_4H_9
b : OMe
c : SPh

Chart 2



7 8a–c 9a–c

R
a : O-*tert* C_4H_9
b : OMe
c : SPh



10a,b 11a,b 12a,b 13a,b 14a,b

a : R=CH_3
b : R=CH_2OCH_3

Chart 3

dimethyl sulfate to give 2-acetyl-3-(2-furyl)-1,4-dimethoxynaphthalenes (**8a**—**c**) in good yields (**8a**, 56%; **8b**, 58%; **8c**, 77%). The two 5-alkoxyfuryl derivatives **8a**, **b** were identified by comparison with the samples prepared from 2-acetyl-1,4-naphthoquinone by reaction with 2-

alkoxyfuran followed by *O*-methylation.[6] Next, 4,7-dimethoxy and 4-methoxy-7-[(methoxy)methoxy]phthalides (**12**) were prepared straightforwardly from the corresponding dialkoxybenzamide **10** by improved procedures based on the reported method[5d] (Chart 3) and subjected to annulation with **6a** using the same protocol as for **7**. Functionalized tetraalkoxynaphthalenes **13** were obtained again in acceptable overall yields.

Transformation of compound **8a** into pyrano-γ-lactones **16a, b** (Chart 4) has already been carried out by Kraus and Roth[6] in three steps: lithium aluminum hydride reduction (formation of the carbinol **9a** in 95% yield), treatment of **9a** with 1 eq of trifluoroacetic acid in dichloromethane (0 °C) to give a butenolide intermediate **15**, which was treated with 1 eq of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene at room temperature to provide a 2.7 : 1 mixture of **16a** and **16b** in 35% yield. However, since the reported yield and stereoselectivity in the pyrano-annulation were unacceptable, we reinvestigated this crucial step. Among various acid-solvent combinations examined for the first step (butenolide formation), *p*-toluenesulfonic acid in acetonitrile (0 °C) was found to be the best in terms of cleanliness of the reaction as judged by thin layer chromatography (TLC). Since prolonged reaction results in the production of a spiro-γ-lactone **17** (*ca.* 1 : 1 mixture of diastereomers) together with a lesser amount of **16a, b**, the acid treatment should be interrupted immediately after consumption of **9a**. Cyclization of crude **15** by treatment with DBU in toluene at −10 °C

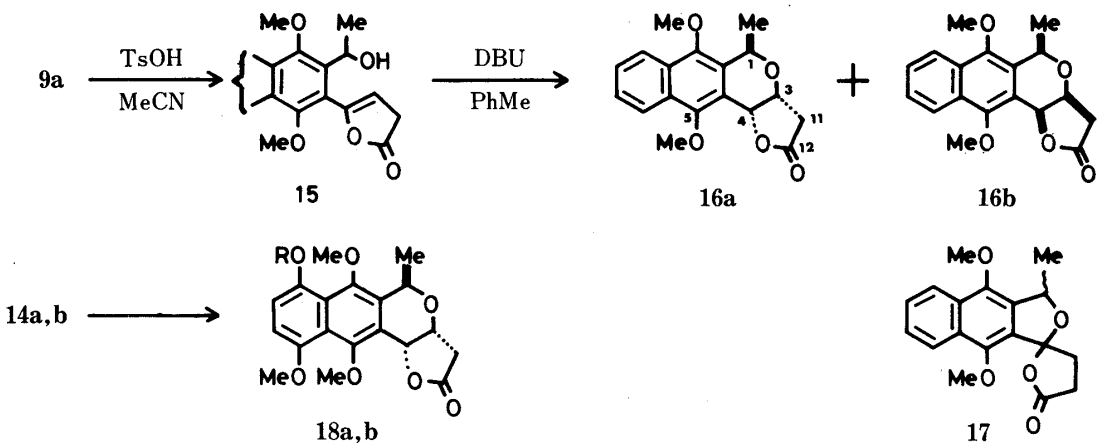


Chart 4

proceeded smoothly to afford a 5.2 : 1 mixture of **16a** and **16b** in an excellent yield (86% from **9a**), and **16a** was readily obtained by recrystallization of the mixture. Use of dichloromethane instead of toluene decreased the ratio to *ca.* 2 : 1. These epimers could be readily identified by nuclear magnetic resonance (NMR) spectroscopy, diagnostic signals being those of C_1-CH_3 (**16a**, δ 1.56; **16b**, δ 1.77) and for C_1-H (**16a**, δ 5.37; **16b**, δ 5.04). By employing the improved protocol, the carbinols **14a** and **14b** could be converted to the corresponding pyrano-γ-lactones **18a** and **18b** in good yields, the isomer ratios [(1*R**,3*R**,4*R**)/(1*R**,3*S**,4*S**)] determined by ^{1}H-NMR (integration of H-1) being 5.5 and 6.2, respectively.

Evaluation of the 5-methoxy-2-furyl compound **8b** as a precursor for **16a** was our next subject. The corresponding carbinol **9b** obtained by $LiAlH_4$ reduction in quantitative yield was subjected to treatment with *p*-toluenesulfonic acid in acetonitrile at room temperature. In this case, the butenolide intermediate **15** was not detected by TLC analysis, and a 4.5 : 1 mixture of **16a, b** and **17** were obtained in 40% and 4.5% yields, respectively. Although a higher yield of **16a, b** (48%) was obtainable with naphthalene-2-sulfonic acid, formation of the undesired by-product **17** became significant (20% yield). Finally, transformation of the phenylthio compound **9c** to **16** by oxidative desulfurization was attempted under various conditions.[10] However, a complex product mixture invariably resulted, and no product could

be identified.

In summary, the cyanophthalide annulation with 4-(5-*tert*-butoxy-2-furyl)-3-butene-2-one (**6a**) has been demonstrated to be an attractive and feasible technique for the construction of the granaticin skeleton. Further work toward the total synthesis of granaticin *via* the key intermediate **2** is in progress in these laboratories.

Experimental

Infrared (IR) spectra were recorded on a Jasco IRA-1 grating spectrometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. ^{1}H-NMR spectra were taken on a JEOL PMX-60 (60 MHz), a Varian XL-200 (200 MHz), or a JEOL GX-270 (270 MHz) spectrometer in deuteriochloroform. Chemical shifts (δ) are reported in parts per million relative to tertramethylsilane as an internal standard. Resonance patterns are described as s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Low-resolution mass spectra (EI-MS) were obtained on a JEOL JMS-D-300 spectrometer. Liquid chromatography under medium pressures was carried out with a UVILOG model ALPC-100 chromatograph. The following adsorbents were used for chromatography: Fuji-Davison BW-200 (150—325 mesh) for column chromatography; Wako precoated Silica gel 70 F-254 plates for analytical TLC. Dry solvents and reagents were obtained by using standard procedures. Anhydrous magnesium sulfate was used for drying all organic solvent extracts in work-up, and removal of the solvents was performed with a rotary evaporator. Melting points were determined by using a Yanagimoto micro melting point apparatus. All melting points and boiling points are uncorrected. Elemental combustion analyses were performed at the Microanalytical Laboratory, Scientific Instrument Center of this university.

4-(5-*tert*-Butoxy-2-furyl)-3-buten-2-one (6a)——A solution of **5a**[11] (4.83 g, 28.8 mmol) and (acetonylidene)-triphenylphosphorane[7] (9.16 g, 28.8 mmol) in dry benzene (50 ml) was stirred and heated at reflux for 3.5 h. The solution was then concentrated under reduced pressure and the residue was extracted with hexane. The hexane extract was concentrated and the remaining oil was distilled with a Kugelrohr apparatus to give **6a** (5.01 g, 84%) as a pale yellow oil, bp 90 °C (0.2 Torr). *Anal.* Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.13; H, 7.72. IR (neat): 1660, 1620 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.43 (9H, s), 2.27 (3H, s), 5.48 (1H, d, J = 3.5 Hz), 6.37 (1H, d, J = 15.5 Hz), 6.52 (1H, d, J = 3.5 Hz), 7.10 (1H, d, J = 15.5 Hz).

4-(5-Methoxy-2-furyl)-3-buten-2-one (6b)——This compound was prepared from 5-methoxy-2-furaldehyde[12] by the same procedure as described for **6a**, bp 110—125 °C (0.6 Torr) (solidified on standing). ^{1}H-NMR (60 MHz) δ: 2.27 (3H, s), 3.90 (3H, s), 5.30 (1H, d, J = 3.5 Hz), 6.37 (1H, d, J = 15.5 Hz), 6.58 (1H, d, J = 3.5 Hz), 7.13 (1H, d, J = 15.5 Hz). IR (KBr): 1655, 1620 cm^{-1}. MS *m/e*: 166 (M^+), 151, 135, 57 (base peak).

4-(5-Phenylthio-2-furyl)-3-buten-2-one (6c)——Water (15 ml) and *p*-toluenesulfonic acid (0.15 g) were added to a solution of 5-phenylthio-2-furaldehyde diethylacetal[8] (5.7 g, 0.02 mol) in ether (15 ml). The mixture was stirred and heated at reflux for 2.5 h. Then, it was cooled and the layers were separated. The organic layer and ether extracts of the water layer were combined, washed with 5% $NaHCO_3$ and brine, dried, and concentrated. The residual red-brown oil (3.7 g, 90%) solidified on standing and on recrystallization from hexane provided an analytical sample of 5-phenylthio-2-furaldehyde as colorless needles, mp 36—36.5 °C. *Anal.* Calcd for $C_{11}H_8O_2S$: C, 64.69; H, 3.95. Found: C, 64.58; H, 3.87. IR (KBr): 1670 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 6.33 (1H, d, J = 3.5 Hz), 7.27 (1H, d, J = 3.5 Hz), 7.43 (5H, s), 9.67 (1H, s).

A mixture of the crude furaldehyde (3.5 g, 17 mmol), acetone (5 ml) and water (10 ml) was stirred at room temperature, and 10% NaOH (1.0 ml) was added. After 9 h, the mixture was extracted with ether. The extract was washed with brine, dried, and concentrated under reduced pressure. The residual brown oil (4.3 g) was purified by MPLC (silica gel, 50 g; elution with 1 : 19 AcOEt–benzene) and then distilled to give **6c** as a pale brown solid (2.0 g, 48%), bp 120—140 °C (0.03 Torr). An analytical sample was obtained by recrystallization from hexane as a colorless sands, mp 37—38 °C. *Anal.* Calcd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95. Found: C, 68.69; H, 4.93. IR (KBr): 1660, 1605 cm^{-1}.

2-Acetyl-3-(5-*tert*-butoxy-2-furyl)-1,4-dimethoxynaphthalene (8a)——a) A solution of *n*-BuLi (1.56 M in hexane, 0.86 ml, 1.34 mmol) was added to a stirred mixture of dry THF (8.7 ml) and dry DMSO (4.3 ml) at −5 °C under nitrogen. After 30 min, a solution of **7** (194 mg, 1.22 mmol) in dry DMSO (0.5 ml) was added to the mixture, which had been cooled to −40 °C. The resulting orange solution was maintained at −5 °C for 20 min, then recooled to −20 °C, and a solution of **6a** (305 mg, 1.47 mmol) in dry THF (0.5 ml) was added. The reaction mixture was allowed to warm to 0 °C and stirred at this temperature for 1 h before treatment with water and neutralization with acetic acid. The mixture was extracted with benzene. The combined benzene layers were washed with aqueous $Na_2S_2O_4$ and brine, dried, and concentrated under reduced pressure. The residue was dissolved in dry acetone (12 ml), and then powdered K_2CO_3 (520 mg) and dimethyl sulfate (0.3 ml) were added to the solution under nitrogen. The stirred mixture was heated at reflux for 5 h, then cooled and filtered. The filtrate was concentrated, and the residue was purified by MPLC (silica gel, 25 g; elution with 2 : 1 benzene–hexane) to give **8a** (254 mg, 56%) as a pale yellow oil. ^{1}H-

NMR (60 MHz) δ: 1.40 (9H, s), 2.53 (3H, s), 3.78 (3H, s), 3.92 (3H, s), 5.60 (1H, d, J=3.5 Hz), 6.82 (1H, d, J=3.5 Hz), 7.43—7.63 (2H, m), 7.93—8.27 (2H, m).

b) 2-*tert*-Butoxyfuran[2d,11] (0.09 ml, 0.6 mmol) was added to a stirred solution of 2-acetyl-1,4-naphthoquinone[13] (0.10 g, 0.5 mmol) in dry acetone (5 ml) at −70 °C under nitrogen. The solution was allowed to warm to *ca.* 0 °C over 1 h. After addition of K_2CO_3 (215 mg) and dimethyl sulfate (125 μl), the mixture was heated at reflux for 1 h. It was cooled and filtered, and the filtrate was concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 8 g; elution with 1:9 AcOEt–hexane) to give **8a** (164 mg, 89%) as an oil.

2-Acetyl-3-(5-methoxy-2-furyl)-1,4-dimethoxynaphthalene (8b)——a) A stirred mixture of dry DMSO (50 ml) and dry THF (100 ml) was cooled to −40 °C, and a solution of *n*-BuLi (1.56 M in hexane, 9.6 ml, 15 mmol) was added over 5 min *via* a syringe. The mixture was then kept at *ca.* 0 °C for 30 min, and a solution of **7** (2.24 g, 14 mmol) in dry DMSO (5 ml) was added over 5 min. Ten minutes after the addition, a solution of **6b** (2.32 g, 14 mmol) in a mixture of dry THF (5 ml) and dry DMSO (2 ml) was added. After being stirred at 0 to −5 °C for 1.25 h, the reaction mixture was treated with aqueous NH_4Cl and extracted with benzene. The extract was washed with brine, dried, and concentrated to give the crude hydroquinone as a reddish oil (4.0 g). This material was dissolved in dichloromethane (70 ml). The following components were added sequentially to the above solution under nitrogen: a solution of $Na_2S_2O_4$ (2.4 g, 14 mmol) in water (30 ml), *n*-Bu_4NBr (0.5 g), an aqueous KOH (4.4 g in 40 ml of water), and dimethyl sulfate (6.0 ml, 32 mmol). The mixture was stirred at room temperarure overnight, and the layers were separated. The organic layer and dichloromethane extract of the aqueous layer were combined, washed with 5% KOH and brine, and dried. Removal of the solvent under reduced pressure afforded a brown oil, which was subjected to MPLC (silica gel, 50 g; elution with benzene) to give **8b** as a pale yellow solid (2.52 g, 58%), mp 92—93 °C after recrystallization from iso-Pr_2O. *Anal.* Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.85; H, 5.49. IR (KBr): 1705 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.52 (3H, s), 3.80 (3H, s), 3.88 (3H, s), 3.92 (3H, s), 5.33 (1H, d, J=3.5 Hz), 6.85 (1H, d, J=3.5 Hz), 7.4—7.63 (2H, m), 7.93—8.23 (2H, m).

b) Anhydrous $MgSO_4$ (1.5 g) and Ag_2O (400 mg, 1.7 mmol) were added to a stirred solution of 2-acetyl-1,4-dihydroxynaphthalene[12] (210 mg, 1.04 mmol) in ether (20 ml) at room temperature. After 15 min, the mixture was filtered and the filtrate was concentrated under reduced pressure. The yellow solid residue (2-acetyl-1,4-naphthoquinone) was dissolved in dry toluene (5 ml). The solution was stirred and cooled to −70 °C under nitrogen, and 2-methoxyfuran (0.12 ml, 1.25 mmol) was added. The reaction mixture was allowed to warm to 0 °C over 1 h, then concentrated under reduced pressure. The residue was dissolved in dry acetone (10 ml) under nitrogen, and after addition of K_2CO_3 (430 mg, 3.1 mmol) and dimethyl sulfate (0.25 ml, 2.6 mmol), the mixture was stirred and heated at reflux. After 1 h, the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 30 g; elution with 1:9 AcOEt–hexane) to give **8b** (253 mg, 77% overall yield).

2-Acetyl-3-(5-phenylthio-2-furyl)-1,4-dimethoxynaphthalene (8c)——A solution of *n*-BuLi (1.56 M in hexane, 2.56 ml) was added to a stirred mixture of dry DMSO (20 ml) and dry THF (40 ml) maintained at 0 °C under nitrogen. After 15 min, a solution of **7** (636 mg, 4.0 mmol) in dry DMSO (5 ml) was added. The resulting orange solution was cooled to −40 °C after 10 min and a solution of **6c** (0.85 g, 3.5 mmol) in dry THF (5 ml) was added over 10 min. The dark-red reaction mixture was allowed to warm to room temperature, and after continued stirring for 2 h, was diluted with water (*ca.* 50 ml) and neutralized with acetic acid. The whole was extracted with benzene, and combined extracts were washed with brine and dried. Removal of the solvent under reduced pressure afforded the crude hydroquinone as a dark-red oil (1.31 g). A solution of this material in dichloromethane (30 ml) was stirred with $Na_2S_2O_4$ (0.3 g, 1.7 mmol) in water (10 ml) in the presence of *n*-Bu_4NBr (0.25 g) for 10 min. Then, aqueous KOH (2.2 g in 20 ml of water) and dimethyl sulfate (1.5 ml, 16 mmol) were added to the mixture under nitrogen, and the whole was stirred overnight at room temperature. The layers were separated, and the organic layer and dichloromethane extracts of the aqueous layer were combined, washed with brine, and dried. Removal of the solvent under reducd pressure afforded a reddish oil (1.84 g), which was purified by MPLC (silica gel, 25 g; elution with benzene) to give **8c** as a pale yellow solid, mp 100—101 °C after recrystallization from hexane. *Anal.* Calcd for $C_{24}H_{20}O_4S$: C, 71.28; H, 4.98. Found: C, 71.43; H, 5.06. IR (KBr): 1700 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.36 (3H, s), 3.80 (3H, s), 3.90 (3H, s), 6.86 (1H, d, J=3.5 Hz), 6.97 (1H, d, J=3.5 Hz), 7.30 (5H, s), 7.45—7.65 (2H, m), 7.95—8.25 (2H, m). MS *m/e*: 404 (M^+), 295 (base peak), 265.

3-(5-*tert*-Butoxy-2-furyl)-2-(1-hydroxyethyl)-1,4-dimethoxynaphthalene (9a)[6]——^{1}H-NMR (60 MHz) δ: 1.42 (9H,s), 1.55 (3H, d, J=7 Hz), 3.63 (3H, s), 3.65 (1H, d, J=10 Hz, OH), 4.03 (3H, s), 5.06 (1H, dq, J=10, 7 Hz), 5.57 (1H, d, J=3 Hz), 6.38 (1H, d, J=3 Hz).

2-(1-Hydroxyethyl)-3-(5-methoxy-2-furyl)-1,4-dimethoxynaphthalene (9b)——A solution of **8b** (490 mg, 1.5 mmol) in dry ether (5 ml) was syringed over 3 min into a stirred suspension of $LiAlH_4$ (60 mg, 1.5 mmol) in dry ether (2 ml) maintained at −20 °C. After being stirred at −10 °C for 30 min, the mixture was treated with wet ether (10 ml) and then with water (10 ml). The ether layer was separated, washed with brine and dried. Removal of the solvent afforded **9b** (490 mg) as a pale yellow oil. *Anal.* Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.49; H, 6.13. ^{1}H-NMR (60 MHz) δ: 1.58 (3H, d, J=7 Hz), 3.70 (3H, s), 3.92 (3H, s), 4.07 (3H, s), 5.35 (1H, d, J=3.5 Hz), 6.45 (1H, d, J=3.5 Hz), 7.4—8.25 (4H, m).

2-(1-Hydroxyethyl)-1,4-dimethoxy-3-(5-phenylthio-2-furyl)naphthalene (9c)——This compound was obtained as an oil (90% yield after silica gel chromatography) by $LiAlH_4$ reduction of **8c** according to the procedure adopted for **8b**. ^{1}H-NMR (60 MHz) δ: 1.43 (3H, d, J=7 Hz), 3.63 (3H, s), 4.02 (3H, s), 6.60 (1H, d, J=3.5 Hz), 6.87 (1H, d, J=3.5 Hz), 7.22 (5H, s), 7.4—7.6 (2H, m), 7.9—8.2 (2H, m). MS *m/e*: 406 (M^+), 255 (base peak), 239.

***N,N*-Diethyl-2-formyl-3,6-dimethoxybenzamide (11a)**——A solution of *tert*-BuLi (2.2 M in pentane, 5.0 ml) was added dropwise to a stirred solution of **10a**[14] (2.23 g, 10 mmol) in dry THF (100 ml) at −78 °C under nitrogen. After continued stirring at the same temperature for 1 h, the yellow turbid mixture was treated with dry DMF (1.55 ml, 20 mmol). After 20 min, the resulting clear solution was allowed to warm to room temperature, and after 1.5 h it was treated with brine, then extracted with AcOEt. The extract was dried and concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 32 g; elution with 1 : 1 AcOEt–benzene) to give **11a** (2.03 g, 81%) as a solid, which was recrystallized from iso-Pr_2O as needles (1.95 g, 78%), mp 110—111 °C (lit.[5c] 97—98 °C). IR (KBr): 1680, 1630 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.02 (3H, t, J=7 Hz), 1.32 (3H, t, J=7 Hz), 3.07 (2H, q, J=7 Hz), 3.53 (2H, q, J=7 Hz), 3.80 (3H, s), 3.90 (3H, s), 6.93 (1H, d, J=9 Hz), 7.13 (1H, d, J=9 Hz).

***N,N*-Diethyl-2-formyl-3-methoxy-6-[(methoxy)methoxy]benzamide (11b)**[15]——A solution of crude 5-methoxysalicylic chloride (prepared from 18.0 g of 5-methoxysalicylic acid)[16] in dry benzene (100 ml) was added dropwise to a stirred solution of diethylamine (33 ml, 0.32 mol) in dry benzene (100 ml) cooled with ice-water. After the addition was completed, the mixture was stirred at room temperature for 2 h, then treated with cold 3% sulfuric acid and benzene. The organic layer was washed with water, dried, and concentrated under reduced pressure. The crystalline residue was recrystallized from AcOEt to give 5-methoxysalicylic diethylamide (15.3 g, 64% overally yield), mp 102—103 °C. IR (KBr): 1590 cm^{-1}. This material was subjected to *O*-(methoxy)methylation in a usual manner (NaH, DMF, $ClCH_2OCH_3$) to give **10b**, mp 76—78 °C from iso-Pr_2O–EtOH, in 84% yield. IR (KBr): 1630 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.07 (3H, t, J=7.3 Hz), 1.25 (3H, t, J=7.3 Hz), 3.25 (2H, q, J=7.3 Hz), 3.4—3.8 (2H, m), 3.47 (3H, s), 3.77 (3H, s), 5.10 (2H, br s), 6.76 (1H, d, J=2.9 Hz), 6.83 (1H, dd, J=9.2, 2.9 Hz), 7.07 (1H, d, J=9.2 Hz). MS *m/e*: 267 (M^+), 236, 222, 45 (base peak).

A stirred solution of **10b** (8.56 g, 32 mmol) in dry THF (130 ml) under argon was cooled at −78 °C, and *tert*-BuLi (2 M in pentane, 24.0 ml, 48 mmol) was added dropwise over *ca.* 10 min. After 10 min, dry DMF (4.0 ml, 48 mmol) was added over 2 min, then the mixture was allowed to warm to room temperature over 2 h. After addition of water followed by removal of the bulk of THF under reduced pressure, the mixture was extracted with ether. The extract was washed with brine, dried, and concentrated. The residue was subjected to chromatography (silica gel, 200 g; elution with 1 : 5 hexane–AcOEt) to give **11b** (5.45 g, 58%) as a pale yellow solid. An analytical sample was obtained by recrystallization from iso-Pr_2O–AcOEt as colorless plates, mp 56—57.5 °C. *Anal.* Calcd for $C_{15}H_{21}NO_5$: C, 61.00; H, 7.17; N, 4.74. Found: C, 61.28; H, 7.11; N, 4.73. IR (KBr): 1675, 1625 cm^{-1}. ^{1}H-NMR (270 MHz) δ: 1.04 (3H, t, J=7.1 Hz), 1.32 (3H, t, J=7.1 Hz), 3.10 (2H, q, J=7.1 Hz), 3.48 (3H, s), 3.54 (1H, dq, J=14.2, 7.1 Hz), 3.69 (1H, dq, J=14.2, 7.1 Hz), 3.90 (3H, s), 5.09 (1H, d, J=9.3 Hz), 5.12 (1H, d, J=9.3 Hz), 6.94 (1H, d, J=9.3 Hz), 7.38 (1H, d, J=9.3 Hz), 10.43 (1H, s). MS *m/e*: 295 (M^+).

3-Cyano-4,7-dimethoxy-1(3*H*)-isobenzofuranone (12a)——A stirred mixture of **11a** (1.0 g, 4 mmol), KCN (50 mg) and 18-crown-6 (50 mg) in dry dichloromethane (10 ml) was cooled with ice-water, and trimethylsilyl cyanide (0.8 ml, 6 mmol) was added. After 10 min, the mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was dissolved in acetic acid (5 ml) and the solution was stirred at room temperature for 5 h. After the bulk of acetic acid was neutralized with saturated aqueous $NaHCO_3$, the mixture was extracted with chloroform. The extract was dried and concentrated under reduced pressure. The residue was subjected to MPLC (silica gel, 15 g; elution with chloroform) and the solid eluate was recrystallized from AcOEt to give **12a** (715 mg, 81%) as colorless needles, mp 162—165 °C (lit.[5d] mp 151—153 °C). IR (KBr): 1790 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.97 (6H, s), 5.90 (1H, s), 7.00 (1H, d, J=8 Hz), 7.20 (1H, d, J=8 Hz).

3-Cyano-4-methoxy-7-(methoxy)methoxy-1(3*H*)-isobenzofuranone (12b)——By using the same procedure as described above for **11a**, compound **11b** was transformed into **12b** in 88% yield. An analytical sample was obtained by recrystallization from iso-Pr_2O as colorless needles, mp 158—160 °C. *Anal.* Calcd for $C_{12}H_{11}NO_5$: C, 57.83; H, 4.45, N, 5.62. Found: C, 57.91; H, 4.58; N, 5.75. IR (KBr): 1785 cm^{-1}. ^{1}H-NMR (200 MHz, acetone-d_6) δ: 3.50 (3H, s), 4.02 (3H, s), 5.34 (2H, s), 6.42 (1H, s), 7.40 (1H, d, J=9 Hz), 7.48 (1H, d, J=9 Hz). MS *m/e*: 249 (M^+, base peak), 219, 45.

2-Acetyl-3-(5-*tert*-butoxy-2-furyl)-1,4,5,8-tetramethoxynaphthalene (13a)——By using the same procedure as employed for the preparation of **8a**, annulation of **12a** (110 mg) with **6a** (dimsyllithium as a base) followed by *O*-methylation of the resulting hydroquinone produced **13a** (85 mg, 40%) as an oil after chromatographic purification. *Anal.* Calcd for $C_{24}H_{28}O_7$: C, 67.28; H, 6.59. Found: C, 67.31; H, 6.70. IR (neat): 1705 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.40 (9H, s), 2.56 (3H, s), 3.68 (3H, s), 3.75 (3H, s), 3.93 (6H, s), 5.57 (1H, d, J=3.5 Hz), 6.82 (2H, s), 6.87 (1H, d, J=3.5 Hz). MS *m/e*: 428 (M^+), 372 (base peak), 357.

2-Acetyl-3-(5-*tert*-butoxy-2-furyl)-1,4,5-trimethoxy-8-[(methoxy)methoxy]naphthalene (13b)——A solution of **12b** (125 mg, 0.50 mmol) in dry THF (4.0 ml) was added dropwise to a cold (−78 °C) stirred solution of lithium diisopropylamide [prepared from *n*-BuLi (1.1 mmol) and diisopropylamine (1.2 mmol) in dry THF (1.5 ml)]. After 30 min, hexamethylphosphoric triamide (0.7 ml) was added and 30 min later a solution of **6a** (250 mg, 1.2 mmol) in

dry THF (1.0 ml) was added. The mixture at −78 °C was allowed to warm to −10 °C over 30 min, and then stirred at room temperature for 4 h. The reaction mixture was treated with 5% aqueous KH_2PO_4 and the whole was extracted with AcOEt. The extract was washed with water, dried, and concentrated under reduced pressure. Chromatography of the residue (silica gel, 16 g; elution with 1 : 9 AcOEt–benzene) gave the crude hydroquinone (160 mg), which was heated in dry acetone (3.5 ml) under nitrogen with K_2CO_3 (200 mg) and dimethyl sulfate (92 μl) over 12 h. Standard work-up of the reaction mixture and product purification by chromatography (silica gel, 6 g; elution with 1 : 9 AcOEt–benzene) afforded **13b** (122 mg, 53%) as a pale yellow oil. *Anal.* Calcd for $C_{25}H_{30}O_8$: C, 65.49; H, 6.60. Found: C, 65.25; H, 6.44. IR (neat): 1705 cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.40 (9H, s), 2.55 (3H, s), 3.60 (3H, s), 3.70 (3H, s), 3.78 (3H, s), 3.97 (3H, s), 5.20 (2H, s), 5.57 (1H, d, J=3.5 Hz), 6.83 (1H, d, J=9 Hz), 6.87 (1H, d, J=3.5 Hz), 7.13 (1H, d, J=9 Hz). MS *m/e*: 458 (M^+), 402 (base peak), 357.

(1*R,3*R**,4*R**)-5,10-Dimethoxy-1-methyl-3,4,11,12-tetrahydro-1*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-12-one (16a)**——A solution of **9a** (122 mg, 0.33 mmol) in dry acetonitrile (3.3 ml) was cooled with ice-water, and a solution of *p*-toluenesulfonic acid in dry acetonitrile (0.5 M, 0.66 ml) was added. When the starting material **9a** was no longer detectable on TLC (*ca.* 20 min, Rf=0.68→0.16 with 1 : 4 AcOEt–benzene), the solution was treated with a calculated amount of aqueous $NaHCO_3$ (20 ml) for neutralization and then extracted with AcOEt. The extract was washed with brine, dried, and concentrated under reduced pressure at room temperature. The residue (**15**, contaminated with conjugated lactone (less than 25% by ^{1}H-NMR) was dried by azeotropic distillation with toluene at room temperature and dissolved in dry toluene (1.5 ml). The solution was cooled at −10 °C and treated with DBU (50 μl, 0.33 mmol) for 30 min. Flash chromatography (silica gel, 4.5 g; elution with 1 : 4 AcOEt–hexane) of the reaction mixture provided a 5.2 : 1 mixture of **16a** and **16b** (89 mg, 86%) as a white solid, Rf=0.55 with 1 : 4 AcOEt–benzene. ^{1}H-NMR (270 MHz) δ: **16a**: 1.56 (3H, d, J=6.8 Hz), 2.72 (1H, d, J=17.6 Hz, H-11), 3.00 (1H, dd, J=17.4, 4.8 Hz, H-11), 3.95 (3H, s), 4.10 (3H, s), 4.76 (1H, dd, J=4.8, 2.6 Hz, H-3), 5.37 (1H, q, J=6.8 Hz, H-1), 5.62 (1H, d, J=2.6 Hz, H-4); **16b**: 1.77 (3H, d, J=6.2 Hz), 2.77 (1H, d, J=15 Hz, H-11), 2.93 (1H, dd, J=17.4, 4.2 Hz, H-11), 3.83 (3H, s), 4.13 (3H, s), 4.38 (1H, dd, J=6.8, 2.6 Hz, H-3), 5.04 (1H, q, J=6.2 Hz, H-1), 5.62 (1H, d, J=2.6 Hz, H-4). Recrystallization of the mixture from iso-Pr_2O afforded **16a** (51 mg) as colorless flakes, mp 192—193.5 °C. *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.50; H, 5.71. MS *m/e*: 314 (M^+, base peak), 299.

(1*R,3*R**,4*R**)-5,6,9,10-Tetramethoxy-1-methyl-3,4,11,12-tetrahydro-1*H*-furo[3,2-*b*]naphtho[2,3-*d*]pyran-12-one (18a)**——Treatment of **13a** (88 mg) with $LiAlH_4$ in ether afforded **14a** (70 mg, 80%) as an oil after chromatographic purification of the product (silica gel, 4 g; elution with 1 : 4 AcOEt–hexane). ^{1}H-NMR (60 MHz, D_2O addition) δ: 1.42 (9H, s), 1.57 (3H, d, J=7 Hz), 3.57 (3H, s), 3.90 (3H, s), 3.93 (6H, s), 5.02 (1H, q, J=7 Hz), 5.62 (1H, d, J=3.5 Hz), 6.40 (1H, d, J=3.5 Hz), 6.85 (2H, s). This carbinol **14a** was subjected to pyrano-annulation under the same conditions as described for **9a**. A 5.5 : 1 mixture of **18a** and its (1*R**,3*R**,4*S**) diastereomer (48 mg, 79%) obtained as a solid by chromatographic isolation (silica gel, 4 g; elution with 1 : 2 AcOEt–hexane) was recrystallized from iso-Pr_2O to give **18a** (29 mg) as colorless prisms, mp 204—205 °C. *Anal.* Calcd for $C_{20}H_{22}O_7$: C, 64.16; H, 5.92. Found: C, 63.94; H, 5.88. IR (KBr): 1785 cm^{-1}. MS *m/e*: 374 (M^+, base peak), 359. ^{1}H-NMR (270 MHz) δ: 1.55 (3H, d, J=6.6 Hz), 2.70 (1H, d, J=17.4 Hz, H-11), 2.99 (1H, dd, J=17.4, 4.95 Hz, H-11), 3.82, 3.93, 3.95, 3.96 (each 3H, s), 4.73 (1H, dd, J=4.95, 2.75 Hz, H-3), 5.36 (1H, q, J=6.6 Hz, H-1), 5.59 (1H, d, J=2.75 Hz, H-4), 6.81 (1H, d, J=8.6 Hz), 6.86 (1H, d, J=8.6 Hz). The minor (1*R**,3*S**,4*S**) isomer was characterized by ^{1}H-NMR spectral data (270 MHz) obtained with an enriched sample: δ 1.73 (d, J=6.2 Hz), 2.76 (d, J=15.75 Hz, H-11), 2.92 (dd, J=15.75, 4.2 Hz, H-11), 3.71, 3.94, 3.98 (each s), 4.35 (dd, J=4.2, 2.4 Hz, H-3), 5.06 (q, J=6.2 Hz, H-1).

(1*R,3*R**,4*R**)-5,6,10-Trimethoxy-9-[(methoxy)methoxy]-1-methyl-3,4,11,12-tetrahydro-1*H*-furo[3,2-*b*]-naphtho[2,3-*d*]pyran-12-one (18b)**——The carbinol **14b** (38 mg) obtained by $LiAlH_4$ reduction of **13b** (88% yield) was transformed into a 6.2 : 1 mixture of **18b** and its C_1-epimer (22 mg, 66%) by the same procedure as described for **14a**. ^{1}H-NMR (270 MHz) δ: for **18a** 1.54 (d, J=6.7 Hz, CH_3-1), 2.70 (d, J=17.4 Hz, H-11), 2.99 (dd, J=17.4, 4.95 Hz, H-11), 3.59, 3.82, 3.93, 3.98 (each s, OCH_3), 4.73 (dd, J=4.95, 2.75 Hz, H-3), 5.18 (s, OCH_2O), 5.37 (q, J=6.7 Hz, H-1), 5.59 (d, J=2.75 Hz, H-4), 6.79 (d, J=8.6 Hz, ArH), 7.16 (d, J=8.6 Hz, ArH); for the epimer (minor product) 1.71 (d, J=6.4 Hz, CH_3-1), 4.35 (dd, J=4.0, 2.4 Hz, H-3), 5.05 (q, J=6.4 Hz, H-1). Crystallization of this material from iso-Pr_2O afforded a 12.5 : 1 mixture as colorless prisms, mp 149—151 °C. *Anal.* Calcd for $C_{21}H_{24}O_8$: C, 62.37; H, 5.98. Found: C, 62.10; H, 6.16. IR (KBr): 1780 cm^{-1}. MS *m/e*: 404 (M^+, base peak), 359.

Acid-Catalyzed Annulation of 9b (Formation of 16a, b and 17)——A solution of naphthalene-2-sulfonic acid monohydrate (170 mg, 0.75 mmol) in acetonitrile (3.0 ml) was added to a stirred solution of **9b** (246 mg, 0.75 mmol) at room temperature. After 22 h, the mixture was diluted with benzene (20 ml). The solution was washed with 5% $NaHCO_3$ and brine, dried, and concentrated under reduced pressure. The residual pale brown oil (243 mg) was subjected to chromatography (silica gel, 12 g; elution with 1 : 9 AcOEt–hexane) to afford, in the order of elution, **17** (48 mg, 20%) and a 4.5 : 1 mixture of **16a** and **16b** (114 mg, 48%). Compound **17**, a colorless oil, was a *ca.* 1 : 1 mixture of diastereomers. *Anal.* Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.52; H, 5.86. IR (neat): 1780 cm. ^{1}H-NMR (200 MHz) δ: 1.68 and 1.69 (3H, d, J=6.5 Hz, C–CH_3), 2.45—2.65 (1H, m), 2.85—3.05 (2H, m), 3.05—3.45 (1H, m), 3.93, 3.95, 3.97, and 3.99 (6H, s, OCH_3), 5.72 and 5.63 (1H, q, J=6.5 Hz, OCH), 7.59 (2H, m), 8.15 (2H, m).

Acknowledgement Support of this work by a Grant-in-Aid (No. 60570981) for Scientific Research from the Ministry of Education, Science and Culture of Japan is gratefully acknowledged.

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