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Synthesis of a Griseofulvin Analogue

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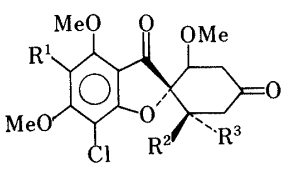
Ring contraction of 6-ethoxycarbonyl-4,5,7-trihydroxycoumarin (**7**) to a 3(2*H*)-benzofuranone (**13**) was achieved. Compound **13** was utilized in a synthesis of a griseofulvin analogue (**1b**) with an ethoxycarbonyl group at the 5 position. However, **1b** was found to be inactive in a test of fungicidal activity.

Keywords——coumarin; 3(2*H*)-benzofuranone; griseofulvin; ring contraction; alkoxycarbonylation; spiro-annelation; fungicidal activity

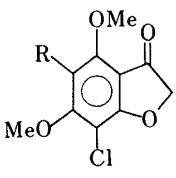
Griseofulvin (**1a**) is now produced industrially by fermentation, but its total synthesis has been studied by several workers. In those studies, 3(2*H*)-benzofuranone derivatives were used as the common synthetic intermediates: the 3(2*H*)-benzofuranone (**3a**) was used in the method of Stork and Tomasz,[1] the 2-methoxycarbonyl analogue (**4a**) in the method of Brossi *et al.*,[2] and the 2-acetyl analogue (**5a**) in the method of Danishefsky and Walker.[3]

Our earlier paper[4] described the self-condensation of diethyl acetonedicarboxylate (**6**) to give 6-ethoxycarbonyl-4,5,7-trihydroxycoumarin (**7**) in a quantitative yield. We thought that if the ring contraction of the 4-hydroxycoumarine (**7**) to 3(2*H*)-benzofuranones (**3b** and **4b**) could be achieved, the griseofulvin analogue (**1b**) with an ethoxycarbonyl group in the benzene ring of **1a** could be conveniently prepared. Moreover, we were interested in determining the influence of an electron-withdrawing group such as an ethoxycarbonyl group in the benzene ring of **1a** on the fungicidal activity.

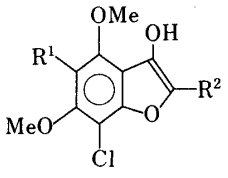
3-Halogenocoumarins are well-known to afford the ring-contracted coumarilic acids (2-carboxybenzofurans) on treatment with alcoholic potassium hydroxide.[5] On the other hand, 3-bromocoumarin, on treatment with sodium methoxide in methanol, gave methyl coumarilate (2-methoxycarbonylbenzofuran) in a high yield.[6] However, ring contraction of 4-hydroxycoumarins to 3(2*H*)-benzofuranones has not been reported. This paper describes the ring contraction of the 4-hydroxycoumarin (**7**) to 3(2*H*)-benzofuranones, and their application to the synthesis of a *dl*-griseofulvin analogue (**1b**).



1a: $R^1=H$, $R^2=Me$, $R^3=H$
1b: $R^1=COOEt$, $R^2=Me$, $R^3=H$
2a: R^1, $R^2=H$, $R^3=Me$



3a: R=H
3b: R=COOEt



4a: $R^1=H$, $R^2=COOMe$
4b: $R^1=COOEt$, $R^2=COOMe$
5a: $R^1=H$, $R^2=COMe$

Chart 1

Results and Discussion

Conversion of **7** to 3(2*H*)-benzofuranones (**3b**, **4b**), which are key intermediates for the synthesis of the *dl*-griseofulvin analogue (**1b**), was undertaken (Chart 2).

Thus, methylation of **7** to give the corresponding trimethoxycoumarin (**8**) was attempted in the usual ways, using dimethyl sulfate, methyl iodide, or diazomethane; however, a satisfactory result could not be obtained. On the other hand, phase-transfer reaction[7] of **7** with dimethyl sulfate in the presence of benzyltrimethylammonium chloride (BTEAC) gave **8** in 55% yield. Treatment of **8** with bromine at 0 °C gave the 3-bromo derivative (**9**). Next, ring contraction of the coumarin (**9**) to the 2-methoxycarbonylbenzofuranone (**10**) was examined by treating **9** with excess sodium methoxide in refluxing methanol for 5 h. However, not **10** but the methyl cinnamate (**11**) was obtained in 43% yield. Heating of **11** with methanolic potassium hydroxide gave the α-bromoacetophenone (**12**), which was cyclized to the benzofuranone (**13**) by heating with sodium acetate in ethanol in 71% yield. Based on these findings, conversion of **9** to **13** was also performed by a one-pot reaction in 75% yield. Treatment of **13** with chlorine at 0 °C gave **3b**, which corresponds to the intermediate of Stork's method.

Since direct ring-contraction of **9** to **10** was unsuccessful, an attempt was made to prepare 2-alkoxycarbonylbenzofuranones (**10** or **4b**) by the alkoxycarbonylation of the benzofuranones (**13** or **3b**). The reaction of **13** with diethyl carbonate in the presence of sodium hydride[8] gave a mixture of many products, from which **10** could not be isolated. In the reaction of **13** with magnesium methylcarbonate (MMC)–diazomethane,[9] the dimer of **13** was obtained and the starting material was recovered. The reaction of **13** with ethyl chloroformate in the presence of lithium diisopropylamide (LDA)[10] gave the 3-ethoxycarbonyloxybenzofuran (**14**) in 84% yield.

Consequently we attempted the reaction of **3b** with methyl cyanoformate (with a soft leaving group) in the presence of LDA,[11] to give the 2-methoxycarbonylbenzofuranone (**4b**), which corresponds to the intermediate of Brossi's method, in 92% yield.

The synthesis of the *dl*-griseofulvin analogue (**1b**) was attempted according to Brossi *et al.*[2] (Chart 3). The Michael condensation of **4b** with 3-penten-2-one in the presence of benzyltrimethylammonium hydroxide (triton-B) was attempted, but the reaction gave a mixture of many products. Potassium fluoride in the presence of a catalytic amount of 18-crown-6-ether was reported to be an effective basic catalyst in the Michael reaction.[12] We used potassium fluoride and 18-crown-6-ether in the same way, and obtained the Michael adduct, the 2-methoxycarbonyl-2-(4-oxo-pentanyl)benzofuranone (**15**) in 98% yield as a 1 : 1 mixture of the diastereomers. Spiro-annelation of **15** to **16** was attempted under the conditions used by Brossi *et al.*[2] However, structurally unknown compounds, probably formed by bimolecular condensation of **15**, were obtained. McMillan *et al.*[13] and Dawkins and Mulholland[14] similarly found that the spiro-annelation of 4,6-dimethoxy-2-methoxycarbonyl-2-(4-oxopentan-2-yl)-3(2*H*)-benzofuranone was unsuccessful, providing the dibenzofuranone derivative.

At this point, we decided to synthesize *dl*-**1b** by using **3b** according to Stork and Tomasz.[1a] Their method has the advantage that the double Michael reaction of **3a** with the 2-propenyl ketone (**17**) is stereospecific, affording *dl*-griseofulvin (**1a**) with no epigriseofulvin (**2a**). However, the preparation of the 2-propenyl ketone (**17**) is troublesome and the yield of *dl*-**1a** is very poor (5%). Considering that the reason for the poor yield of *dl*-**1a** may have been insufficient base, we carried out the reaction of **3b** with **17** in diglyme, using 1.2 mol eq of potassium *tert*-butoxide with respect to **3b**, and *dl*-**1b** was obtained in 25% yield. When the same reaction was undertaken in dimethoxyethane (DME), the 2-(1-methoxy-3-oxo-4-hexenylidene)benzofuranone (**18**) was obtained in 32% yield with no formation of *dl*-**1b**. It is

unclear whether the sterochemistry of the side chain of **18** is *E*- or *Z*-form. Stirring of **18** with potassium *tert*-butoxide in the presence of 18-crown-6-ether in benzene gave *dl*-**1b** in 90% yield with no formation of the epi analogue.

The stereochemistry of *dl*-**1b** was determined by comparison of its nuclear magnetic resonance (NMR) spectrum with those reported for griseofulvin (**1a**) and epigriseofulvin

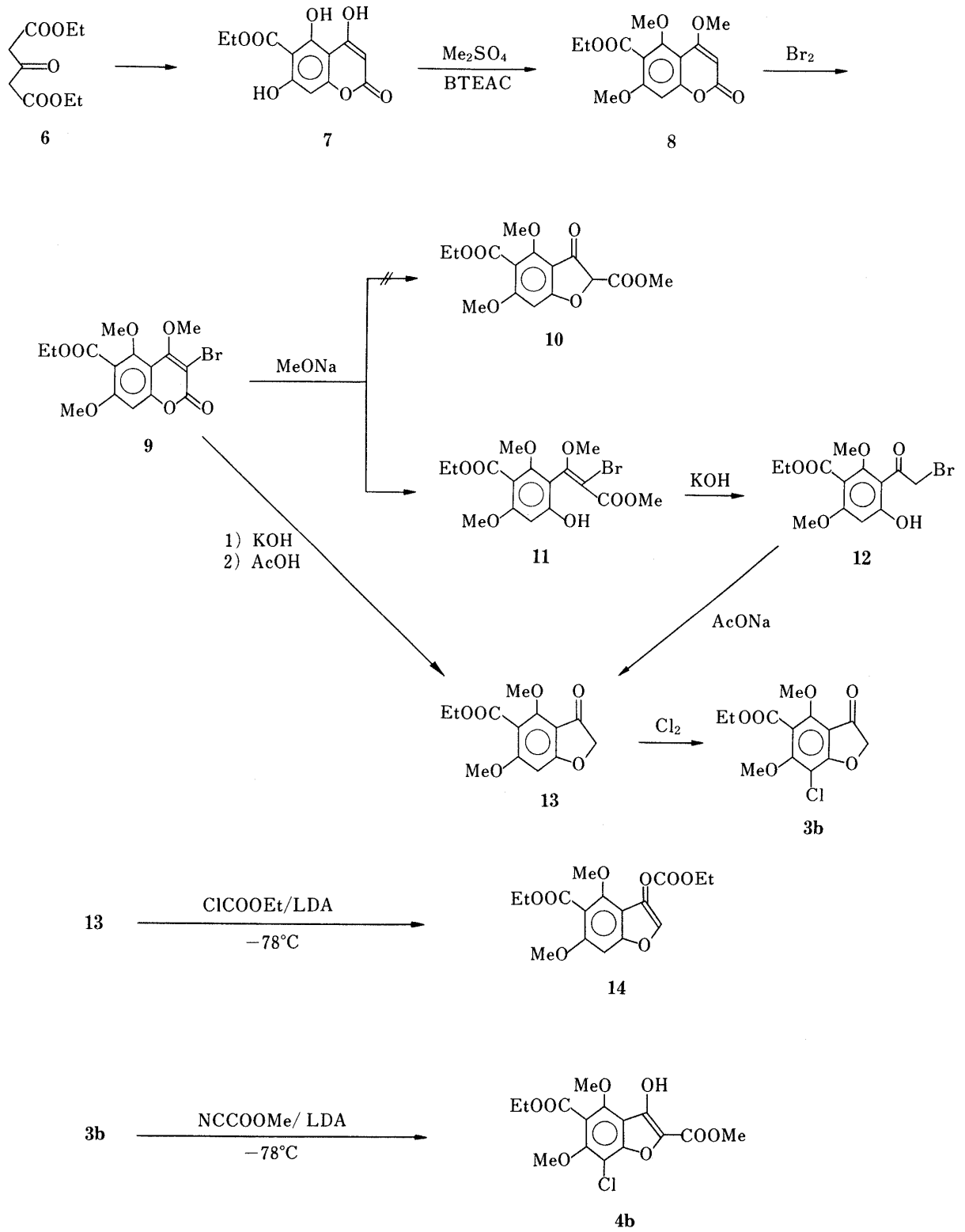


Chart 2

(**2a**).[15] The signal due to the 6′-methyl group of **1b** appeared at δ 0.97 ppm, which is closer to that of griseofulvin (δ 0.98 ppm) than to that of epigriseofulvin (δ 0.90 ppm); moreover, the signals due to the 5′-methylene and 6′-methine of **1b** were analogous to those of griseofulvin and different from those of epigriseofulvin.

Compound *dl*-**1b** was tested for growth-inhibitory activity on various eumycetes (tricophyton, microporum, and archroderma genera) by the agar dilution method. However, the activity was considerably inferior to that of griseofulvin or clotrimazol.

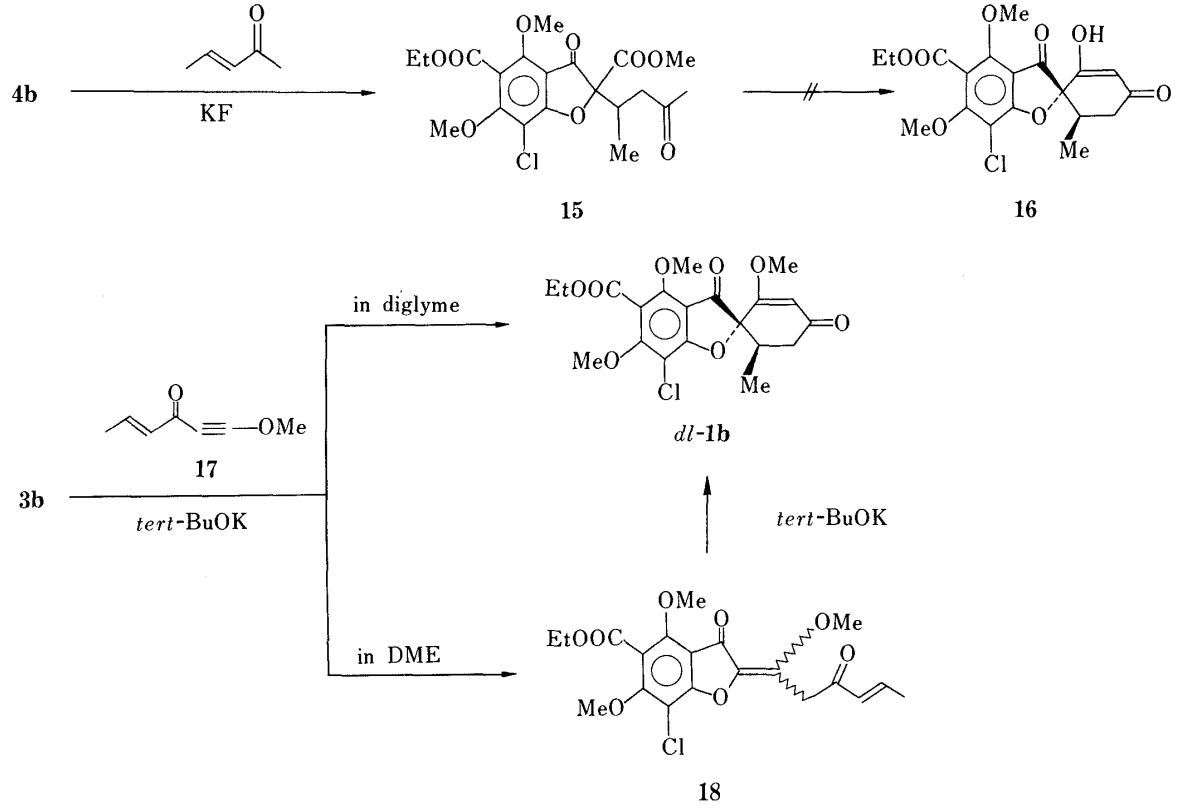


Chart 3

Experimental

All melting points are uncorrected. NMR spectra were taken with a Hitachi R-24 spectrometer (60 MHz), with tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Nippon Bunko A-102 spectrometer. Mass spectrum (MS) were obtained on a Shimadzu LKB-9000 spectrometer.

6-Ethoxycarbonyl-4,5,7-trimethoxycoumarin (8)——Dimethyl sulfate (57 g, 450 mmol), benzyltrimethylammonium chloride (3 g, 13.2 mmol), and CH_2Cl_2 (135 ml) were successively added to a solution of 6-ethoxycarbonyl-4,5,7-trihydroxycoumarin[4] (**7**) (30 g, 110 mmol) in 10% NaOH solution (135 ml), and the mixrure was vigorously stirred at room temperature for 2 d. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The extracts and the CH_2Cl_2 layer were collected, dried over $MgSO_4$, and concentrated. Crystallization of the residue from MeOH gave **8** (19 g, 55%), mp 186—188 °C. *Anal.* Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.07; H, 5.16. IR ν_{max}^{Nujol} cm^{-1}: 1725 (CO), 1710 (CO). NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.87, 3.92, 4.02 (each 3H, each s, each OMe), 4.42 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$), 5.60 (1H, s, 3-H), 6.69 (1H, s, 8-H). MS *m/z*: 308 (M^+).

3-Bromo-6-ethoxycarbonyl-4,5,7-trimethoxycoumarin (9)——A solution of bromine (4.25 g, 26.6 mmol) in $CHCl_3$ (30 ml) was added dropwise to a mixture of **8** (7.25 g, 23.5 mmol), $CaCO_3$ (7 g, 7 mmol), and $CHCl_3$ (60 ml) at 0 °C. The mixture was stirred for 2 h at 0 °C and the precipitate was filtered off. The filtrate was washed with 10% HCl, dried over $MgSO_4$, and concentrated to give **9** (6.9 g, 76%), mp 145—147 °C (from MeOH). *Anal.* Calcd for $C_{15}H_{15}BrO_7$: C, 46.52; H, 3.91. Found: C, 46.18; H, 3.75. IR ν_{max}^{Nujol} cm^{-1}: 1750 (CO), 1725 (CO). NMR ($CDCl_3$) δ: 1.33 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.89, 3.99, 4.03 (each 3H, each s, each OMe), 4.43 (2H, q, J=7H, $OC\underline{H_2}CH_3$), 7.22

(1H, s, 8-H). MS *m/z*: 388 ($M^+ + 2$), 386 (M^+).

Methyl α-Bromo-3-ethoxycarbonyl-6-hydroxy-β,2,4-trimethoxycinnamate (11)——A mixture of **9** (3.1 g, 8 mmol), MeONa (43.5 mmol), and abs. MeOH (70 ml) was refluxed for 5 h, poured into ice-water, made acidic with 10% HCl, and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated. Crystallization of the residue from MeOH gave **11** (1.4 g, 43%), mp 142—144 °C. *Anal.* Calcd for $C_{16}H_{19}BrO_8$: C, 45.84; H, 4.57. Found: C, 45.68; H, 4.54. IR ν_{max}^{Nujol} cm^{-1}: 3230 (OH), 1725 (CO), 1655 (CO). NMR (Me_2CO-d_6) δ: 1.32 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.58 (6H, s, OMe × 2), 3.70, 3.78 (each 3H, each s, each OMe), 4.33 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.39 (1H, s, 5-H), 8.85 (1H, s, OH). MS *m/z*: 420 ($M^+ + 2$), 418 (M^+).

Ethyl 3-(Bromoacetyl)-4-hydroxy-2,6-dimethoxybenzoate (12)——A solution of **11** (1 g, 2.4 mmol) and KOH (0.4 g, 7.1 mmol) in 95% MeOH (5 ml) was refluxed for 2 h, poured into ice-water, made acidic with 10% HCl, and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated to give **12** (0.7 g, 87%), mp 110—111 °C (from Et_2O). *Anal.* Calcd for $C_{13}H_{15}BrO_6$: C, 44.98; H, 4.36. Found: C, 44.85; H, 4.27. IR ν_{max}^{Nujol} cm^{-1}: 1710 (CO), 1635 (CO). NMR ($CDCl_3$) δ: 1.27 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.78, 3.87 (each 3H, each s, each OMe), 4.30 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.55 (2H, s, CH_2Br), 6.18 (1H, s, 5-H). MS *m/z*: 348 ($M^+ + 2$), 346 (M^+).

5-Ethoxycarbonyl-4,6-dimethoxy-3(2*H*)-benzofuranone (13)——Method A: A solution of **12** (2 g, 5.8 mmol) and $AcONa \cdot 3H_2O$ (1.8 g, 13.2 mmol) in 95% EtOH (20 ml) was refluxed for 1 h, poured into ice-water, and extracted with AcOEt. The AcOEt layer was washed with 10% HCl, dried over $MgSO_4$, and concentrated. Crystallization of the residue from Et_2O gave **13** (1.1 g, 71%), mp 102 °C. *Anal.* Calcd for $C_{13}H_{14}O_6$: C, 58.65; H, 5.30. Found: C, 58.37; H, 5.30. IR ν_{max}^{Nujol} cm^{-1}: 1725 (CO), 1690 (CO). NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.96, 4.20 (each 3H, each s, each OMe), 4.41 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.65 (2H, s, 2-H_2), 6.37 (1H, s, 7-H). MS *m/z*: 266 (M^+).

Method B: A solution of **9** (9.75 g, 25 mmol) and KOH (6.2 g, 110 mmol) in 95% EtOH (120 ml) was refluxed for 2 h and cooled to 0 °C, then AcOH (6.6 g, 110 mmol) was added dropwise. The solution was refluxed for 1 h and the solvent was removed. The residue was extracted with AcOEt, then the AcOEt layer was dried over $MgSO_4$ and concentrated to give **13** (5 g, 75%), after recrystallization from Et_2O.

7-Chloro-5-ethoxycarbonyl-4,6-dimethoxy-3(2*H*)-benzofuranone (3b)——A solution of chlorine (6.6 mmol) in dry $CHCl_3$ was added dropwise to a solution of **13** (1.71 g, 6.43 mmol) in dry CH_2Cl_2 (30 ml) at 0 °C, then the mixture was washed successively with 10% HCl, 10% $Na_2S_2O_3$, and H_2O, dried over $MgSO_4$, and concentrated.Chromatography of the residue on silica gel with AcOEt–petr. ether (1 : 9) gave **3b** (1.37 g, 71%), mp 111—113 °C. *Anal.* Calcd for $C_{13}H_{13}ClO_6$: C, 51.92; H, 4.36. Found: C, 52.03; H, 4.30. IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO), 1710 (CO). NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.05, 4.08 (each 3H, each s, each OMe), 4.44 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.77 (2H, s, 2-H_2). MS *m/z*: 302 ($M^+ + 2$), 300 (M^+).

5-Ethoxycarbonyl-3-ethoxycarbonyloxy-4,6-dimethoxybenzofuran (14)——A solution of LDA (8.6 mmol) in tetrahydrofuran (THF, 22 ml) was added dropwise to a solution of **13** (2 g, 7.5 mmol) in dry THF (100 ml) at −78 °C in an Ar atmosphere. The mixture was stirred for 30 min at −78 °C, then ethyl chloroformate (0.98 g, 9 mmol) was added at −78 °C. The mixture was stirred for an additional 1 h at room temperature, neutralized with 10% NH_4Cl, and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and the solvent was removed. Chromatography of the residue on silica gel with AcOEt–petr. ether (1 : 10) gave **14** (2.13 g, 84%), mp 55—56 °C (from Et_2O). *Anal.* Calcd for $C_{16}H_{18}O_8$: C, 56.84; H, 5.36. Found: C, 56.72; H, 5.49. IR ν_{max}^{Nujol} cm^{-1}: 1765 (CO), 1720 (CO). NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.89, 4.04 (each 3H, each s, each OMe), 4.44, 4.49 (each 2H, each q, J= 7 Hz, each $OC\underline{H}_2CH_3$), 6.86 (1H, s, 7-H), 7.90 (1H, s, 2-H).

7-Chloro-5-ethoxycarbonyl-3-hydroxy-4,6-dimethoxy-2-methoxycarbonylbenzofuran (4b)——A solution of LDA (3.7 mmol) in THF (9 ml) was added dropwise to a solution of **3b** (1 g, 3.3 mmol) and hexamethylphosphoramide (HMPA, 5 ml) in THF (50 ml) at −78 °C under an Ar atmosphere. The mixture was stirred for 30 min at −78 °C, then methyl cyanoformate (0.32 g, 3.8 mmol) was added. The mixture was stirred for an additional 30 min at −78 °C, neutralized with 10% NH_4Cl and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel with AcOEt–petr. ether (1 : 10) gave **4b** (1.1 g, 92%), mp 117—118 °C. *Anal.* Calcd for $C_{15}H_{15}ClO_8$: C, 50.22; H, 4.21. Found: C, 50.41; H, 4.18. IR ν_{max}^{Nujol} cm^{-1}: 3350 (OH), 1725 (CO), NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 4.09, 4.11, 4.19 (each 3H, each s, each OMe), 4.44 (2H, q, J= 7 Hz, $OC\underline{H}_2CH_3$), 8.60 (1H, s, OH).

7-Chloro-5-ethoxycarbonyl-2-methoxycarbonyl-4,6-dimethoxy-2-(4-oxopentan-2-yl)-3(2*H*)-benzofuranone (15)——A solution of **4b** (2.12 g, 5.9 mmol), 3-penten-2-one[16] (1.6 g, 18 mmol), KF (0.17 g, 3 mmol), and 18-crown-6-ether (0.16 g, 0.6 mmol) in CH_3CN (50 ml) was refluxed for 4 h under an Ar atmosphere, poured into ice-water, and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel with AcOEt–hexane (1 : 9) gave **15** (2.56 g, 98%) as an oil. *Anal.* Calcd for $C_{20}H_{23}ClO_9$: C, 54.23; H, 5.23. Found: C, 54.43; H, 5.11. IR ν_{max}^{Nujol} cm^{-1}: 1755 (CO); 1735 (CO), 1725 (CO), 1720 (CO), NMR ($CDCl_3$) δ: 0.84 (3H × 1/2, d, J=7 Hz, C-Me), 1.03 (3H × 1/2, d, J=7 Hz, C-Me), 1.33 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.20—3.40 (3H, m, $CHCH_2$), 3.79 (3H, s, COOMe), 4.04, 4.10 (each 3H, each s, each OMe), 4.35 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/z*: 344 ($M^+ + 2$), 342 (M^+).

***dl*-7-Chloro-5-ethoxycarbonyl-6′-methyl-2′,4,6-trimethoxyspiro[benzofuran-2(3*H*),1′-(2-cyclohexene)]-3,4′-dione (*dl*-1b)**——Potassium *tert*-butoxide (0.32 g, 2 mmol) was added to a solution of **3b** (0.6 g, 2 mmol) and 1-methoxy-3-

oxo-4-hexen-1-yne[1b] (**17**) (0.3 g, 2.4 mmol) in dry diglyme (45 ml) at 0 °C under a N_2 atmosphere, and the mixture was stirred for 24 h at room temperature, poured into ice-water and extracted with AcOEt. The AcOEt layer was dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel with Et_2O–petr. ether (1 : 4) gave *dl*-**1b** (0.21 g, 25%), mp 138—140 °C (from CH_2Cl_2–petr. ether). *Anal.* Calcd for $C_{20}H_{21}ClO_8$: C, 56.50; H, 4.98. Found: C, 56.41; H, 5.03. IR ν_{max}^{Nujol} cm^{-1}: 1740 (CO), 1715 (CO), 1660 (CO). NMR ($CDCl_3$) δ: 0.97 (3H, d, J=6 Hz, 6′-Me), 1.41 (3H, t, J=7 Hz, OCH_2CH_3), 2.20—3.10 (3H, m, 5′-H_2 and 6′-H), 3.72 (3H, s, 2′-OMe), 4.10, 4.18 (each 3H, each s, each OMe), 4.48 (2H, q, J=7 Hz, OCH_2CH_3), 5.65 (1H, s, 3′-H).

7-Chloro-4,6-dimethoxy-5-ethoxycarbonyl-2-(1-methoxy-3-oxo-4-hexenylidene)-3(2*H*)benzofuranone (18)——Potassium *tert*-butoxide (0.19 g, 1.7 mmol) was added to a solution of **3b** (0.5 g, 1.7 mmol) and **17** (0.33 g, 2.7 mmol) in dimethoxyethane (40 ml) at room temperature, then the mixture was stirred for 1 h at room temperature and worked up as described for **1b**. The crude product (**18**) was recrystallized from benzene, yield 0.23 g (32%), mp 92—94 °C. *Anal.* Calcd for $C_{20}H_{21}ClO_8$. C, 56.54; H, 4.98. Found: C, 56.24; H, 4.90. IR ν_{max}^{Nujol} cm^{-1}: 1720 (CO), 1690 (CO), 1670 (CO). NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz, OCH_2CH_3), 1.95 (3H, dd, J=7, 2 Hz, C-Me), 4.06 (3H, s, OMe), 4.22 (6H, s, OMe×2), 4.39 (2H, s, CH_2CO), 4.48 (2H, q, J=7 Hz, OCH_2CH_3), 6.34 (1H, d, J=18 Hz, CH=CH-Me), 7.15 (1H, dd, J=18, 2 Hz, CH=CH-Me). MS *m/z*: 426 (M^++2), 244 (M^+).

Cyclization of 18 to *dl*-1b——A mixture of **18** (97 mg, 0.23 mmol), *tert*-BuOK (26 mg, 0.23 mmol), and 18-crown-6-ether (20 mg, 0.08 mmol) in dry benzene (10 ml) was heated at 60 °C for 4 h, poured into ice-water, made acidic with 10% HCl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. Chromatography of the residue on silica gel with AcOEt–petr. ether (1 : 4) gave *dl*-**1b** (87 mg, 90%).

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