Syntheses and Antifungal Activities of *dl*-Griseofulvin and Its Congeners. I

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dl-Griseofulvin (1a) was prepared by two synthetic pathways. New 6′-congeners (3 and 4) of griseofulvin were also prepared. Their antifungal activities were evaluated and compounds 3 and 4 were found to be less active than 1a. Molecular calculations on 1a, *dl*-epigriseofulvin (1b), 3 and 4 were undertaken.

Keywords *dl*-griseofulvin; antifungal activity; molecular calculation; Diels–Alder reaction

Griseofulvin, an antifungal agent, has attracted attention because of its unique structure, and the total synthesis of *dl*-griseofulvin (**1a**) has been achieved by several groups[1a-e] *via* the intermediates I—IV shown in Chart 1.

Some studies[2a-d] on the molecular modification of **1a** have been undertaken and showed that *dl*-epigriseofulvin (**1b**), the diastereomer of **1a**, does not have antifungal activity.[3] However, the relationship between the structure and antifungal activity has not been thoroughly examined. In particular, the effect of a 6′-substituent on the antifungal activity is not clear. Sato and co-workers[4] reported the structure–activity relationships of griseofulvin and its analogues for microtubulin-binding ability, and showed that the conformation of the cyclohexenone ring might play an important role in the activity.

On the basis of these facts, it seems reasonable to assume that the nature of the 6′-substituent of **1a** and its stereochemistry play an important role in the antifungal activity. Consequently, we decided to synthesize various griseofulvin analogues including 6′-congeners (**2a**, **b**, **3**, or **4**) and to study their structure–activity relationships in more detail. However, the methods previously reported were considered to be unsuitable for the preparation of our desired congeners because each of these methods suffers from at least one serious disadvantage such as very poor yield or hazardous or tedious procedures. We have therefore developed new synthetic methods for the preparation of 6′-congeners of **1a**.

This paper describes syntheses of **1a** and its 6′-congeners *via* the Diels–Alder reaction of 2-alkylidene-3(2*H*)-benzofuranones (**5**) as shown in Chart 2. The antifungal activities of the compounds synthesized and the results of molecular calculation are also reported.

Chemistry First, we examined the preparation of the intermediates, 2-alkylidene-3(2*H*)-benzofuranones (**5**). The base-catalyzed aldol condensation of 7-chloro-4,6-dimethoxy-3(2*H*)-benzofuranone (**6**) with aldehydes was attempted according to Danishefsky and Etheredge.[5] However, we considered that this method was not satisfactory for the preparation of all of compounds **5**, because it requires the use of lithium diisopropylamide (LDA) as a base, as well as a subsequent dehydration process. Therefore, **6** was treated with the corresponding diethyl acetal in the presence of titanium tetrachloride. The desired (*Z*)-2-ethylidene derivative ((*Z*)-**5a**)[5] was obtained in 70% yield. According to this method, (*Z*)-2-(1-propylidene)-3(2*H*)-benzofuranone ((*Z*)-**5b**) was prepared in 89% yield. In the case of 2-(2-propylidene)-3(2*H*)-benzofuranone (**5c**), it was prepared in 83% yield using zinc chloride as the catalyst in place of titanium chloride (Table I).

However, 2-methylene-3(2*H*)-benzofuranone (**5d**) could not be obtained by this method. It was prepared by a modification of the method of Miller and Behare[6] (Chart 3). Namely, 2-methoxycarbonyl-3(2*H*)-benzofuranone derivatives (**7**) were treated with dimethylamine and formaldehyde to generate the Mannich base (**7′**), which was methylated with methyl iodide. Subsequently, the resulting trimethylammonium iodide (**7″**) was heated *in situ* to give **5d** in 51% yield.

The first approach for the synthesis of **1a** and its 6′-congeners was as follows. The Diels–Alder reaction[5] of (*Z*)-**5a**,**b** with 1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene (**8**) gave *dl*-epigriseofulvin (**1b**) and its 6′-ethyl con-

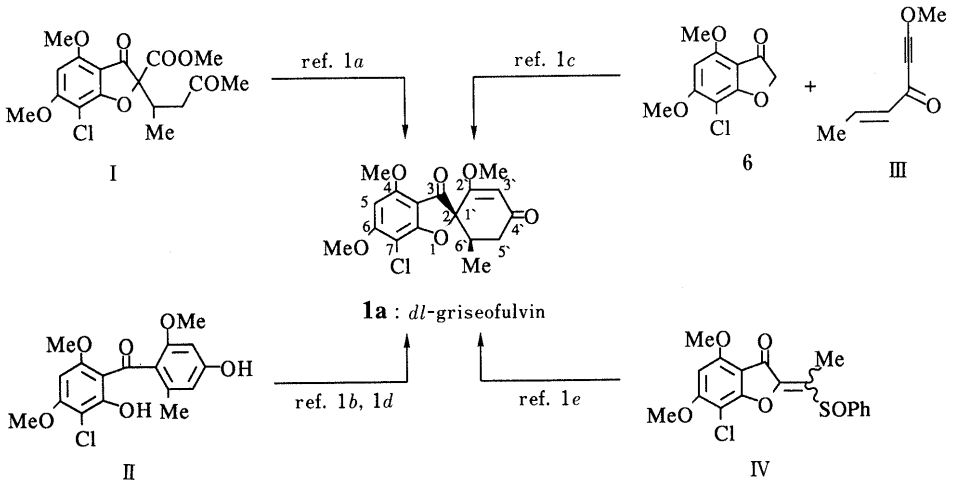
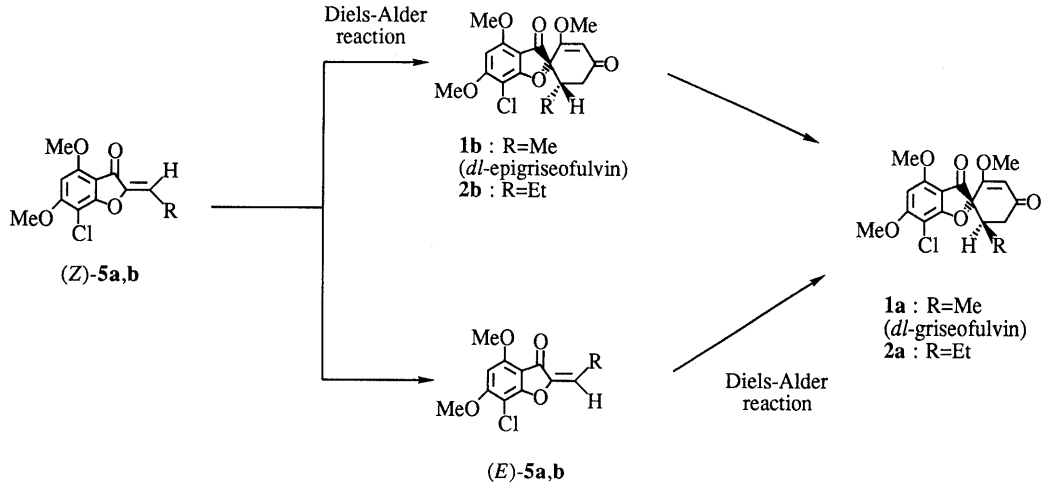


Chart 1



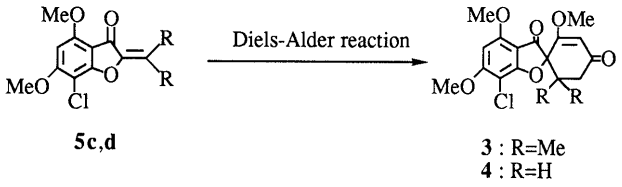
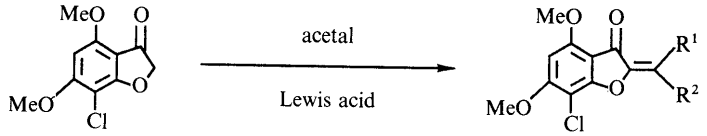


Chart 2

TABLE I. Reaction of Compound **6** with Various Acetals in the Presence of Lewies Acids



Acetal (eq)	Lewis acid (eq)	Solvent	Temp./Time (h)	Product			
				Compd. No.	R^1	R^2	Yield (%)
$MeCH(OEt)_2$ (1.5)	$TiCl_4$ (1.2)	CH_2Cl_2	r.t./10	(*Z*)-**5a**	H	Me	70
$EtCH(OEt)_2$ (10)	$TiCl_4$ (1.2)	CH_2Cl_2	r.t./24	(*Z*)-**5b**	H	Et	89
$Me_2C(OMe)_2$ (1.5)	$ZnCl_2$ (0.5)	$Cl_2CHCHCl_2$	Reflux/ 3	**5c**	Me	Me	83

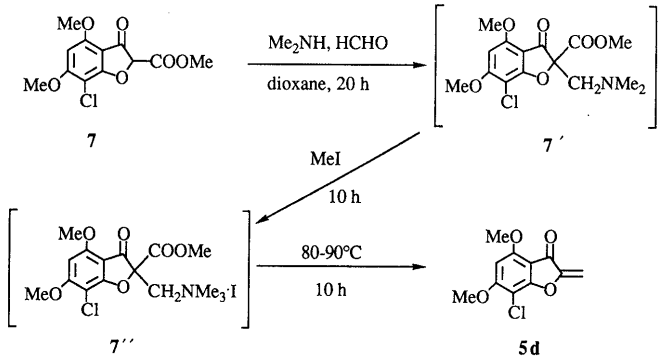
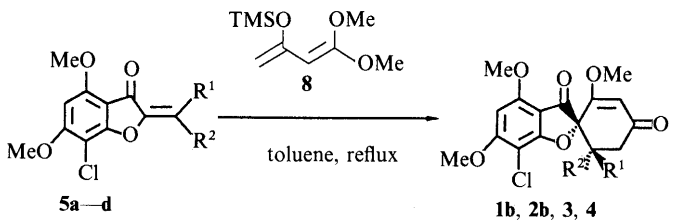


Chart 3

gener (**2b**) in 73% and 66% yields, respectively. *dl*-6′-Methylgriseofulvin (**3**) and *dl*-6′-demethylgriseofulvin (**4**) were also obtained by the similar reaction of **5c** and **5d** with **8** in 24% and 61% yields, respectively (Table II).

TABLE II. Preparation of **1b**, **2b**, **3**, and **4** by Means of the Diels–Alder Reaction



R^1	R^2	Time (h)	Product	
			Compd. No.	Yield (%)
H	Me	6	**1b**	73
H	Et	7	**2b**	66
Me	Me	10	**3**	24
H	H	0.5	**4**	61

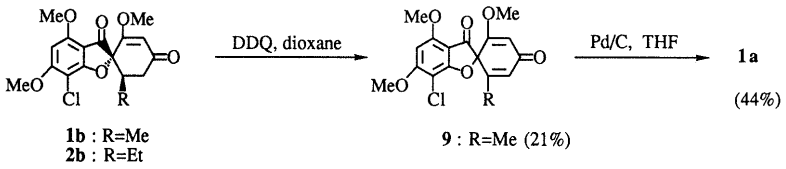


Chart 4

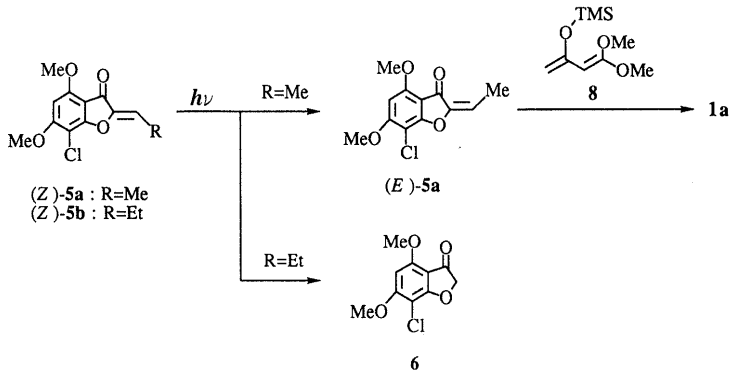


Chart 5

In order to obtain griseofulvin-type compounds, **1a** and **2a**, conversion of *dl*-epigriseofulvin, **1b**, and its congener **2b** was examined. The conversion of **1b** to *dl*-dehydrogriseofulvin (**9**) was achieved in 21% yield by using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) oxidation. Compound **9** was then hydrogenated to **1a** with diastereoselectivity according to the method of Danishefsky and Walker.[1e] An attempt to employ this method for the conversion of **2b** to **2a**, however, was unsuccessful.

Another second approach for the synthesis of **1a** and its 6′-congeners was examined. Photochemical isomerization of the intermediate (*Z*)-**5a** to (*E*)-**5a** was attempted. Compound (*E*)-**5a** was expected to give **1a** by Diels–Alder reaction with **8**. Compound (*Z*)-**5a**, when exposed to sunlight, gave a 61 : 39 mixture of (*Z*)-**5a** and (*E*)-**5a**, which was separated by chromatography on silica gel to give pure (*E*)-**5a** in 23% yield. On heating with 10 eq of **8**, (*E*)-**5a** gave **1a** in 46% yield, with diastereoselectivity. This method was used for the preparation of the 6′-ethyl congener (**2a**). However, (*Z*)-**5b**, on exposure to sunlight, did not give the desired (*E*)-**5b** but 3(2*H*)-benzofuranones (**6**). The photochemichal isomerization of (*Z*)-**5b** to (*E*)-**5b** did not succeed.

Biological Activity Antifungal activity of the compounds presently synthesized was examined and the minimum inhibitory concentration (MIC) values are listed in Table III. Because the difference in antifungal activities between *dl*-griseofulvin (**1a**) and *dl*-epigriseofulvin (**1b**) is obviously due to the steric environment around the carbon atom at the 6′-position, we expected that the introduction of a methyl group at the 6′-position of *dl*-griseofulvin (**1a**), which leads **3**, would cause loss of the activity due to the steric hindrance of the two methyl groups at the 6′-position, by analogy with *dl*-epigriseofulvin (**1b**). On the other hand, the replacement of the 6′-methyl group of griseofulvin (**1a**) by a hydrogen, which leads **4**, might enhance the activity. The results were different from our expectation. Both compounds **3** and **4** were found to be less active than **1a** against *Trichophyton mentagrophytes*. Moreover, compound **3** was found to be more potent than **4**.

TABLE III. *In Vitro* Antifungal Activity of Compound **1a**, **b**, **3**, **4**, and **5a**, **d** (Measured as MIC, mg/ml)

Compd.	*C.a.* CAA-14[a]	*C.a.* IFO-1594[b]	*T.m.* T-14[c]	*T.m.* T-16[d]
1a (*dl*-griseofulvin)	>100	>100	6.25	3.13
1b (*dl*-epigriseofulvin)	>100	>100	>100	>100
3	>100	>100	25	12.5
4	>100	>100	50	50
5a	>100	NT[e]	25	12.5
5d	25	25	12.5	6.25

a) *C.a.* CAA-14 = *Candida albicans* CAA-14. *b*) *C.a.* IFO-1594 = *Candida albicans* IFO-1594. *c*) *T.m.* T-14 = *Trichophyton mentagrophytes* T-14. *d*) *T.m.* T-16 = *Trichophyton mentagrophtes* T-16. *e*) Not tested.

In general, compounds with an α-methylene carbonyl group have effective biological activity.[7] Compound **5d** lacks the spiro-ring system, but has the above functional group. So, the antifungal activity of **5d** was examined and found to be potent. Interestingly, **5d** showed an exceptionally broad antifungal spectrum against both *Trichophyton mentagrophytes* and *Candida albicans*, although the potency was somewhat weak.

Molecular Calculations[8] From the above biological results, we could not explain why *dl*-epigriseofulvin **1b** is inactive and why both **3** and **4** were very much less active than griseofulvin **1a**. For the purpose of solving the above problem, we carried out a molecular modeling study. Energy calculations on **1a**, **3**, **4**, and **1b** were performed using the MNDO[9a,b] program in MOPAC.[10] The software for molecular display and data extraction was internally developed. Starting geometries for optimization molecular structure were based on X-ray data.[11a,b] Two energy-optimized conformers for each compound were obtained and were classified into type I and type II accoding to the bending orientation form of their cyclohexenone ring. The value of the calculated heat of formation energy (H_f) for each optimized conformer is shown with the molecular

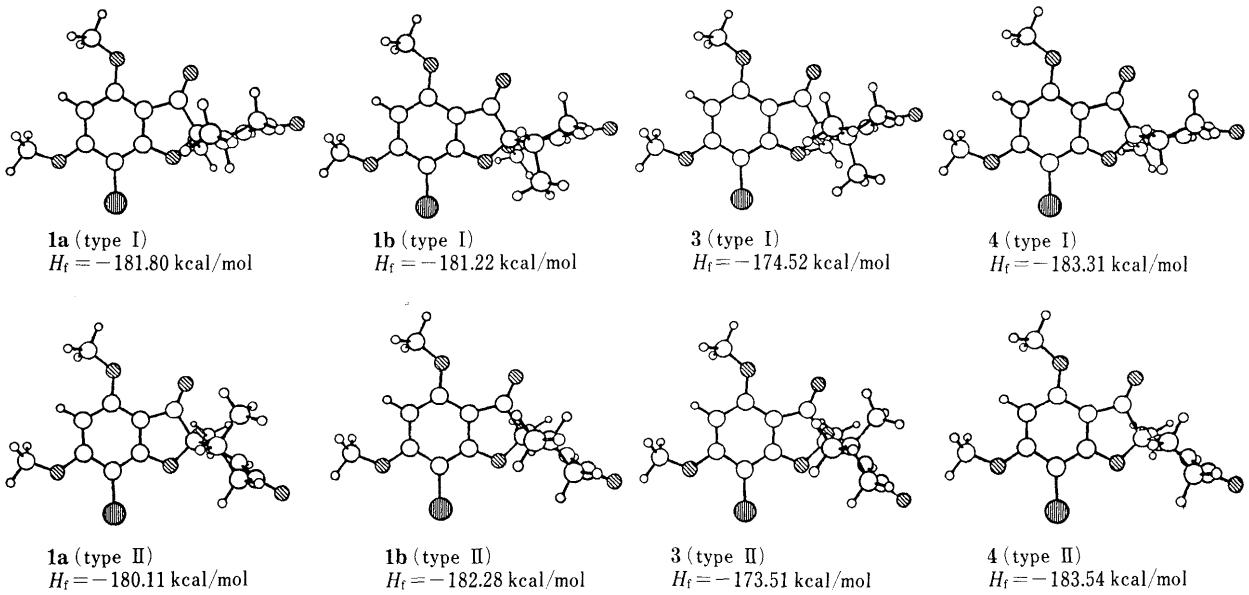


Fig. 1

graphics in Fig. 1. The energy of the type I conformer of **1a** was lower by 1.69 kcal/mol than that of the type II conformer. Similarly, the energy of the type I conformer of **3** was lower by 1.01 kcal/mol than that of the type II conformer. On the other hand, the energy of the type I conformer of **4** was higher by 0.23 kcal/mol than that of the type II conformer. Similarly, the energy for the type I conformer of **1b** was higher by 1.06 kcal/mol than that of the type II conformer. These results showed that the type I conformer of **1a** and **3** is preferred while, in the cases of **4** and **1b**, the type II conformer is perferred.

It has been argued[12] that conformational energy penalties as small as 3—4 kcal/mol lead to biological inactivity. In the present case, the difference in the heat of formation energy between the two conformers (type I and type II) for each compound is 1 kcal/mol or so, which is smaller than the above value. Therefore, it is difficult to conclude on this basis that the type I conformer is the active form of griseofulvin. However, it is interesting that a relationship between antifungal activity and preferred conformer of each compound seems to exist.

Further studies are needed to clarify fully the relationship between the structure and antifungal activity of griseofulvin 6′-congeners.

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a Hitachi R-24 (60 MHz) or R-22 FTS (90 MHz) spectrometer. Mass spectra (MS) were recorded on a Shimadzu LKB-9000 or VG-70SE spectrometer, and infrared (IR) absorption spectra on a JASCO A-102 spectrometer.

(*Z*)-7-Chloro-2-ethylidene-4,6-dimethoxy-3(2*H*)-benzofuranone [(*Z*)-5a] A mixture of **6**[5] (652 mg, 2.9 mmol), diethyl acetal (0.6 ml, 4.3 mmol), titanium tetrachloride (0.38 ml, 3.5 mmol), and dry CH_2Cl_2 (32 ml) was stirred at room temperature for 10 h. The mixture was diluted with CH_2Cl_2 and water, then the organic layer was separated, successively washed with 10% Na_2CO_3 solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3) to give (*Z*)-**5a** (511 mg, 70%) as colorless needles, mp 176—178 °C (CH_2Cl_2 and ether) (lit.[5] 176—178 °C). IR ν(Nujol): 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, d, J=7 Hz, CH_3), 4.01 (6H, s, 4- and 6-OCH_3), 6.10 (1H, q, J=7 Hz, C<u>H</u>–CH_3), 6.18 (1H, s, 5-H).

(*Z*)-7-Chloro-4,6-dimethoxy-2-(1-propylidene)-3(2*H*)-benzofuranone [(*Z*)-5b] A mixture of **6** (1.00 g, 4.4 mmol), propionaldehyde diethylacetal (7.10 ml, 44 mmol), titanium tetrachloride (0.58 ml, 5.3 mmol), and dry CH_2Cl_2 (45 ml) was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 and water, then the organic layer was separated, successively washed with 10% Na_2CO_3 solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3) to give (*Z*)-**5b** (1.05 g, 89%) as colorless needles, mp 110—112 °C (AcOEt and hexane). *Anal.* Calcd for $C_{13}H_{13}ClO_4$: C, 58.11; H, 4.88. Found: C, 58.38; H, 4.76. IR ν(Nujol): 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, t, J=7.2 Hz, CH_3), 2.27—2.66 (2H, m, CH_2), 4.00 (6H, s, 4- and 6-OCH_3), 6.10 (1H, t, J=7.0 Hz, C<u>H</u>–CH_2), 6.16 (1H, s, 5-H). MS *m/z*: 270 (M^++2), 268 (M^+).

7-Chloro-4,6-dimethoxy-2-(2-propylidene)-3-(2*H*)-benzofuranone (5c) A mixture of **6** (200 mg, 0.87 mmol), 2,2-dimethoxypropane (0.16 ml, 1.3 mmol), zinc chloride (60 mg, 0.44 mmol), and dry $Cl_2CHCHCl_2$ (8.7 ml) was heated at 100 °C for 2 h. The mixture was diluted with CH_2Cl_2 and water, then the organic layer was separated, successively washed with 10% Na_2CO_3 solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3) to give **5c** (194 mg, 83%) as colorless needles, mp 161—163 °C (CH_2Cl_2 and ether). *Anal.* Calcd for $C_{13}H_{13}ClO_4$: C, 58.11; H, 4.88. Found: C, 57.82; H, 4.76. IR ν(Nujol): 1695 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, CH_3), 2.32 (3H, s, CH_3), 3.97, 3.99 (each 3H, each s, 4- and 6-OCH_3), 6.12 (1H, s, 5-H). MS *m/z*: 270 (M^++2), 268 (M^+).

7-Chloro-4,6-dimethoxy-2-methylene-3(2*H*)-benzofuranone (5d) A mixture of 50% aqueous dimethylamine (31.8 ml, 0.33 mmol), dimethylamine hydrochloride (0.65 g, 6.8 mmol), 37% aqueous formaldehyde (2.2 ml, 28 mmol), and dioxane (44 ml) was stirred at room temperature for 30 min, then **7**[1a] (570 mg, 2.0 mmol) was added. The mixture was stirred at room temperature for 10 h, then AcOEt was added. The organic layer was washed successively with 25% sodium hydroxide solution, water, and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solvent was removed to yield the crude Mannich base (450 mg).

The crude product was dissolved in methyl iodide (11 ml), and the mixture was stirred at room temperature for 10 h. Excess methyl iodide was removed, and the solid was triturated with ether to yield the crystalline quaternary ammonium salt (550 mg).

A mixture of the quaternary salt (550 mg) and dimethylformamide (30 ml) was heated at 80 °C for 10 h. Ether was added to the cooled solution, and the organic layer was washed with water and saturated NaCl solution and dried over anhydrous $MgSO_4$. The solvent was removed to give **5d** (250 mg, 51%) as colorless needles, mp 215—218 °C (CH_2Cl_2 and ether). *Anal.* Calcd for $C_{11}H_9ClO_4$: C, 54.46; H, 3.65. Found: C, 54.60; H, 3.77. IR ν($CHCl_3$): 1700 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.01 (6H, s, 4- and 6-OCH_3), 5.27 (1H, d, J=2.9 Hz, 2-CH), 5.61 (1H, d, J=2.9 Hz, 2-CH), 6.17 (1H, s, 5-H). MS *m/z*: 242 (M^++2), 240 (M^+).

***dl*-Epigriseofulvin (1b)** **1b** was prepared by the method of Danishefsky and Etheredge.[5]

***dl*-6′-Demethyl-6′-ethylepigriseofulvin (2b)** A mixture of (*Z*)-**5b** (300 mg, 1.1 mmol), **8** (1.4 ml), and dry toluene (5.6 ml) was refluxed for 2 h under an Ar atmosphere. After removal of excess toluene *in vacuo*, the residue was taken up in tetrahydrofuran (THF) (15 ml), water (5 ml), and 5% HCl (3 ml). This reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with AcOEt and water, the organic layer was separated, successively washed with saturated $KHCO_3$ solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **2b** (277 mg, 66%) as colorless needles, mp 244—245 °C (benzene). *Anal.* Calcd for $C_{18}H_{19}ClO_6$: C, 58.94; H, 5.22. Found: C, 59.03; H, 5.33. IR ν(Nujol): 1710, 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.86 (3H, t, J=6.7 Hz, CH_3), 1.10—1.46 (2H, m, 6′-CH_2), 2.37—2.85 (3H, m, 5′-H_2 and 6′-H), 3.63 (3H, s, 2′-OCH_3), 4.01, 4.03 (each 3H, each s, 4- and 6-OCH_3), 5.58 (1H, s, 3′-H), 6.16 (1H, s, 5-H). MS *m/z*: 368 (M^++2), 366 (M^+).

***dl*-6′-Methylgriseofulvin (3)** A mixture of **5c** (230 mg, 0.86 mmol), **8** (1.4 ml), and dry toluene (50 ml) was heated at 160 °C for 10 h in a sealed tube. After removal of excess toluene *in vacuo*, the residue was taken up in a mixture of THF (15 ml), water (5 ml), and 5% HCl (3 ml). This reaction mixture was stirred at room temperature for 30 min. The mixture was diluted with AcOEt and water, then the organic layer was separated, successively washed with saturated $KHCO_3$ solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **3** (77 mg, 24%) as colorless needles, mp 138—145 °C (CH_2Cl_2 and ether). *Anal.* Calcd for $C_{18}H_{19}ClO_6$: C, 58.94; H, 5.22. Found: C, 58.85; H, 5.00. IR ν($CHCl_3$): 1710, 1655 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98, 1.24 (each 3H, each s, CH_3 × 2), 2.27, 3.31 (each 1H, each d, J=16.8 Hz, 5′-H_2), 3.60 (3H, s, 2′-OCH_3), 3.96, 4.01 (each 3H, each s, 4- and 6-OCH_3), 5.49 (1H, s, 3′-H), 6.13 (1H, s, 5-H). MS *m/z*: 368 (M^++2), 366 (M^+).

***dl*-6′-Demethylgriseofulvin (4)** A mixture of **5d** (240 mg, 1.0 mmol), **8** (2.0 ml), and dry toluene (6.6 ml) was heated at 70 °C for 30 min under an Ar atmosphere. After removal of excess toluene *in vacuo*, the residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **4** (206 mg, 61%) as colorless needles, mp 231—232 °C (AcOEt). *Anal.* Calcd for $C_{16}H_{15}ClO_6$: C, 56.37; H, 4.34. Found: C, 56.63; H, 4.46. IR ν(Nujol): 1710, 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.15—2.50 (2H, m, 6′-H_2), 2.58—2.83 (2H, m, 5′-H_2), 3.65 (3H, s, 2′-OCH_3), 4.00, 4.04 (each 3H, each s, 4- and 6-OCH_3), 5.59 (1H, s, 3′-H), 6.17 (1H, s, 5-H). MS *m/z*: 340 (M^++2), 338 (M^+).

***dl*-Dehydrogriseofulvin (9)** A mixture of **1b** (100 mg, 0.29 mmol), DDQ (600 mg, 2.6 mmol), *p*-nitrophenol (80 mg, 0.57 mmol), and dry dioxane (12 ml) was heated under reflux for 21 h. The mixture was diluted with AcOEt and water, then the organic layer was separated, successively washed with 10% HCl solution and saturated NaCl solution, and dried over anhydrous $MgSO_4$. The solution was concentrated *in vacuo*. The residue was chromatographed on silica gel with AcOEt–hexane (1 : 1) to give **9** (21 mg, 21%) as colorless needles, mp 287—290 °C (lit.[1e] mp 285—286 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.79 (3H, s, CH_3), 3.64 (3H, s, 2′-OCH_3), 4.00, 4.05 (each 3H, each s, 4- and 6-OCH_3), 5.66 (1H, d, J= 1.6 Hz, 3′-H), 6.17 (2H, each s, 5-H and 5′-H).

***dl*-Griseofulvin (1a) from 9** A mixture of **9** (130 mg, 0.37 mmol), 5% Pd/C (60 mg), and THF (30 ml) was stirred for 3 h under a H_2 atmosphere. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel with AcOEt–hexane (2 : 3) to give **1a** (58 mg, 44%). This compound was identical with an authentic sample by ^{1}H-NMR.[13]

(*E*)-7-Chloro-2-ethylidene-4,6-dimethoxy-3(2*H*)-benzofuranone [(*E*)-5a] A mixture of (*Z*)-**5a** (208 mg, 0.91 mmol) and degassed dry benzene (300 ml) was stirred at room temperature for 3 h under an Ar atmosphere while exposed to sunlight. After removal of excess benzene *in vacuo* at below room temperature, the residue was chromatographed on silica gel with AcOEt–hexane (1 : 3) to give (*E*)-**5a** (50 mg, 23%) as colorless needles, mp 165—167 °C (CH_2Cl_2 and Et_2O). *Anal.* Calcd for $C_{12}H_{11}ClO_4$: C, 56.60; H, 4.35. Found: C, 56.23; H, 4.03. IR ν(Nujol): 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, d, J=8 Hz, CH_3), 3.97 (6H, s, 4- and 6-OCH_3), 6.13 (1H, q, J=8 Hz, 2-CH), 6.15 (1H, s, 5-H). MS *m/z*: 256 (M^++2), 254 (M^+).

Exposure of (*Z*)-5b to Sunlight A mixture of (*Z*)-**5b** (60 mg, 0.22 mmol) and degassed dry benzene (60 ml) was stirred at room temperature for 3 h under an atmosphere of Ar while exposed to sunlight. After removal of excess benzene *in vacuo* at below room temperature, and the residue was chromatographed on silica gel with AcOEt–hexane (1 : 3) to give **6** (48 mg, 95%). This compound was identical with an authentic sample of **6** by ^{1}H-NMR.

***dl*-Griseofulvin (1a) from (*E*)-5a** A mixture of (*E*)-**5a** (82 mg, 0.32 mmol), **8** (1.5 ml), and dry toluene (1.4 ml) was refluxed for 2 h under an Ar atmosphere. After removal of excess toluene *in vacuo*, the residue was chromatographed on silica gel with AcOEt–hexane (1 : 3) to give **1a** (52 mg, 46%). This compound was identical with an authentic sample by ^{1}H-NMR.[13]

***In Vitro* Assay for Antifungal Activity** The antifungal activity was assayed *in vitro* on solid agar. The test medium was prepared by diluting the test compound two-fold in 1% yeast extract + Sabouraud's dextrose agar. The test was performed by using a eight-point (100, 50, 25, 12.5, 6.25, 3.13, 1.56, 0.78 mg/ml) dilution scheme. All test organisms were grown on 1% yeast extract + Sabouraud's dextrose agar at 27 °C for 15 d. The cell were washed from the surface of the plate with aq. yeast nitrogen base and collected by filtration on sterile gauze. The suspensions were diluted to 1×10^6 cells/ml. The test and control plates were inoculated with 0.005 ml of the fungal suspension and were incubated at 26 °C for 14 d. MIC values were determined as the lowest dilution at which no visible growth occurred.

References and Notes

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