(12) U. R. Ghatak, Sh. K. Alam, P. C. Chakraborti, and B. C. Ranu, *J. Chem. Soc., Perkin Trans. 1*, 1669 (1976).
(13) G. S. Krishna Rao and Sukh Dev, *J. Indian Chem. Soc.*, **34**, 255 (1957).
(14) U. R. Ghatak and B. Sanyal, *J. Chem. Soc., Chem. Commun.*, 876 (1974).
(15) J. F. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).
(16) We are deeply indebted to Professor J. W. ApSimon for kindly providing us with an 80 MHz NMR spectrum of our synthetic sample of **10**; however, no comparison data with their sample has been available.

Synthesis of *dl*-Epigriseofulvin

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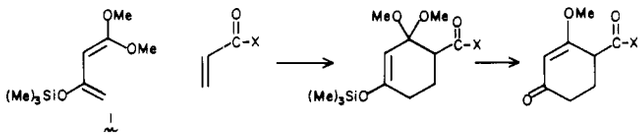
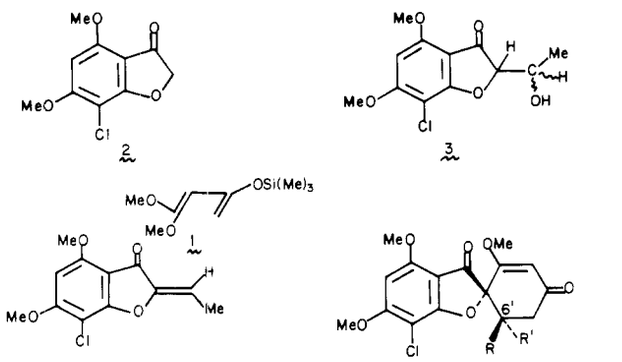
Diels–Alder reaction of (*Z*)-2-ethylidene-7-chloro-4,6-dimethoxycoumaran-3-one with 1,1-dimethoxy-3-(trimethylsilyloxy)-1,3-butadiene, followed by acidification, affords *dl*-epigriseofulvin.

Recently we described some cycloaddition reactions of the 1,1-disubstituted diene **1** with electrophilic dienophiles.[1,2]



Acid-catalyzed unraveling of the adducts of **1** with α,β-unsaturated carbonyl systems affords specific monoenol ethers of β-diketones.

It was of interest to examine the extension of this reaction to include α-alkylidinecycloalkanones as dienophiles, thereby providing a route to structurally defined spirocyclic β-methoxyenones. With this in mind, we addressed the synthesis of griseofulvin (**6**),[3,4] an antifungal agent of some importance. Our results are described herein.

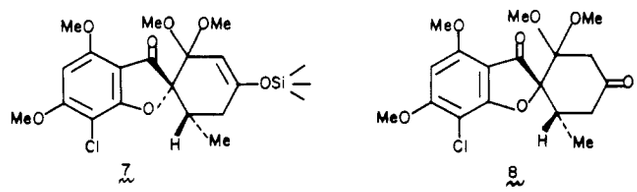


The known[4d] coumaranone (**2**) was treated with lithium diisopropylamide in tetrahydrofuran. The resultant enolate, at −78 °C, reacted instantaneously with acetaldehyde to afford a nearly quantitative yield of a stereoisomeric mixture of β-aldols **3** [($CDCl_3$) 2CHCH_3 doublets at δ 1.35 and 1.39].

While in some cases a given β-aldol can be converted to a geometrically defined alkylidenecycloalkanone by trans elimination of a suitably activated derivative of the alcohol,[5] a recent finding of Katzenellenbogen[6] suggests that such a stereospecific transformation is not always possible. Since chromatographic separation of **3** into its components appeared to be inconvenient, we first investigated the dehydration of the mixture. Treatment of a mixture **3** with methanesulfonyl chloride in pyridine containing 4-(dimethylamino)pyridine afforded an 89% yield of a single ethylidene ketone. Thus, even under these mild conditions, the presumed intermediate β-mesyloxy ketone was unstable to β elimination.

That **4** is, in fact, a single substance was suggested by its NMR spectrum [($CDCl_3$) δ 1.95 (3, d, J = 6 Hz), 5.98 (q, J = 6 Hz)]. Since only one isomer was available to us, we could not at this stage assign its configuration. This was ascertained through its cycloaddition with compound **1**.

Reaction of **4** with **1** was carried out in toluene at 115 °C. Two procedures were employed to convert the resultant adduct **7** into the desired β-methoxyenone. In method A the



residue, upon evaporation of the toluene, was directly chromatographed on silica gel. Elution with ethyl acetate–benzene afforded a mixture of *dl*-epigriseofulvin (**5**) and its β-methoxy derivative **8**. This mixture was treated with tosyl acid–benzene under reflux for 2 h to afford an 82% yield of essentially pure **5**.

Alternatively, the adduct was treated with aqueous HCl–THF. By this method, the adduct **7** suffered direct conversion to **5**, effectively bypassing the β-methoxy derivative **8**. Chromatography afforded **5** in 55% yield. An authentic sample of epigriseofulvin (**5**) was obtained by known procedures,[7] involving the base-catalyzed equilibration of griseofulvin (**6**)[8] with **5**. The spectral and chromatographic properties of the synthetic material were identical with those of the authentic, optically active sample. At no point, in either method of workup, was there any indication for the formation of griseofulvin (**6**) itself.

Assuming the stereochemical integrity of the ethylidene group under the conditions of the cycloaddition, it is surmised that **4** is of the *Z* configuration shown. Whether this is the result of equilibration of the hypothetical *E* isomer, formed from trans elimination of the erythro version of **3**, or whether **4** is the kinetic β-elimination product of both isomers of **3** can not be ascertained at this stage.

It will be noted that in light of the base-induced equilibration of **5** and **6**,[7] this work constitutes a formal total synthesis of griseofulvin (**6**) itself. Given the inefficiency of conducting this equilibration, separation, and recycling sequence, the method can not be regarded as an optimal path to griseofulvin.[9] However, in view of the excellent yields of Diels–Alder reactions of 2-alkylidenecoumaranones with diene **1**, several alternative routes to griseofulvin itself appear possible. These are now under active investigation in our laboratory.

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Experimental Section[10]

(Z)-2-Ethylidene-7-chloro-4,6-dimethoxycoumaran-3-one (4). To a solution of diisopropylamine (162 mg, 1.6 mmol) in 3 mL of dry tetrahydrofuran under nitrogen and at −78 °C was added *n*-BuLi (1.04 mL of a 1.53 M solution in hexane) in a rapid dropwise manner. The resulting solution was stirred at −78 °C for 15 min. To this solution was added dropwise a solution of ketone **2**[4d] (300 mg, 1.32 mmol) in 60 mL of dry tetrahydrofuran over ca. 30 min. The resulting solution was stirred at −78 °C for 30 min. To this solution at −78 °C was added a single portion of acetaldehyde (124 mg, 2.8 mmol) in 0.5 mL of dry tetrahydrofuran. This solution was allowed to stir for ca. 10–15 s[11] and was quenched by adding 10 mL of saturated ammonium chloride in a single portion.

The reaction mixture was poured into 200 mL of ether. The organic phase was washed with brine and dried over anhydrous sodium sulfate. When freed of solvent, it afforded 358 mg of a glass, whose NMR spectrum (see text) indicated it to be a mixture of the β-aldols **3**, containing a trace of starting **2**.

To a solution of mixture **3** (358 mg, 1.6 mmol), obtained as above, and 30 mg of 4-(dimethylamino)pyridine in 7.7 mL of dry pyridine was added methanesulfonyl chloride (893 mg, 7.8 mmol) over ca. 1 min. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The volatiles were removed in vacuo, and the residual solid was treated with 10 mL of methylene chloride and 10 mL of saturated ammonium chloride and poured into 200 mL of ether. The organic layer was washed with 20 mL of 0.1 N hydrochloric acid and 20 mL of brine and dried over anhydrous magnesium sulfate. Evaporation of the volatiles afforded 298 mg (89%) of crude ethylidene compound **4** as an off-white solid.

An analytical sample, mp 176–178 °C, was prepared by recrystallization from ethyl acetate: IR ($CHCl_3$) ν_{max} 1710, 1675, 1615, 1600 cm^{-1}; see text for NMR. Anal. Calcd for $C_{12}H_{11}ClO_4$: C, 56.59; H, 4.35. Found: C, 56.38; H, 4.40.

***dl*-Epigriseofulvin (5).** A solution of enone **4** (298 mg, 1.17 mmol), obtained as above, and diene **1** (1.22 g, 6 mmol) in 5 mL of dry toluene under nitrogen was heated at 115 °C for 18 h. The reaction mixture was cooled to room temperature, and the volatiles were removed in vacuo.

An NMR spectrum of the residue at this point showed the presence of adduct **7** in crude form. This material was chromatographed on 15 g of silica gel. Elution with 10% EtAc–benzene removed nonpolar impurities. Elution with 20% EtAc–benzene afforded 380 mg of a crude yellow solid whose NMR spectrum indicated it to be a mixture of (±)-epigriseofulvin contaminated with β-methoxy compound **8**.

A solution of 308 mg of this mixture and 40 mg of *p*-toluenesulfonic acid in 120 mL of benzene was heated under reflux for 2 h. Upon cooling, it was poured into 100 mL of ether and 40 mL of saturated $NaHCO_3$. The organic layer was washed with saturated ammonium chloride, dried over anhydrous magnesium sulfate, and freed of solvent to afford 308 mg (82%) of a yellow solid, mp 220–245 °C, whose NMR spectrum was essentially that of (±)-epigriseofulvin (containing ca. 5% of **8**).

One recrystallization from ca. 10 mL of benzene afforded 167 mg (44.5%) of *dl*-epigriseofulvin (**5**), mp 249–251 °C, whose NMR, IR, and mass spectra were identical with those of an authentic sample of epigriseofulvin prepared by a known procedure[7,8] from griseofulvin.

***dl*-Epigriseofulvin via Acidic Hydrolysis of the Diels–Alder Adduct.** A solution of enone **4** (180 mg, 0.7 mmol) and diene **1** (811 mg, 4 mmol) in 3 mL of dry toluene was heated under N_2 at 115 °C for 18 h. The volatiles were removed in vacuo, and the residue was taken up in 15 mL of tetrahydrofuran, 6 mL of water, and 1 mL of 0.1 N hydrochloric acid. This reaction mixture was stirred at room temperature for 30 min and then poured into 75 mL of ether layered on 50 mL of water. The aqueous layer was extracted with an additional 50 mL of ether, and the combined organic phases were washed with saturated sodium bicarbonate and brine. When dried and freed of volatiles, there was obtained 288 mg of a crude orange solid whose NMR spectrum indicated that it was substantially *dl*-epigriseofulvin (**5**).

Chromatography on 10 g of silica gel afforded 138 mg (55%) of **5**, mp 230–240 °C.

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Registry No.—**1**, 61539-61-5; **2**, 3261-06-1; **3** (isomer 1), 67844-78-4; **3** (isomer 2), 67844-79-5; **4**, 67844-80-8; **5**, 67890-77-1; acetaldehyde, 75-07-0.

References and Notes

(1) S. Danishefsky, R. K. Singh, and R. B. Gammill, *J. Org. Chem.*, **43**, 379 (1978).
(2) J. Banville and P. Brassard, *J. Chem. Soc., Perkin Trans. 1*, 1852 (1976).
(3) For a review, see W. Huber, *Antibiotics, 1975*, 606–613 (1975).
(4) For previous total syntheses, see (a) A. C. Day, J. Nabney, and A. I. Scott, *J. Chem. Soc.*, 4067 (1961); (b) A. Brossi, M. Baumann, M. Gerecke, and E. Kyburz, *Helv. Chim. Acta*, **43**, 207 (1960); (c) D. Taub, C. H. Kuo, H. L. Slates, and N. L. Wendler, *Tetrahedron*, **19**, 1 (1963); (d) G. Stork and M. Tomasz, *J. Am. Chem. Soc.*, **86**, 471 (1964).
(5) Cf. D. B. Johnston, S. M. Schmitt, F. A. Boufford, and B. G. Christensen, *J. Am. Chem. Soc.*, **100**, 315 (1978).
(6) R. A. Amos and J. A. Katzenellenbogen, *J. Org. Chem.*, **43**, 560 (1978).
(7) J. MacMillan, *J. Chem. Soc.*, 1823 (1959).
(8) We thank Dr. David Taub of Merck Sharp & Dohme Laboratories for a generous sample of griseofulvin.
(9) The synthesis of Stork and Tomasz[4d] is the only one which provides a direct solution to the stereochemical issue.
(10) Melting points are uncorrected. NMR spectra were measured on a Varian Associates T-60 system on a Jeolco-MH-100. Chemical shifts are reported in parts per million (δ) from an internal tetramethylsilane standard. The microanalysis was performed by Galbraith Associates.
(11) The procedure was based on the method of Heathcock and represented an attempt to avoid reversibility in the aldol step. The ratio of β-aldol products, as measured by NMR analysis, was variable: C. T. Buse and C. H. Heathcock, *J. Am. Chem. Soc.*, **99**, 8110 (1977).