Synthesis of Disodium Prephenate and Disodium Epiprephenate. Stereochemistry of Prephenic Acid and an Observation on the Base-Catalyzed Rearrangement of Prephenic Acid to *p*-Hydroxyphenyllactic Acid

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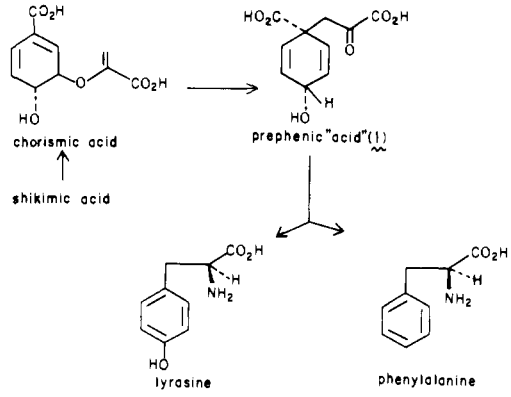
Abstract: The total synthesis of disodium prephenate and epiprephenic acid as its disodium and barium salts was accomplished. The stereochemistry of prephenate and epiprephenate was rigorously established by crystallographic and chemical correlation. The mechanism for the base-induced conversion of prephenate to *p*-hydroxyphenyllactate is shown to involve an unusual 1,6-hydride migration.

Introduction

Prephenic acid (**1**), stable only in its dicarboxylate form, arises biosynthetically from shikimic acid by way of chorismate. Its name bespeaks its biological role, i.e., that of a central intermediate for the biosynthesis of the crucial aromatic amino acids phenylalanine and tyrosine[2a,b] in plants and bacteria. Mammalian systems, apparently lacking the capability of synthesizing and exploiting prephenic acid in these ways, must rely on lower order organisms for their aromatic amino acids. Prephenate thus serves as a vital connecting link between the "aliphatic" and "aromatic" domains.

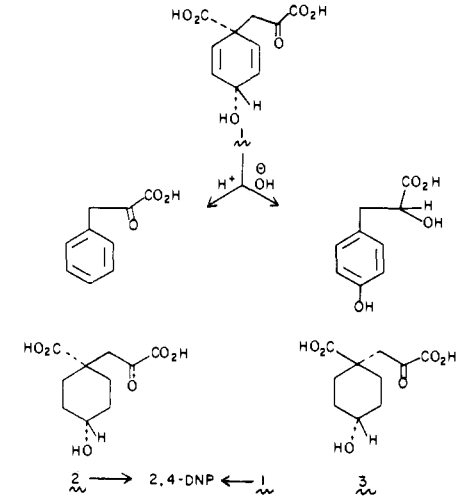


From a chemical standpoint, the level of characterization of prephenate was far from ideal. The deduction of the structure of prephenic acid by Weiss et al. was a noteworthy intellectual achievement since it was based on a minimum of hard chemical or analytical data.[2c,3] *In fact, the formulation was accomplished without the benefit of a single fully characterized nonaromatic transformation product.*

The chemistry of prephenic acid in acid medium is dominated by its extremely facile transformation to phenylpyruvic acid. In base, though under more forcing conditions, it suffers conversion to *p*-hydroxyphenyllactic acid.[4]

The assignment of the stereochemistry of prephenic acid rested on two types of supports. Since it is biosynthetically derived from chorismate, it was assumed that the pyruvyl chain of prephenate is introduced cis to the enol pyruvate function of chorismate. It must be emphasized that this type of stereochemical reasoning is, in principle, unsound since the mechanism and thus the topology of the enzymatically mediated chorismate → prephenate transformation are not known in detail. *The fact that in the case at hand the overall conclusion about the stereochemistry of prephenate shall be shown to be correct (vide infra) should not obscure the logical gap in this type of deductive process.*

A more soundly based type of stereochemical analysis was provided by Plieninger.[5] The Heidelberg group had synthesized epimers **2** and **3**, whose stereochemistry could be assigned with some confidence. Reduction of barium prephenate derived from natural sources gave rise, in very low yield, to an apparent tetrahydro compound (the main product being one of hydrogenation and hydrogenolysis) from which there was obtained a 2,4-dinitrophenylhydrazone derivative whose paper chromatogram matched that of **2**.[3,5]



Plieninger had also described synthetic efforts aimed at prephenic acid itself.[6] Dienone **4** was subjected to the action of sodium borohydride. This was followed by acid-catalyzed deketalization. After basification, a mixture of various barium salts was obtained. Some kinetic evidence was marshalled to the effect that these salts may have contained prephenate.[6]

Our previously described findings[7a,b] engendered serious doubts that cleavage of a simple acetal such as **5** could be achieved in a manner which was consistent with survival of the acid-labile prephenate functionality. Indeed, it seemed likely that provision must be made for generating the pyruvyl keto group in base, if we were to capitalize on our Diels–Alder route[7a,b] (**6** → **7** → **8** → **9**) to achieve an actual synthesis of prephenate in the laboratory.

While a number of recently developed ketal arrangements[8] might have been invoked to facilitate deprotection, it should be noted that even these schemes do not involve alkaline conditions.

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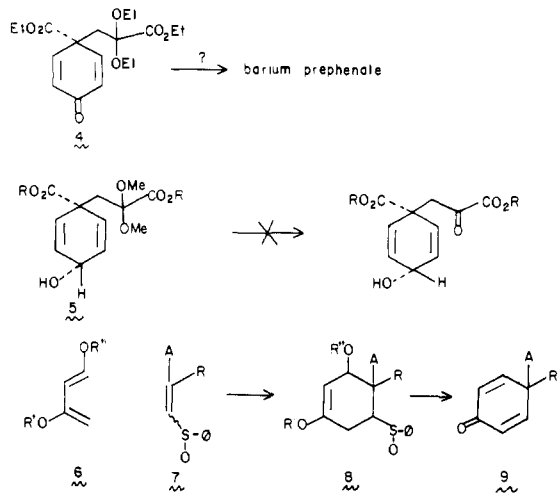
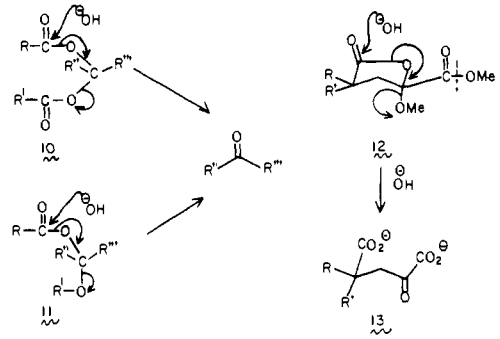


A generic solution to a base-sensitive protecting group for a ketone would involve an acylal (**10**) or an acylated hemiacetal (**11**). These have not enjoyed wide usage because they are difficult to prepare and, in fact, do not provide a broad range of protection. In the case at hand, it was recognized that a cyclic version of **11**, i.e., **12**, might well afford simultaneous protection for the future quaternary carboxy and keto groups of **1**, both of which would concurrently be exposed under alkaline circumstances, to afford **13**. It was on such an intermediate that we placed our reliance.

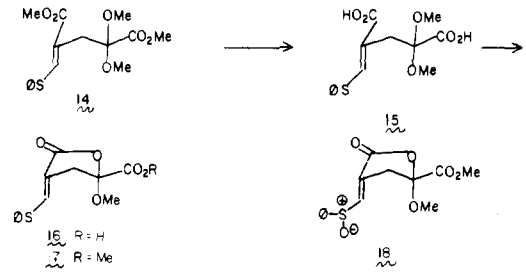


Below we describe (1) the total synthesis and characterization of prephenic acid as its disodium and barium salts as well as the synthesis and characterization of the epiprephenate system,[9] (2) the rigorous demonstration of the stereochemistry of prephenic acid, and (3) the clarification of the prephenate → *p*-hydroxyphenyllactate rearrangement.[10]

Results

(1) Total Synthesis of Prephenate. Our synthesis started with compound **14**, whose preparation from the commercially available 2-oxyglutaric acid we have already described.[7a,b] It was first necessary to ascertain the relative vulnerability of the vinylogous thioester and ester groupings toward alkaline hydrolysis. Happily, for the outcome of our plan, it was found that, at room temperature, the methyl esters could be saponified without competing cleavage of the thiophenyl group, thereby providing diacid **15**, mp 108–110 °C, in 92% yield.

Compound **15** was treated with 2:1 0.012 N HCl–THF at room temperature. After 73 h, there was obtained what we deemed to be the lactone monoacid **16**. This compound was never fully characterized, but its NMR spectrum [$\delta(CDCl_3)$ 2.93 (dd, J_1 = 18, J_2 = 2.5 Hz, 1 H), 3.20 (dd, J_1 = 18, J_2 = 2.5 Hz, 1 H), 3.51 (s, 3 H), 7.4 (m, 5 H), 7.76 (t, J = 2.5 Hz, 1 H) ppm] seemed convincing. The presumed **16** was treated with diazomethane to afford, after silica gel chromatography, the fully characterized lactone ester **17** (see Experimental Section for spectral and analytical data). The crucial step (**15** → **16**) involves the terminal thiophenylmethylene carboxylic acid function in the cleavage of the acetal. Whether this carboxyl "participates" in the sense of interdicting "internal return" of methanol to the alkoxy carbonium ion which would, in any case, have arisen from the acetal, or whether it operates as a nucleophile in the displacement of methanol from the protonated acetal, is a matter of some conjecture, and is not resolvable by the data at hand. The transformation of **14** → **17**, without isolation of **15** or **16**, could be carried out in 60–70% yield. The stage for launching the Diels–Alder reaction was completed when it was found that treatment of **17** with *m*-chloroperoxybenzoic acid at low temperature afforded sulfoxide **18** in 69% yield. While this oxidation might have produced a mixture of diastereomers owing to sulfoxide chirality, in fact compound **18** was, by NMR analysis, a single substance (of undetermined relative configuration).



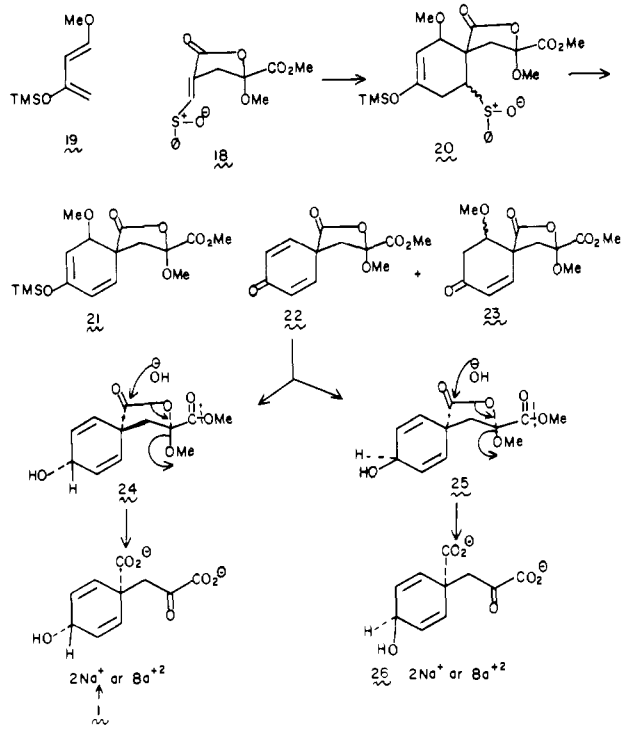
Diels–Alder reaction between **18** and **19**[7a,b] was carried out, most effectively in a sealed tube, without solvent at 100 °C for 26 h. Since an excess of **19** was employed, it was difficult by NMR analysis to sort out the status of the ensuing reaction at this stage. However, it seemed likely that compound **21** was present. The reaction mixture was treated with 2.4% acetic acid in ethyl acetate for 21 h. Rapid chromatography on silica gel produced a 76% yield of an oily mixture whose NMR spectrum indicated it to be comprised of 70–80% of the desired **22**, ca. 15% of the β-methoxy ketone epimers **23**, and several other unidentified components. Unfortunately, compound **22** could not be purified in an efficient manner by direct crystallization. Thus, crystalline **22**, mp 128–130 °C, was only obtained in 31% yield.

In other runs, rechromatography of the mixture of **22** and **23** was attempted. The isolated yield of **22** was lowered to 26%. There were now isolated two of the four possible diastereometric versions of **23** in 4 and 6% yields. (See Experimental Section for analytical and spectral details.)

Treatment of dienone **22** with 9-BBN[7a,b,11] in THF at 0 °C afforded, after chromatography, two dihydro compounds. The major product (30% isolated yield) was obtained as a crystalline solid, mp 106.5–108 °C. The minor dienol, obtained in 19% yield, has thus far resisted our best efforts at crystallization. *It will be shown rigorously* (vide infra) *that the crystalline product has the configuration shown in structure* **24**. Hence, its closely related isomer is assigned to be structure **25**. The NMR spectrum of the crude reduction mixture indicated that the ratio of **24**:**25**, which was produced by 9-BBN reduction of **22**, was more favorable (ca. 3:1). Thus the dienol is significantly less stable to silica gel chromatography than **25**.

Treatment of compound **24** with sodium hydroxide in methanol followed by suitable workup afforded disodium prephenate. The infrared (KBr) spectrum was identical with that of sodium prephenate obtained by ion exchange of the naturally derived barium salt obtained from natural sources.[12] The NMR spectra (D_2O) at 250 MHz of the synthetically and naturally derived materials were identical.

In a similar way, compound **25** was converted to disodium epiprephenate, whose spectral properties differed slightly, but clearly, from those of the authentic material. The total synthesis of prephenate salts had thus been achieved.[13]



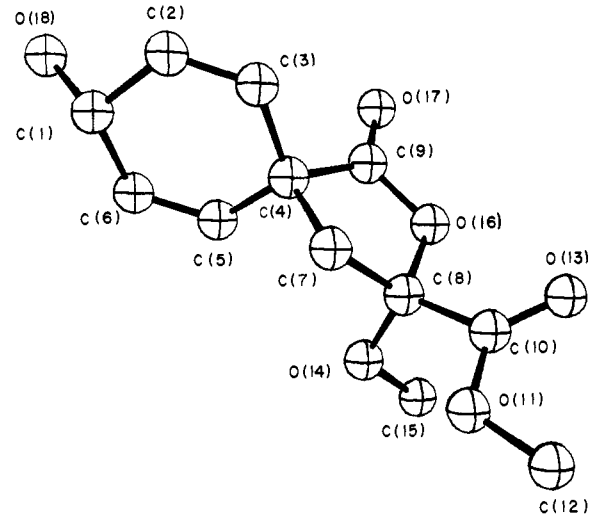


Figure 1. Computer-generated perspective drawing of compound **24.**

(2) **Stereochemistry of Prephenic Acid.** An excellent opportunity now presented itself to rigorously establish the stereochemistry of prephenic "acid". Since dienol **24** had in fact been cleanly converted to prephenate salts of the natural series, while **25** was converted equally cleanly to the epiprephenate system, it was clear that the cis-trans relationship of **24** and **25** mirrors that of prephenate and epiprephenate, respectively. A crystallographic examination of **24** was thus undertaken.[14]

Preliminary X-ray photographs showed that crystals of the spirolactone **24** belonged to the monoclinic crystal class. Cell constants, determined by a least-squares fit of 15 diffractometer-measured 2θ values between 35 and 45°, were $a = 10.675$ (4) Å, $b = 8.021$ (2) Å, $c = 14.317$ (8) Å, and $\beta = 94.39$ (7)°. A rough experimental and calculated ($Z = 4$) density of ~1.38 g/cm^3 indicated one molecule of composition $C_{12}H_{14}O_6$ per asymmetric unit. Systematic extinctions indicated space groups $P2_1/n(C^5_{2h}$, alternate setting). All unique diffraction maxima with $2\theta \leq 114°$ were collected on a computer-controlled four-circle diffractometer with graphite monochromated Cu Kα (1.541 78 Å) radiation and a variable speed ω scan. Of the 1796 reflections surveyed in this fashion, 1513 (84%) were judged observed ($I \geq 3\sigma(I)$) after correction for Lorentz, polarization, and background effects.

The structure was solved uneventfully using a multisolution, weighted sign determining procedure.[14] All nonhydrogen atoms were visible on the first weighted E synthesis and hydrogen atoms were located on a difference synthesis following partial refinement. Full-matrix least-squares refinements with anisotropic temperature factors for the nonhydrogen atoms and isotropic temperature factors for the hydrogens have converged to the current value of the crystallographic residual of 0.062. Tables of the final fractional coordinates, thermal parameters, bond distances, bond angles, and observed and calculated structure factors can be found in the supplementary material described at the end of this paper. In general, the metric details agreed well with generally accepted values and there were no abnormally short intermolecular contacts. A final difference synthesis showed no high unaccounted for electron density.

A computer-generated perspective drawing of the final X-ray model of **24** is shown in Figure 1. Hydrogens are omitted for clarity and the crystal is racemic so the enantiomer shown is an arbitrary choice. The molecule is clearly bicyclic with essentially orthogonal cyclohexadiene and γ-lactone rings. The cyclohexadiene is in the anticipated flattened boat conformation with C(1) and C(4) ~0.13 Å removed from the plane defined by C(2), C(3), C(5), and C(6). The hydroxyl substituent at C(1) and the carbonyl substituent at C(4) are cis disposed and in pseudoaxial or flagpole positions. The γ-lactone ring is in the envelope conformation with C(7) serving as the flap and ~0.50 Å removed from the plane of the remaining four atoms. The bond distances and angles generally agree well with anticipated values.

The stereochemistry of prephenate is rigorously established to be that indicated in structure **1.** Epiprephenic acid is thus properly represented by **26.**

(3) **Base-Induced Conversion of Prephenate to *p*-Hydroxyphenyllactate.** With the syntheses of **1** and **26** achieved, and their stereochemistry on a sure footing, we were in a favorable position to examine[10] the base-induced conversion of prephenate to *p*-hydroxyphenyllactate (**28**).[3,4,15] Several formalisms have been advanced to account for this transformation. Possibility (a)[3] contemplates a 1,2-hydride shift "driven" by decarboxylation. Pathway (b)[4] envisages enolization of the ketone as setting the stage for decarboxylation of the vinylogous malonic (glutaconate) system. Plieninger also proposed[3] a somewhat unusual 1,6-hydride transfer (path d) of **1a** leading to **27.** This is then followed by decarboxylation of the vinylogous β-keto acid, affording the observed **28.**

We first carried out the reaction on pure synthetic **1a** under the previously described conditions[4] (heating the prephenate in 2 N sodium hydroxide at 100 °C). After heating for 20 min, acidification afforded a 90–98% yield of essentially pure **28.** Attempts to effect similar reaction of the synthetic epi compound **26** were unsuccessful. Acidification after prolonged heating afforded a near-quantitative yield of phenylpyruvic acid (**29**). This transformation implies the absence of any reaction for **26,** under the basic treatment, and that the epiprephenate undergoes the usual dehydrative decarboxylation upon acidification.

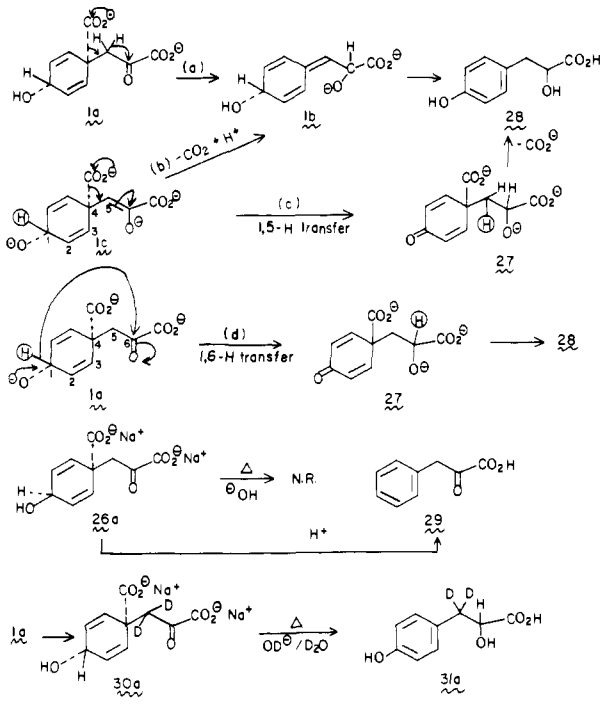
The sensitivity of the reaction to the relative stereochemistry of the carbinyl and quaternary carbons is best accommodated by an intramolecular Cannizzaro-like process. In addition to the 1,6-hydride transfer possibility, which is contemplated in path (d), one might also consider a 1,5-hydride transfer (cf. path (c)), which is a vinylogous Cannizzaro reaction, via intermediate **1c.** This would lead again to **27.** *Of the pathways considered, the 1,6-hydride transfer (path d) uniquely pre-*

dicts the appearance of the original carbinyl proton of **1** *at the hydroxyl-bearing carbon of* **28.**

Fortunately, this distinction could be subjected to experimental scrutiny. The disodium salt **1a** is rapidly converted to its dideuterio derivative **30a** (see NMR chemical shifts of **1** in D_2O in the Experimental Section). However, **28** does not suffer a noticeable exchange of any of the carbon-bound protons even at 100 °C in 2 N NaOD-D_2O. Accordingly, **30a** was subjected to the action of 2 N NaOD-D_2O as described above. NMR analysis of the resultant D_2O solution demonstrated the exclusive emergence of *p*-hydroxyphenyllactate of the labeling pattern shown in **31a** ($\delta(D_2O)$ 4.14 (1 H, s), 6.54 (2 H, d, J = 8 Hz), 6.98 (2 H, J = 8 Hz) ppm).

Given the failure of the epiprephenate **26** to suffer conversion to *p*-hydroxyphenyllactate (**28**), the intramolecular nature of the hydride transfer seems secure. The clean conversion of **30a** → **31a** would appear to establish the 1,6-hydride transfer advocated by Plieninger.[3]

In summary, the structure, synthesis, and chemistry of prephenate have been placed on secure footing. It will be of interest to ascertain, by analogue synthesis and evaluation, the extent of structural variations which are possible, while still allowing for enzymic recognitions in the biosynthesis of aromatic amino acids. Such studies are envisioned.



Experimental Section[16]

Preparation of 2-Thiophenylmethylene-4,4-dimethoxyglutaric Acid (15). A mixture of diester **14**[7a,b] (1.500 g, 4.41 mmol), 14.7 g (25 mmol, 6 molar equiv) of 10% aqueous KOH, and 18 mL of methanol was stirred at room temperature under nitrogen for 36 h. After the solution was diluted with water and ethyl acetate it was acidified to pH 4 with 2 N aqueous HCl. The system was thoroughly extracted with ethyl acetate. The organic extracts were dried over anhydrous sodium sulfate. Evaporation of the volatiles afforded a residue which crystallized from ether to afford 1.271 g (92%) of pure **15**: mp (ether) 108–110 °C; λ_{max} ($CHCl_3$) 3.0–4.3, 5.82, 5.90 (sh), 6.09, 6.26 μ; $\delta(CDCl_3)$ 3.09 (s, 2), 3.42 (s, 6), 7.4 (m, 5), 7.98 (s, 1), 8.1 (br m, 2) ppm.

Anal. Calcd for $C_{14}H_{16}O_6S$: C, 53.84; H, 5.16. Found: C, 53.90; H, 5.14.

Conversion of Diacid 15 to Lactone Ester 17. The diacid **15** (1.271 g, 4.07 mmol) was mixed with 200 mL of tetrahydrofuran and 400 mL of 0.012 N HCl. The system was stirred for 73 h at room temperature. Most of the THF was evaporated at the water pump. The aqueous system was extracted with ethyl acetate and the combined organic extracts were dried over sodium sulfate. Evaporation of the volatiles left an oily residue which was dissolved in methanol. To this was added a solution of diazomethane in ether at 0 °C, until gas evolution ceased. Evaporation of the volatiles left a residue which was chromatographed on 80 g of silica gel. Elution with 40:1 benzene-ethyl acetate afforded 642 mg (54%) of **17** of spectral properties identical with those described in the next experiment.

Direct Conversion of Diester 14 to Lactone Ester 17. A solution of diester **14** (6.977 g, 0.021 mol) in 145 mL of methanol and 116 g of 10% aqueous KOH (0.207 mmol) was stirred at room temperature for 47 h. The resulting clear solution was acidified to pH 2 with 2 N aqueous HCl at 0 °C and diluted with 400 mL of methanol. This system was stirred at room temperature for 21 h. Most of the methanol was removed and evaporated by warming at 35 °C at the water pump. The aqueous system was thoroughly extracted with ethyl acetate. The volatiles of the dried (sodium sulfate) organic extracts were concentrated in vacuo, affording 5.323 g of residue assumed to be **16** (see text for NMR spectrum). This was dissolved in 50 mL of methanol, and the resultant solution treated dropwise with diazomethane in ether at 0 °C until gas evolution ceased. Evaporation of the volatiles left a residue which was chromatographed on 250 g of silica gel. Elution with 50:1 benzene-ethyl acetate afforded 4.178 g (69%) of lactone ester **17** as a pale yellow oil: λ_{max} ($CHCl_3$) 5.68, 6.17 μ; λ_{max} (EtOH) 205 nm (log ϵ 4.12), 256 (log ϵ 3.78), 294 (4.24); $\delta(CDCl_3)$ 2.87 (dd, J_1 = 18, J_2 = 2.5 Hz, 1), 3.14 (dd, J_1 = 18, J_2 = 2.5 Hz, 1), 3.47 (s, 3), 3.85 (s, 3), 7.4 (m, 5), 7.71 (t, J = 2.5 Hz, 1) ppm.

Anal. Calcd for $C_{14}H_{14}O_5S$: C, 57.14; H, 4.80. Found: C, 57.38; H, 4.74.

Preparation of 3-Phenylsulfinylmethylene-5-methoxy-5-carbomethoxybutyrolactone (18). To a solution of **17** (6.319 g, 0.022 mol) in 100 mL of methylene chloride at −24 °C was added, dropwise over 1 h, a solution of 85% *m*-chloroperoxybenzoic acid (4.367 g, 0.022 mol) in 140 mL of methylene chloride. The solution was allowed to warm to 0 °C over 2 h, then cooled to −78 °C. A colorless solid was removed by filtration. The filtrate was washed with 5% sodium bicarbonate and the organic layer was dried over sodium sulfate. The residue left upon evaporation of the volatiles in vacuo was chromatographed on 300 g of silica gel. Elution with 10:1 benzene-ethyl acetate afforded 4.596 g (69%) of sulfoxide **18** as a pale yellow oil: λ_{max} ($CHCl_3$) 5.68, 6.14 μ; λ_{max} (EtOH) 207 nm (log ϵ 4.16), 238 (4.09), 292 (3.21); $\delta(CDCl_3)$ 3.48 (s, 3), 3.62 (t, J = 3 Hz, 2), 3.85 (s, 3), 7.22 (t, J = 3 Hz, 1), 7.6 (m, 5) ppm.

Anal. Calcd for $C_{14}H_{14}O_6S$: C, 54.19; H, 4.55. Found: C, 53.98; H, 4.58.

Preparation of Spirodienone 22. The sulfoxide **18** (4.19 g, 0.0135 mmol) and diene **19**[7a,b] (8.1 g, 0.047 mol) were heated at 100 °C for 26 h in a sealed tube. Excess diene was removed by warming from 60 to 70 °C at the water pump. To the residue was added 987 mL of 2.4% acetic acid in ethyl acetate. The solution was stirred at room temperature for 21 h, then washed with three 750-mL portions of 5% aqueous sodium bicarbonate followed by saturated brine. Evaporation of the volatiles from the dried (sodium sulfate) organic phase afforded a residue which was dissolved in a minimum volume of 4:1 benzene-ethyl acetate and chromatographed quickly on 150 g of Merck 70–230 mesh silica gel 60. Elution with 4:1 benzene-ethyl acetate (elution rate ca. 50 mL/min) yielded 2.58 g of crude dienone of 70–80% purity. This crystallized from ether to afford 1.04 g (31%) of pure **22** (mp 128–130 °C): λ_{max} ($CHCl_3$) 5.56, 5.68, 5.98, 6.12 μ; λ_{max} (EtOH) 238 nm (log ϵ 4.16), 285 shoulder (1.77); $\delta(CDCl_3)$ (250 MHz) 2.67 (d, J = 14.3 Hz, 1), 2.80 (d, J = 14.3 Hz, 1), 3.55 (s, 3), 3.91 (s, 3), 6.43 (dd, J_1 = 10.0, J_2 = 1.6 Hz, 1), 6.48 (dd, J_1 = 10.0, J_2 = 1.6 Hz, 1), 6.73 (dd, J_1 = 10.0, J_2 = 2.9 Hz, 1), 7.04 (dd, J_1 = 10.0, J_2 = 2.9 Hz, 1) ppm.

Anal. Calcd for $C_{12}H_{12}O_6$: C, 57.14; H, 4.80. Found: C, 57.10; H, 4.76.

Cycloaddition of 18 + 19. Isolation of Methoxy Ketone Epimers 23a and 23b. A mixture of sulfoxide **18** (780 mg, 2.52 mmol) and diene **19** (1.5 g, 8.7 mmol) was heated at 100 °C for 28 h in a sealed tube. Workup and chromatography as above, though at a slower elution rate (25 mL/min), afforded 318 mg of a residue which was judged to contain 80% of dienone **22** (R_f silica gel plates, ether 0.42) and indeterminate amounts of methoxy ketones **23a** (R_f 0.38) and **23b** (R_f 0.29). Crystallization from ether yielded 162 mg (26%) of pure **22**, mp 128–130 °C (see spectral data above). The mother liquors and the later eluants which contained **23b** mainly were rechromatographed

under the same conditions except with slow elution. There was thus obtained methoxy ketone **23a** (6%), mp 117–118 °C, and methoxy ketone **23b** (4%), mp 130–131.5 °C.

For **23a:** λ_{max} ($CHCl_3$) 5.60, 5.75, 5.95 μ; δ($CDCl_3$) 2.50 (d, J = 15 Hz, 1), 2.89 (dd, J_1 = 17, J_2 = 6 Hz, 1), 2.98 (d, J = 15 Hz, 1), 3.18 (dd, J_1 = 17, J_2 = 13 Hz, 1), 3.34 (s, 3), 3.45 (s, 3), 3.89 (s, 3), 3.68 (dd, J_1 = 13, J_2 = 6 Hz, 1), 6.18 (d, J = 10 Hz, 1), 6.74 (d, J = 10 Hz, 1) ppm.

Anal. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 55.16; H, 5.62.

For **23b:** λ_{max} ($CHCl_3$) 5.61, 5.74, 5.94 μ; δ($CDCl_3$) 2.66 (d, J = 15 Hz, 1), 2.72 (d, J = 15 Hz, 1), 2.84 (dd, J_1 = 17, J_2 = 6 Hz), 3.24 (dd, J_1 = 17, J_2 = 12 Hz, 1), 3.78 (dd, J_1 = 12, J_2 = 6 Hz, 1), 3.44 (s, 3), 3.54 (s, 3), 3.91 (s, 3), 6.16 (d, J = 10 Hz, 1), 6.64 (d, J = 10 Hz, 1) ppm.

Reaction of Dienone 22 with 9-BBN. Formation of Dienols 24 and 25. To a solution of dienone **22** (411 mg, 1.63 mmol) in 2 mL of freshly dried tetrahydrofuran was added 10 mL (5 mmol) of 0.5 M 9-BBN in THF at 0 °C. After the system was stirred at room temperature for 3 h, methanol (2 mL) was added and the system was stirred at room temperature for 5 min. There was then added 2 mL of water. After 5 min, 150 mL of water was added and the mixture was thoroughly extracted with methylene chloride. The organic phase was dried over anhydrous $MgSO_4$ and the volatiles were removed in vacuo. The residue was chromatographed (dry column) on 60 g of silica gel. Elution with ether afforded 438 mg of the crude dienols which were rechromatographed on 90 g of silica gel. Elution with chloroform (ca. 0.8 mL/min) afforded 126 mg (30%) of **24,** mp (ether) 106.5–108 °C, and 79 mg (19%) of **25.**

For **24** (R_f 0.61, 9:1 chloroform–ethanol): λ_{max} ($CHCl_3$) 2.8, 5.60, 5.70 μ; δ($CDCl_3$) (250 MHz) 2.07 (br s, 1), 2.51 (s, 2), 3.49 (s, 3), 3.88 (s, 3), 4.46 (ddt, J_1 = 3.9, J_2 = 3.8, J_3 = 1.0 Hz, 1), 5.71 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, 1), 6.02 (ddd, J_1 = 9.9, J_2 = 2.2, J_3 = 1.0 Hz, 1), 6.18 (ddd, J_1 = 9.9, J_2 = 3.8, J_3 = 1.5 Hz, 1), 6.25 (ddd, J_1 = 9.9, J_2 = 3.9, J_3 = 1.5 Hz, 1) ppm.

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.80; H, 5.52.

For **25** (R_f 0.53, 9:1 chloroform–ethanol): λ_{max} ($CHCl_3$) 2.70, 5.60, 5.68 μ; δ($CDCl_3$) (250 MHz) 1.80 (br s, 1), 2.53 (d, J = 14.2 Hz, 1), 2.56 (d, J = 14.2 Hz, 1), 3.48 (s, 3), 3.88 (s, 3), 4.71 (ddt, J_1 = 3.0, J_2 = 2.7, J_3 = 1.9 Hz, 1), 5.64 (dt, J_1 = 9.9, J_2 = 1.9 Hz, 1), 5.97 (dt, J_1 = 9.9, J_2 = 1.9 Hz, 1), 6.09 (ddd, J_1 = 9.9, J_2 = 2.7, J_3 = 1.9 Hz, 1), 6.17 (ddd, J_1 = 9.9, J_2 = 3.0, J_3 = 1.9 Hz, 1) ppm.

Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.76; H, 5.64.

Preparation of Disodium Prephenate (1a). To a solution of dienol **24** (100 mg, 0.394 mmol) in 0.5 mL of methanol was added 0.433 mL of 2 N aqueous sodium hydroxide (0.866 mmol of hydroxide). The solution was stirred at room temperature for 24 h. The volatiles were evaporated in vacuo. The residue was triturated with 2 mL of methanol which was cooled to 0 °C. Disodium prephenate (77.2 mg) was obtained by filtration.

The filtrate was evaporated to dryness and the residue was triturated with 1 mL of methanol. An additional 7.2 mg of **1** was obtained by filtration. Again the filtrate was evaporated to dryness. The residue was triturated with 2 mL of ethanol. There was thus obtained an additional 17.5 mg of disodium prephenate, this fraction as a pale yellow powder. The infrared spectra (KBr) of each crop were identical with one another and were identical with that of disodium prephenate obtained as described in the next experiment. Combined yield was 102 mg (96%): λ_{max} (KBr) 5.92, 6.17, 6.45, 6.96 μ; δ(D_2O) (250 MHz) 4.50 (tt, J_1 = 3.1, J_2 = 1.4 Hz), 5.92 (dd, J_1 = 10.4, J_2 = 3.1 Hz, 2), 6.01 (dd, J_1 = 10.4, J_2 = 1.4 Hz) ppm. The OH and $CH_2C(O)$ hydrogens of the disodium salt are rapidly exchanged in D_2O.

Conversion of Barium Prephenate to Disodium Prephenate. A suspension of 66.5 mg of barium prephenate (Sigma Chemicals, 90% assay) in 4 mL of water was stirred at room temperature for 10 min. To the resulting clear solution was added 3 g of Dowex 50W-X8 (Na^+ form) resin and the system was stirred at room temperature for 26 h. The resin was separated by filtration and washed with 2 mL of water. The combined filtrates were concentrated in vacuo and the residue was dried to yield 42 mg (99%) of disodium prephenate as a colorless powder. The infrared and NMR spectra were identical with those of the synthetic disodium prephenate.

Preparation of Disodium Epiprephenate (26a). The oily dienol **25** (38.7 mg) was hydrolyzed in the same way as described for **24.** There was thus obtained 23 mg (55%) of pure disodium epiprephenate (**26a**): λ_{max} (KBr) 5.90, 6.10, 6.45 μ; δ 4.55 (tt, J_1 = 3.1, J_2 = 1.5 Hz, 1), 5.89 (dd, J_1 = 10.3, J_2 = 3.1 Hz, 2), 5.99 (dd, J_1 = 10.3, J_2 = 1.5 Hz, 2) ppm.

Anal. Calcd for $C_{10}H_8O_6Na_2{\cdot}2H_2O$: C, 39.23; H, 3.95. Found: C, 39.72; H, 3.21.

Conversion of Barium Prephenate to *p*-Hydroxyphenyllactic Acid (28). A solution of 31.5 mg of barium prephenate and 2 mL of 2 N aqueous sodium hydroxide was heated for 20 min at 100 °C. After acidification with 2 N aqueous HCl, the system was extracted with ethyl acetate. The organic extracts were dried over sodium sulfate. Evaporation of the volatiles in vacuo afforded 14.7 mg of **28** (98%): mp 147.5–149 °C (lit.[17] 143–145 °C); $\delta((CD_3)_2C{=}O)$ 2.78 (dd, J_1 = 14, J_2 = 7 Hz, 1), 3.04 (dd, J_1 = 14, J_2 = 5 Hz, 1), 4.29 (dd, J_1 = 7, J_2 = 5 Hz, 1), 6.69 (d, J = 8 Hz, 2), 7.04 (d, J = 8 Hz, 2) ppm.

Conversion of Barium Prephenate to 3,3-Dideuterio-*p*-hydroxyphenyllactic Acid (31a). Barium prephenate (18.3 mg) was treated with 0.5 mL of 2 N NaOD in D_2O for 70 min. NMR analysis showed the solution to contain dideuterioprephenate **30a.** This solution was heated to 100 °C for 20 min. Workup as above afforded 7.9 mg of **31a:** $\delta((CD_3)_2CO)$ 4.29 (br s, 1), 6.69 (d, J = 8 Hz, 1), 7.04 (d, J = 8 Hz, 1) ppm.

Conversion of Disodium Epiprephenate (26a) to Phenylpyruvic Acid (29). A solution of the dienol **25** (9.4 mg) and 0.046 mL of 2 N aqueous sodium hydroxide in 0.1 mL of methanol was stirred at room temperature for 14 h. The volatiles were removed in vacuo. To the residual salt **27** was added 1.5 mL of 2 N aqueous sodium hydroxide. The solution was heated at 100 °C for 20 min. Acidification with 2 N aqueous HCl and extraction with ethyl acetate afforded 6.0 mg (99%) of **29,** mp 148–152 °C (lit.[18] 150–154 °C).

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Supplementary Material Available: Tables of fractional coordinates, structure factors, and bond distances and angles (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) (a) University of Pittsburgh. (b) Cornell University.
(2) (a) Haslam, E. "The Shikimate Pathway"; Halsted Press, Wiley: New York, 1974. (b) Ganem, B. *Tetrahedron*, **1978**, *34*, 3353. (c) Weiss, U.; Gilvarg, C.; Mingioli, E. S.; Davis, B. S. *Science* **1954**, *119*, 774.
(3) For a review of the field see: Plieninger, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 367.
(4) Gilvarg, C. "A Symposium on Amino Acid Metabolism", McElroy, W. D., Glass, H. B., Eds.; Johns Hopkins Press: Baltimore, Md., 1955; pp 812–814.
(5) Plieninger, H.; Keilich, G. *Chem. Ber.* **1959**, *92*, 2897.
(6) Plieninger, H.; Arnold, L.; Fischer, R.; Hoffmann, W. *Chem. Ber.* **1965**, *98*, 1774.
(7) (a) Danishefsky, S.; Singh, R. K.; Harayama, T. *J. Am. Chem. Soc.* **1977**, *99*, 5810. (b) Danishefsky, S.; Harayama, T.; Singh, R. K. *ibid.* **1979**, *101*, 7008.
(8) (a) Isidor, J. L.; Carlson, R. M. *J. Org. Chem.* **1973**, *38*, 554. (b) Corey, E. J.; Ruden, R. A. *Ibid.* **1973**, *38*, 834. (c) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 3775. (d) Corey, E. J.; Trybulski, E. J.; Suggs, J. W. *Ibid.* **1976**, 4577.
(9) For a preliminary communication of the synthetic work see: Danishefsky, S.; Hirama, M. *J. Am. Chem. Soc.* **1977**, *99*, 7740.
(10) For a preliminary account of these studies see: Danishefsky, S.; Hirama, M. *Tetrahedron Lett.* **1977**, 4565.
(11) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197.
(12) Crude barium prephenate could be obtained from the Sigma Chemical Co., St. Louis, Mo. 63178.
(13) For an alternative route to the ethyl ether–ethyl ester version of **22** see: Gramlich, W.; Plieninger, H. *Tetrahedron Lett.* **1978**, 475.
(14) All crystallographic calculations were done on a Prime 400 computer operated by the Materials Science Center and the Department of Chemistry, Cornell University. The principal programs used were REDUCE and UNIQUE, data reduction programs, Leonowicz, M. E., Cornell University, 1978; BLS, block-diagonal least-squares refinement, Hirotsu, K., Cornell University, 1978; ORFLS (modified), full-matrix least squares, Busing, W. R.; Martin, K. O.; Levy, H. S., Oak Ridge, ORNL-TM-305; ORTEP, crystallographic illustration program, Johnson, C., Oak Ridge, ORNL-3794; BOND, structural

parameters and errors, Hirotsu, K., Cornell University, 1978; MULTAN-76, direct methods and fast Fourier transform, Germain, G.; Main, P.; Woolfson, M., University of York.
(15) Quoted as a personal communication from U. Weiss to H. Plieninger; see ref 3, footnote 13.
(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.
(17) Matsuura, T.; Cahnmann, H. J. *J. Am. Chem. Soc.* **1959**, *81*, 871.
(18) Herbst, R. M.; Shemin, D. "Organic Syntheses", Collect. Vol. II; Wiley: New York, 1943; p 519.

A Stereospecific Synthesis of Griseofulvin

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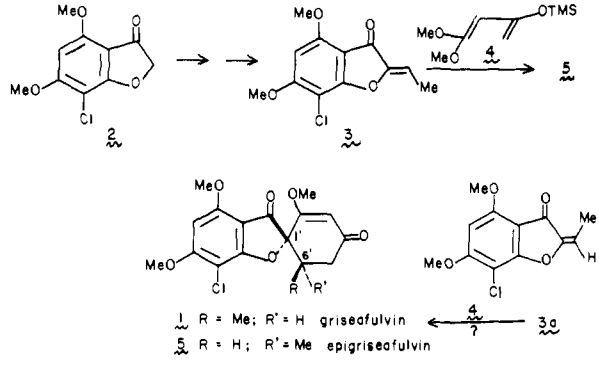
Abstract: A total synthesis of griseofulvin has been achieved. The key step involved is a Diels–Alder cycloaddition between 1,1-dimethoxy-3-trimethylsilyloxy-1,3-butadiene (**4**) and 7-chloro-4,6-dimethoxy-2-(1-phenylsulfinylethylidene)-3(2*H*)-benzofuranone (**20**) to afford *dl*-5′,6′-dehydrogriseofulvin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

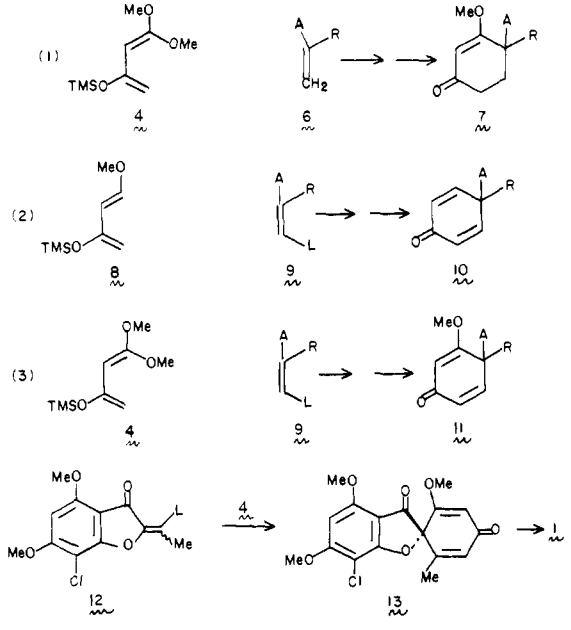
Unfortunately, in our hands, the crossed aldol condensation between coumaranone **2** and acetaldehyde afforded, after dehydration, the *Z* isomer, **3**.[1] Cycloaddition of **3** with **4** gave, in good yield, *dl*-epigriseofulvin (**5**).[5]



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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