aqueous EtOH as described earlier was added an equimolar amount of α-bromo ketone (10) in H_2O–THF. The resultant homogeneous solution was stirred at room temperature for 2 hr and the precipitated product collected by filtration and washed with AcONa in H_2O–EtOH, H_2O, and EtOH: yield 1.1 g (65%); mp 219–221°; nmr (1 *M* Na_2CO_3 in D_2O) 3.51 ppm; λ_{max} nm (ε × 10^3) (0.01 *N* NaOH) 262 (sh, 22.5), 272 (24.0), 335 (6.1). *Anal.* ($C_{15}H_{16}N_6O_2S$) C, H, N.

4-*N*-(*p*-Carboxyphenyl)amino-2-butanone (8). A solution of methyl vinyl ketone (7 g, 0.1 mol) and *p*-aminobenzoic acid (15 g, 0.1 mol) in EtOH (200 ml) was heated under reflux for 17 hr. The mixture was filtered through charcoal when hot. Crystalline product was precipitated on standing at room temperature. After collection of a first crop by filtration, the filtrate was concentrated to give an additional crop: total yield 8.2 g (41%); mp 191–192°. *Anal.* ($C_{11}H_{13}NO_3$) C, H, N.

1-Bromo-4-*N*-(*p*-carboxyphenyl)amino-2-butanone (10). Upon addition of Br_2 (2.4 g) in AcOH (5 ml) to a heterogeneous mixture of 8 (6.0 g, 0.03 mol) in 30% HBr in AcOH (23 ml) with stirring at room temperature, the solution became homogenous. Within a few minutes a solid product began to precipitate. Stirring was continued for an additional 1 hr and Et_2O (400 ml) was added. The solid product was collected by filtration, suspended in H_2O, and stirred at room temperature for 10 min. The product was collected by filtration and washed with EtOH and Et_2O, respectively, to give 3.6 g (42%) of the desired α-bromo ketone, mp 137–139°. *Anal.* ($C_{11}H_{12}BrNO_3 \cdot 0.5H_2O$) C, H, N.

Microbiological Assay. Antibacterial activity of pyrimido[4,5-*b*][1,4]-7-hydrothiazines was determined using the *Streptococcus faecalis* system of Kisliuk.[16]

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Total Synthesis and Resolution of Terreic Acid

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Terreic acid, an antibiotic metabolite of the mold *Aspergillus terreus*, was isolated by Abraham and Florey[1a,†] in 1949. Although the antibiotic showed *in vitro* activity against gram-positive and gram-negative bacteria and fungi, *in vivo* tests were unpromising.[2] In 1958, the structure of the antibiotic was determined to be 6-epoxy-3-hydroxytoluquinone (4) by work in this laboratory.[3] The synthesis of (±)-terreic acid was reported by Rashid and Read in 1967;[4] in this note an alternative route of synthesis and the resolution of the racemic terreic acid are presented.

†The discovery that *Aspergillus terreus* produces an antibiotic substance was made by Wilkins and Harris.[1b]

Table I

	$[\alpha]^{22}D$, deg (*c*, $CHCl_3$)	Mp, °C
Natural (−)-terreic acid	−16.6 (1)[a] −26.1 (10.4)[b]	127–127.5
Synthetic (−)-terreic acid	−24.9 (1.8)	124.5–125
Synthetic (+)-terreic acid	26.5 (0.5)	124.5–125

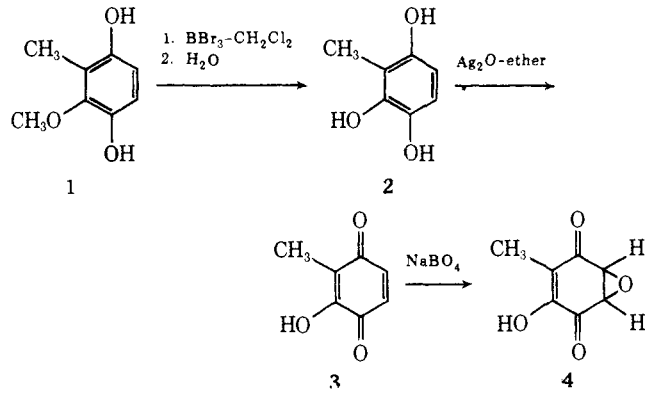
[a]Taken from ref 3. [b]Determined on a sample of natural (−)-terreic acid kindly supplied by Bristol Laboratories, Syracuse, N. Y.

Table II. Biological Activities of Terreic Acids

	Activity, %
Natural (−)-terreic acid	100
(−)-Terreic acid	90
(+)-Terreic acid	97
(±)-Terreic acid	125

The synthetic route is outlined in Scheme I. Preparation of 2-methyl-3-methoxy-1,4-hydrobenzoquinone (1) from *o*-toluidine was accomplished according to the method of Winzor.[5] The product was demethylated with boron tribromide to give a syrup (2) which was oxidized directly to 2-methyl-3-hydroxy-1,4-benzoquinone (3) by silver oxide.

Scheme I



2-Methyl-3-hydroxy-1,4-benzoquinone (3) was also the intermediate in Rashid and Read's synthesis[4] and their method was used for the formation of the epoxide 4. The spectral data for compounds 3 and 4 closely correlated with those of Rashid and Read[4] for (±)-terreic acid and those of Sheehan and coworkers[3] for naturally occurring (−)-terreic acid; however, the melting points differ somewhat.

Resolution of the (±)-terreic acid into (+) and (−) antipodes was achieved with (+)- and (−)-ephedrine,‡ respectively. The results are shown in Table I. The optical rotation of terreic acid is sensitive to solvent[3] which could explain the rotation reported in the literature. The rotations and melting points for (+)- and (−)-4 are self-consistent.

Bioassays of the racemic and resolved terreic acids gave interesting results. All samples were tested against *Staph-*

‡We thank Drs. Hiroshi Kotake, Tomoo Saito, and Kazuo Okubu who generously provided us with the *d*-ephedrine hydrochloride ([α]D + 34° (H_2O)) used in the resolution.

ylococcus aureus using natural (−)-terreic acid of 1000 μg/mg activity as a standard. The unnatural isomer, (+)-terreic acid, was as active as the (−)-terreic acid used as a standard (Table II). The synthetic (−) isomer was slightly less active than the natural compound, which could be due to decomposition. There is only one other report of the unnatural isomer of an antibiotic possessing biological activity.[6] Cycloserine has been found to be active against *E. coli* B in the D (natural) and L forms; the racemate is more active than either isomer alone. The racemic form of terreic acid is more active than either optical antipode alone, suggesting some form of synergistic behavior.

Experimental Section

General. Melting points were determined on a Fisher-Johns hot-stage melting point apparatus. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., or by Mrs. Nancy Alvord at MIT. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nuclear magnetic resonance spectra were obtained on a Varian T-60 using tetramethylsilane as an internal standard. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6. Optical rotations were measured at 546 and 578 nm on a Zeiss photoelectric precision polarimeter, and the values at 589 nm (sodium D line) were obtained by using the equations§

$$X = \alpha_{578}/(\alpha_{546} - \alpha_{578})$$

$$\alpha_D = X(\alpha_{546})/(X + 1.37)$$

Thin-layer chromatography was performed on Baker-flex silica gel 1B or 1B-F.

2-Methyl-3-methoxy-1,4-hydrobenzoquinone (1). The compound is available from *o*-toluidine by a five-step reaction sequence according to Winzor.[5] The following data were obtained: mp 118–119° (lit.[5] 117–118°); ir ($CHCl_3$) 3575, 3520, 3400–3300, 1480, 1075 cm^{-1}; nmr ($DCCl_3$) δ 6.74 (d, J = 9 Hz, 1 H), 6.48 (d, J = 9 Hz, 1 H), 4.65 (br, 2 H), 3.70 (s, 3 H), 2.20 ppm (s, 3 H); mass spectrum m/e 154 (100), 152 (46), 139 (78.7), 122 (18.7), 111 (33.7), 18 (31.3); metastable peaks at m/e 88 and 125.

2-Methyl-3-hydroxy-1,4-benzoquinone (3). Cold boron tribromide (1 ml, 15.25 mmol) was added by pipet to a suspension of 2-methyl-3-methoxy-1,4-hydrobenzoquinone (1, 1 g, 6.50 mmol) in methylene chloride (15 ml) at −80°. The resulting mixture was kept cold for 0.5 hr and then stirred overnight at room temperature. Complete solution was achieved by the end of the reaction. The excess boron tribromide and the solvent were removed at reduced pressure to give the boric acid ester as a glass. It was hydrolyzed by water (10 ml) for 1 hr at 0° and the resulting mixture extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, treated with activated charcoal, filtered, and evaporated to give 0.63 g of a brown syrup: R_f 0.47 (1:1 C_6H_6–EtOAc); ir (film) 3490, 3400–2500, 1495, 1250–1220, 1070 cm^{-1}; nmr (acetone-d_6) δ 6.68 (d, J = 9 Hz, 1 H), 6.36 (d, J = 9 Hz, 1 H), 3.30 (br, 3 H), 2.10 ppm (br, methyl proton signal mixed with acetone-d_6 peaks). This compound was used without further purification.

Silver oxide was prepared immediately before use according to Cason.[8]

2,3,6-Trihydroxytoluene (2, 0.63 g, 4.50 mmol) dissolved in anhydrous ether (50 ml) was added quickly to a suspension of silver oxide (about 10 g) and anhydrous sodium sulfate (5 g) in anhydrous ether (100 ml). The reaction mixture was swirled for 15 min and filtered. The solid was washed with portions of anhydrous ether. Evaporation of the ether solution at reduced pressure gave a brown-yellow solid which was purified by sublimation to give orange crystals: 0.57 g (64% from 1); mp 115–120° dec (lit. 134–135°,[4] 110–134° dec);[9] ir (CCl_4) 3400, 1665, 1650, 1070 cm^{-1}; nmr ($DCCl_3$) δ 6.93 (s, 1 H), 6.70 (s, 2 H), 1.95 ppm (s, 3 H). The spectroscopic data agree with that recorded in the literature.[4]

(±)-Terreic Acid (4). 2-Methyl-3-hydroxy-1,4-benzoquinone (3, 0.57 g, 4.13 mmol) in 95% ethanol (90 ml) was treated with a solution of sodium perborate[4] (3.20 g, 39.50 mmol) in water (250 ml). After standing for 18 min at room temperature, 1 N acetic acid (15 ml) was added to stop the reaction. The solution was extracted with benzene and the extract dried over anhydrous magnesium sulfate. The solvent was removed at reduced pressure leaving a pale yellow solid which was purified by sublimation to give pale yellow crystals: 101.7 mg (16%); mp 131.5–132° (lit.[4] 124–125°); ir (KBr) 3250, 1690, 1655, 1625, 1375, 1345, 1300, 1190 cm^{-1}; nmr ($DCCl_3$) δ 7.11 (s, 1 H), 4.06 (s, 2 H), 2.11 ppm (s, 3 H). Spectroscopic data for comparison are available in the literature.[3,4] *Anal.* Calcd for $C_7H_6O_3$ (138): C, 54.50; H, 3.90. Found: C, 54.65; H, 3.89.

Resolution of (±)-Terreic Acid (4) with (+)- and (−)-Ephedrine. (±)-Terreic acid (0.40 g, 2.94 mmol) was mixed with *l*-ephedrine (0.47 g, 2.85 mmol) in anhydrous ethyl ether (410 ml) and cooled in an acetone–Dry Ice bath. The deposited solid was redissolved in excess anhydrous ethyl ether. Partial evaporation of the solvent to the saturation point was carried out at reduced pressure. The saturated solution was cooled in the cold bath again. The salt was deposited in this manner ten times. Hydrochloric acid (1 N) was added to recover the resolved terreic acid from the last crop of deposited salt. The acidic solution was extracted with benzene and the extract was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave crude terreic acid which was then purified by sublimation to give 67 mg (17%) of pale yellow crystals. The terreic acid recovered from the salt formed with *l*-ephedrine was the (+) enantiomer: $[\alpha]^{25}D$ +26.5° (*c* 0.5, $CHCl_3$); mp 124.5–125°. The (−)-terreic acid could be obtained from the salt formed with *d*-ephedrine by the same method: $[\alpha]^{25}D$ −24.9° (*c* 1.8, $CHCl_3$); mp 124.5–125°. The authentic terreic acid had $[\alpha]^{25}D$ −26.1° (*c* 10.4, $CHCl_3$); mp 127–127.5°.

§Instruction Manual G50-381/I-e for the Zeiss photoelectric polarimeter. The equation is the first approximation of Drude's formula[7] for normal rotatory dispersion and includes an apparatus constant.

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Synthesis of 2,4-Diamino-5-[4-arylthiophenyl]- and 5-[4-Arylsulfonylphenyl]pyrimidines as Antimalarials

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The value of 2,4-diaminopyrimidine antifols such as pyrimethamine[1,2] and trimethoprim[3] as antiparasitic agents has long been recognized.[4,5] Recently, a wide variety of 2,4-diaminoquinazoline antifols which are generally related by structure and mode of action to the 2,4-diaminopyrimidines has been reported to be potent antimalarials.[6-11] The exceptional activity observed for the 6-arylthio- and 6-arylsulfonyl-2,4-diaminoquinazolines[11] led us to prepare a limited series of 5-[4-arylthiophenyl]- and 5-[4-arylsulfonylphenyl]-2,4-diaminopyrimidines for evaluation as potential antimalarials.

Chemistry. The synthesis of the title compounds was achieved by an approach analogous to the reported synthesis of pyrimethamine.[1,2] The synthesis (Scheme I) begins with an arylthiotoluene (I) and the first step involves simple monobromination of the methyl group followed by bromide displacement with cyanide to form the arylthio-