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(16) Melting points are uncorrected. Combustion analyses were conducted by Galbraith Associates. Infrared spectra were obtained on a Perkin-Elmer Model 137 or 237 spectrometer. Unless indicated otherwise, NMR spectra were measured in $CDCl_3$ solution at 60 MHz with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from the Me_4Si resonance.
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A Stereospecific Synthesis of Griseofulvin

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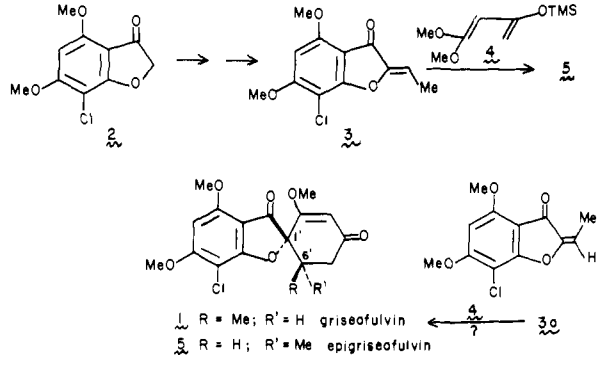
Abstract: A total synthesis of griseofulvin has been achieved. The key step involved is a Diels–Alder cycloaddition between 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**4**) and 7-chloro-4,6-dimethoxy-2-(1-phenylsulfinylethylidene)-3(2*H*)-benzofuranone (**20**) to afford *dl*-5′,6′-dehydrogriseofulvin (**13**).

Background

Recently we described an approach directed at the synthesis of the commercially important antifungal agent griseofulvin[1,2] (**1**). The key projected reaction was to be the cycloaddition between **3a** and the highly functionalized diene **4**, whose chemistry we have described in an earlier paper in this series.[3a,b] Such a reaction would simultaneously solve two of the major issues of a griseofulvin synthesis, i.e., control in the construction of a monoenol ether of a β-diketone as well as control over the relative configurations of carbons 1′ and 6′.[4]

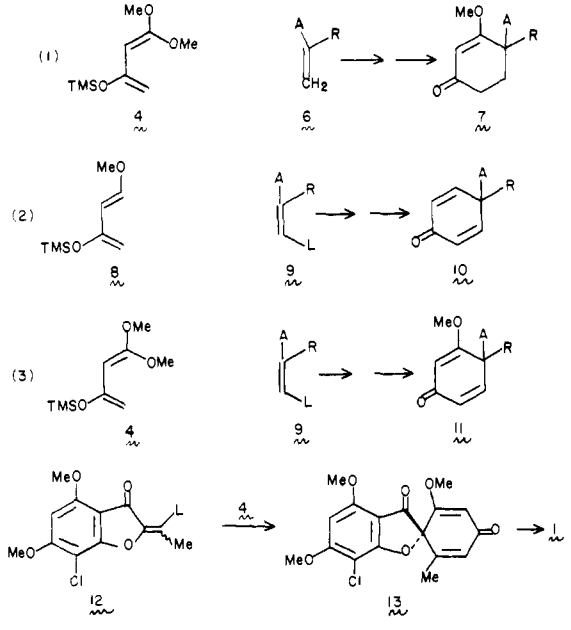
Unfortunately, in our hands, the crossed aldol condensation between coumaranone **2** and acetaldehyde afforded, after dehydration, the *Z* isomer, **3**.[1] Cycloaddition of **3** with **4** gave, in good yield, *dl*-epigriseofulvin (**5**).[5]



A potential solution to the stereochemical problem presented itself through the detailed investigations of Taub,[4b] who reported that catalytic hydrogenation of dehydrogriseofulvin (**13**) occurs with high positional and stereochemical selectivity to afford griseofulvin (**1**). Indeed, this forms the basis of the Merck synthesis of the antifungal agent. Several attempts in our laboratory to transform synthetic *dl*-epigriseofulvin into its dehydro derivative resulted in poor yields.[6]

A more interesting scheme to **13** could be envisioned. In essence, our route to **5** had involved the adaptation of the formalism **4** + **6** → **7** (eq 1).[3a,b] Moreover, in our synthesis of prephenic acid, we had taken advantage of another sequence, **8** + **9** → **10**,[7a,b] wherein elimination of HL could be anticipated at some stage of the sequence. It will be recognized that the final products, **7** and **10**, resulting from the processes summarized in eq 1 and 2 are at the same (phenolic) oxidation level, arising from variations in the respective oxidation levels of the dienes and dienophiles.

The hypothesis for the synthesis of griseofulvin is summarized in eq 3. It was hoped that diene **4**[3a,b,8] would combine with a dienophile of the type **9** to produce, eventually, product **11** which is at the resorcinol level of oxidation. Applied to the synthesis of the desired **13**, this would require access to the dienophile type **12** wherein, the function L, would be a phenylsulfinyl group.[9a,b] It was with the synthesis of a dienophile of the type **12** that we were first concerned.



Discussion

We defined as our first objective the preparation of the 2-acylcoumaranone **15**. It was hoped that reaction of this compound, or tautomers thereof, with thiophenol might occur at the less hindered exocyclic "carbonyl" center. Several attempts to prepare **15** by direct acylation of the previously reported[4] coumaranone **14** gave, largely, O-acylation.

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Compound **14,** which is a key intermediate in the well-known Stork synthesis of griseofulvin,[4a] had been prepared by base-induced cyclization of the *o*-chloroacetylphenol derivative **16.**[10a] Compound **16** was the starting point of our synthesis which is described below.

The phenol **16** was smoothly converted to its acetate, **17.** Treatment of **17** with sodium hydride in THF containing small amounts of HMPA gave, as expected,[10b] a 64% yield of a crystalline dehydrochlorinated product. Its NMR spectrum (see Experimental Section) clearly defined it not to be the β-diketone **15,** in that no resonance corresponding to that of a methine proton of a β-diketone was observed. The spectrum exhibited two singlets at δ 2.5 and 2.3 ppm in a 9:1 ratio (combined 3 H) which might well correspond to the *E* and *Z* versions of enolized system **18.** It is recognized that they might also correspond to one of the geometric isomers of **18,** and to the alternate endocyclic enolic tautomer. This issue was not necessarily of importance to the eventual outcome of the synthesis.

Treatment of **18** with thiophenol in benzene under reflux afforded a 73% yield of a product, whose mass spectrum revealed it to be derived from the replacement of OH by SPh. Its NMR spectrum exhibited two singlets in a 2.4:1 ratio at δ 2.15 and 1.96, respectively. Again, these data did not resolve all doubts as to the structure of the thiophenyl compound, but there were reasonable grounds for assuming that these signals might correspond to the *E* and *Z* versions of the desired **19.** The mixture of sulfides was treated with *m*-chloroperoxybenzoic acid in methylene chloride at −20 °C. There was thus obtained, in 91% yield, a product, whose NMR spectrum exhibited, as before, two singlets in a 3:1 ratio at δ 2.20 and 2.05, respectively, which were provisionally assigned to arise from the geometrically isomeric sulfoxides **20.**

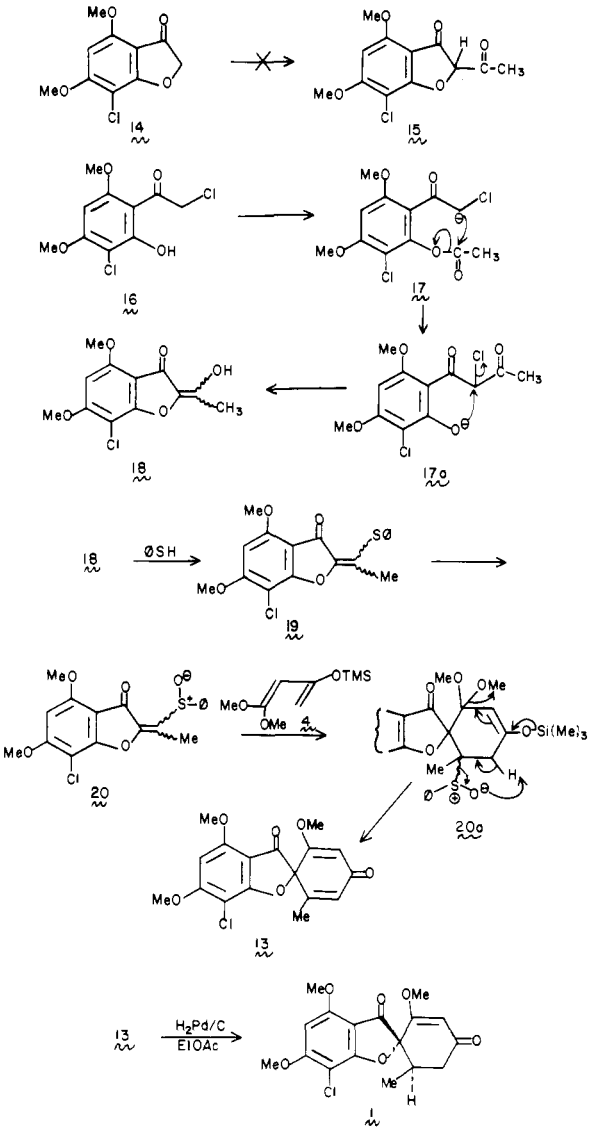
Uncertainties as to the structures of the sulfides **19** and sulfoxides **20** were allayed by the outcome of the Diels–Alder cycloaddition of the latter with the highly functionalized diene **4.** The reaction was carried out in toluene in a sealed tube from 100 to 135 °C over 6 h. The crude product was directly chromatographed on silica gel to afford a 54% yield of crystalline *dl*-dehydrogriseofulvin (**13**), mp 285–286 °C (lit.[4b] 288–290 °C), whose infrared and NMR spectra were identical with those of the authentic (+) isomer, obtained by selenium dioxide dehydrogenation of griseofulvin.[11] The chromatographic mobilities of the two specimens were also identical.

This Diels–Alder reaction is remarkable in that the dienophile, **20,** is tetrasubstituted, and the diene, **4,** is 1,1-disubstituted. *Thus three contiguous quaternary carbons are generated in the cycloaddition step.* Our data do not forcefully speak to the interesting theoretical question pertaining to the degree of concert in cycloadditions of such highly hindered, yet complementary, addends. They do, however, hold open the prospect that, in the face of such polarity differences, the traditional problem of steric hindrance in cycloadditions may prove to be more manageable than was hitherto supposed.

As in the model[7a,b] series, the β-phenylsulfinyl group does not materially compete with the ketone for regiochemical control. In the case at hand, the acid which is eliminated from intermediate **20a** under the conditions of its formation is presumably sufficiently acidic to trigger the decomposition of the β-trimethylsilyloxyallylic acetal. This has been observed in the epigriseofulvin synthesis.[1]

To complete the total synthesis of *dl*-griseofulvin (**1**), the synthetic *dl*-dehydro compound, **13,** was subjected to catalytic reduction. Following the conditions of Taub,[4b] without recycling any hydrogenolysis product,[12] *dl*-griseofulvin (**1**) was obtained in 58% yield from **13.**

Thus with no serious attempt at optimization, griseofulvin was obtained in 21% overall yield from **18** via simple reagents. Of course, any attempts at the commercialization of this process must provide for a regiospecific, high-yield route to **16.**[10a] A similar difficulty is inherent in the stereospecific synthesis of griseofulvin of Stork and Tomasz,[4a] which involved a very interesting spiroannelation of coumaranone **14** (with 1-ethoxypent-1-yn-4-en-3-one), since the coumaranone is also obtained from **16.** This problem remains, for the moment, unsolved.



Experimental Section[13]

Preparation of 2,4-Dimethoxy-5-chloroacetyl-6-acetoxychlorobenzene. To a slurry of phenol **16**[10a] (1.50 g, 5.7 mmol) in 6 mL of acetic anhydride was added 1 drop of 70% perchloric acid. During this time the reaction mixture turned into a stiff paste. It was kept at room temperature for 3 h. Water (40 mL) was added and the reaction mixture was stirred for several hours. The mixture was filtered and washed with water to give 1.57 g (91%) of **17**: mp 174.5–176 °C; λ_{max} ($CHCl_3$) 5.62, 5.88, 6.25, 6.33 μ; δ($CDCl_3$) 2.30 (s, 3), 3.85 (s, 3), 3.95 (s, 3), 6.40 (s, 1) ppm. An analytical sample (mp 176–177 °C) was prepared by recrystallization from ethanol.

Anal. Calcd for $C_{12}H_{12}O_5Cl_2$: C, 46.93; H, 3.94; Cl, 23.09. Found: C, 46.66; H, 4.11; Cl, 23.21.

Preparation of 2-Acetyl-7-chloro-4,6-dimethoxy-3(2*H*)-benzofuranone (18). To a solution of **17** (2.54 g, 8.3 mmol) in 200 mL of tetrahydrofuran containing 2 mL of hexamethylphosphorous triamide, under nitrogen, was added sodium hydride (0.960 g, 50% oil dispersion) in one portion. After being heated to 55 °C for 24 h, the mixture was treated with methanol (0.75 mL). A precipitate was collected and washed with ether. The brittle solid was partitioned in 1 N HCl and CH_2Cl_2. The aqueous phase was extracted twice with CH_2Cl_2 (50 mL). The combined extracts were dried and concentrated in vacuo.

The residue was passed through a small column of silica gel. Elution with chloroform afforded 1.44 g (64%) of **18**: mp (from ethanol) 148-150 °C; λ_{max} ($CHCl_3$) 6.17, 6.25 μ; δ($CDCl_3$) 2.3, 2.5 (singlets, combined 3 H), 3.98 (s, 6), 6.72 (s, 1), 8.0 (br s, 1) ppm; *m/e* 270.029 46 (calcd for $C_{12}H_{11}O_5Cl$, 270.029 06).

Preparation of 7-Chloro-4,6-dimethoxy-2-(1-phenylthioethylidene)-3(2*H*)-benzofuranone (19). A solution of benzofuranone, **18** (1.440 g, 5.3 mmol), thiophenol (2.44 g, 2.28 mL, 22.3 mmol), and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.06 mmol) in 80 mL of degassed benzene was heated under reflux with azeotropic removal of water for 36 h. The dark solution was freed of solvent and the residue was chromatographed on 100 g of silica gel (Brinkmann silica gel 60). Elution with 5% ethyl acetate-benzene gave 1.4 g (73%) of **19** as a mixture of geometric isomers: λ_{max} ($CHCl_3$) 5.95, 6.13, 6.27 μ; δ($CDCl_3$) 1.96-2.15 (singlets, combined 3 H), 3.98 (s, 6), 6.10 (s, 1), 7.4 (m, 5) ppm; *m/e* 362.0380 (calcd for $C_{18}H_{15}O_4ClS$, 362.0379).

Preparation of 7-Chloro-4,6-dimethoxy-2-(1-phenylsulfinylethylidene)-3(2*H*)-benzofuranone (20). To a solution of **19** (1.400 g, 3.86 mmol) in 40 mL of CH_2Cl_2, cooled to −20 °C, was added, over 2 h, a solution of *m*-chloroperoxybenzoic acid (0.785, 3.86 mmol) in 20 mL of CH_2Cl_2. The reaction mixture was stirred for an additional 1 h and filtered. The filtrate was extracted 5 × with 5% $KHCO_3$ (50 mL). The yellow organic solution was dried (Na_2SO_4) and concentrated to give 1.32 g (91%) of **20** as a yellow solid which was not purified further: λ_{max} ($CHCl_3$) 5.88, 6.06, 6.21, 6.25 μ; δ($CDCl_3$) 2.05 and 2.20 (singlets, combined 3 H), 3.88 and 3.94 (singlets, combined 6 H), 6.04 (s, 1), 7.4 (m, 5) ppm; *m/e* 362 (P − 16).

Preparation of *dl*-Dehydrogriseofulvin (13). The sulfoxide **20** (1.000 g, 2.64 mmol) and 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**4**, 2.13 g, 10.5 mmol) in 10 mL of dry toluene in a sealed tube were heated from 100 to 135 °C over a 6-h period. The solution was cooled, diluted with ethyl acetate, and extracted with 1 N HCl and brine. Evaporation of the dried organic layer afforded a residue which was chromatographed on 100 g of Brinkmann silica gel 60. Elution with 5% ethyl acetate-benzene afforded 500 mg (54%) of *dl*-dehydrogriseofulvin (**13**), mp 285-286 °C (lit.[4b] 288-290 °C), whose infrared and NMR spectra coincided with those of an authentic sample, obtained by selenium dioxide dehydrogenation of **1**.[4b]

Preparation of *dl*-Griseofulvin (1). A solution of synthetic dehydrogriseofulvin (**13**, 50 mg, 0.14 mmol) in 8 mL of EtOH was injected into a reaction vessel containing prereduced 10% Pd/C (100 mg) slurried in 3 mL of EtOH. After 6 min, the reaction mixture was filtered (under nitrogen) and the filtrate was concentrated to afford 49 mg of an off-white foam. Chromatography (1 g, Brinkmann silica gel 60) and elution with 10% ethyl acetate-benzene afforded 30 mg (58%) of griseofulvin, mp 219.5-221 °C (lit.[4b] 222-223.5 °C). The infrared and NMR spectra as well as mobility on TLC of this material were identical with those of authentic (+)-griseofulvin.[11]

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(11) We thank Dr. David Taub of Merck Sharp and Dohme for providing us with a generous sample of griseofulvin for comparison for preparing an authentic sample of **13**.
(12) Regio- and stereoselectivity in the catalytic reduction of **13** appear to be complete. The only side reaction is that of hydrogenolysis, affording in ca. 24% yield the well-known 3-chloro-2,4′-dihydroxy-4,6,2′-trimethoxy-6′-methylbenzophenone, which can be recycled by the Merck procedure (cf. ref 4b) to **13**.
(13) Melting points are uncorrected. Combustion analyses were conducted by Galbraith Associates. Infrared spectra were obtained on a Perkin-Elmer Model 137 or 237 spectrometer. High-resolution mass spectra were measured on a Varian Associates CH-5 instrument by direct insertion. NMR spectra were measured in the indicated solvents with tetramethylsilane as an internal standard. Chemical shifts are reported in parts per million (δ) from the Me_4Si resonance.

Total Synthesis of *dl*-Pentalenolactone

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Abstract: The synthesis of *dl*-pentalenolactone has been achieved in a stereospecific way. The key features of the synthesis were (1) a Diels-Alder route to 5-acylcyclohexenones via selective deacylation of a 4,5-diacylcyclohexenone (see **30** → **31**), (2) a new route to α-methylene-δ-lactones via the Brederick reagent (see **4** → **64** → **65** → **66** → **66a** → **5**), and (3) the stereospecific introduction of an epoxymethylenelactone via an epoxyhemiacetal (see **5** → **6**).

Background

In a 1957 disclosure from the Pfizer Co., Celmer reported the isolation of a new antibiotic from a *Streptomyces* broth culture.[1] The substance, named PA-132, was reported to have excellent antibiotic activity against Gram-positive and Gram-negative bacteria as well as against pathogenic and saprophytic fungi. In 1969, Takeuchi described the isolation of PA-132 from *Streptomyces* sp no. 8403-MC.[2] It was also shown to have inhibitory activity against nucleic acid synthesis in bacterial cells. This substance, named pentalenolactone, was obtained as a white, hygroscopic powder. Preliminary chemical and spectroscopic studies led to the provisional assignment of structure **2** to this antibiotic.

Subsequently, an Upjohn group, using antitumor assays, described the isolation of pentalenolactone from a fermentation broth of *Streptomyces* UC 5319. Its structure assignment was

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