land). Compound **1b** was prepared from **3b** as described by us previously (ref 1b, experiment 3, Tables I and II) and had $[\alpha]_D$ −160° ($CHCl_3$); >97% pure by glc. Compound **2b** was prepared according to a literature procedure.[14] (−)-Cannabidiol (**3a**) and **3b** were prepared by the wet *p*-toluenesulfonic acid method.[1b]

(±)-6aβ,7,8,10aβ-Tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b,d*]pyran-1-ol (4a) and (±)-6aβ,7,8,10aβ-Tetrahydro-6,6,9-trimethyl-1-pentyl-6*H*-dibenzo[*b,d*]pyran-3-ol (4b). To 1.8 g (0.01 mol) of olivetol and 1.5 g (0.01 mol) of citral in 50 ml of benzene was slowly added 20 ml of 0.5 *N* HCl in ethanol with vigorous stirring. After 1 hr the reaction mixture was neutralized with 1 *N* NaOH. Ether was added to the mixture and the organic phase, after separation, was washed with 1 *N* NaOH, water, and brine. After drying the solution was concentrated to give 3 g of an orange oil. Chromatography on Florisil and gradient elution with ether–petroleum ether (30–40°) mixtures gave 0.3 g (10%) of **4a**[11] and 0.64 g (20%) of **4b** as a resin: nmr (CCl_4) δ 0.90 (3 H, t, ω-CH_3), 1.27 (6 H, s, *gem*-dimethyl), 1.63 (3 H, s, vinylic CH_3), 3.43 [1 H, br, C(10a)-H], 5.60 (1 H, br, vinylic), 5.80 (1 H, br, D_2O exchangeable), 6.17, 6.03 (2 H, 2 d, J = 2 Hz, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 314 (100), 299 (90), 271 (75), 258 (55), and 231 (80). *Anal.* ($C_{21}H_{30}O_2$) C, H.

Pharmacology. The compounds were tested in selected neuropharmacological test procedures using male albino CD-1 mice (18–22 g). The drug was administered intravenously (iv) or intraperitoneally (ip) as a solution in 0.06 ml of polyethylene glycol 400 per 25-g mouse. Various doses of the compounds were given iv to at least six mice per dose to determine approximate LD_{50}. Similarly, MED's were determined for ataxia and sensitivity to touch ("popcorn") which are characteristic of THC's.[2] The spontaneous activity and the mouse hot-plate data were obtained (ip route) according to the procedure described previously.[15] The ED_{50} values and 95% confidence limits were determined[16] using data obtained from three groups of six mice each. The anticonvulsant activity of these compounds was determined using the antimetrazole procedure.[17] Mice were premedicated with the drug or the vehicle alone and after 30 min were challenged with a dose of metrazole (33 mg/kg iv). The number of animals which convulsed in each group was counted. The vehicle was inactive in this test.

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A Stereoselective Synthetic Route to (*R*)-Zearalanone

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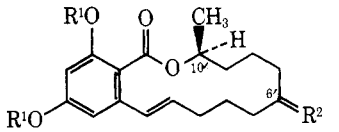
(*R*)-Zearalanone (**11**) was prepared stereoselectively from the naturally occurring (*S*)-zearalenone. (*R*)-Zearalanone (**11**) had no mouse uterotropic activity, but it did have a synergistic effect on the activity of (*S*)-zearalanone.

In studying the biological activities of zearalenone and several of its derivatives,[1-3] it became desirable to determine the effect of absolute configuration on uterotropic activity. Since the configuration at C-10′ in naturally occurring zearalenone had been determined as *S* by Kuo, *et al.*,[4] a synthetic sequence was developed to invert this center to the *R* configuration.

Starting with (*S*)-zearalenone (**1**), the phenolic functions and the carbonyl group at C-6′ were protected during the course of inverting the C-10′ position. This was accomplished by converting the phenolic groups into their respective benzyl ethers (**1** → **2**), followed by ketalization of the C-6′ carbonyl function using ethylene glycol to give **3** in high yield.

With the carbonyl group protected in **3**, the 14-membered lactone could then be opened without racemization of the C-10′ position.[5] This was accomplished by treatment of **3** with 40% sodium hydroxide in dimethyl sulfoxide at 120° to give **4**. Hydroxy acid **4** was then converted to its methyl ester **5** with diazomethane.

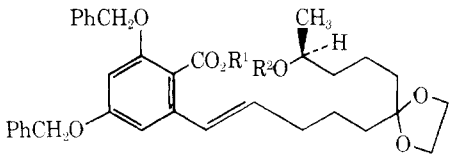


1, R^1 = H; R^2 = O
2, R^1 = $PhCH_2$; R^2 = O
3, R^1 = $PhCH_2$; R^2 = OCH_2CH_2O

Toluenesulfonic ester **6** was prepared from the reaction of hydroxy ester **5** with *p*-toluenesulfonyl chloride in pyridine. Inversion of the C-10′ position was accomplished by reaction of **6** with tetraethylammonium acetate in refluxing methyl ethyl ketone to give **7**. The conversion of **7** to **8**

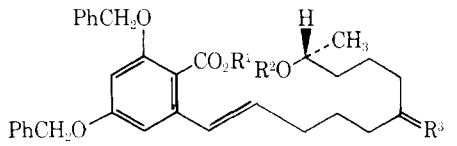
Table I. Uterotropic Activity in Mice

Test compd	Total dose, μg	Final body wt, g	Uterine wt, mg	% body wt
Control		26.1	11.3	0.043
(*R*)-Zearalanone (**11**)	150	26.5	9.8	0.037
	300	26.4	11.6	0.044
	900	26.5	9.6	0.036
(*S*)-Zearalanone	150	26.2	28.1	0.107
	300	26.0	34.5	0.133
	900	27.2	50.7	0.187
(*R*)-Zearalanone/ (*S*)-zearalanone (1:1 mixture)	150	23.5	25.5	0.108
	300	22.9	34.3	0.149
	900	24.0	53.6	0.223



4, $R^1 = R^2 = H$
5, $R^1 = CH_3$; $R^2 = H$
6, $R^1 = CH_3$; $R^2 = p\text{-}CH_3C_6H_4SO_2$

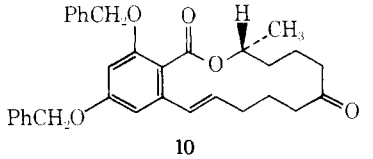
proved to be difficult. Ordinary methods of saponification (*e.g.*, K_2CO_3/H_2O–MeOH) resulted in hydrolysis of only the acetate group, and it was necessary to employ the conditions used in opening the macrolide ring (40% NaOH–DMSO) to hydrolyze the methyl ester group in **7**.



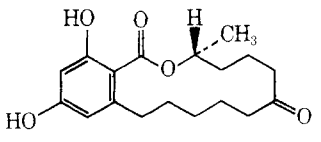
7, $R^1 = CH_3$; $R^2 = CH_3C{=}O$; $R^3 = OCH_2CH_2O$
8, $R^1 = R^2 = H$; $R^3 = OCH_2CH_2O$
9, $R^1 = R^2 = H$; $R^3 = O$

The ketal moiety of **8** was hydrolyzed in aqueous tetrahydrofuran using perchloric acid as a catalyst to yield **9**. Hydroxy acid **9** was then cyclized using trifluoroacetic anhydride in benzene[5] to give **10**. Catalytic reduction and hydrogenolysis of **10** over 5% Pd/C in methanol gave (*R*)-zearalanone (**11**): mp 190–191°; $[\alpha]^{25}D$ (MeOH) +36.8°.

The mouse uterotropic activity data are summarized in Table I. (*R*)-Zearalanone (**11**) showed no activity, but a 1:1 mixture of (*R*)-zearalanone and (*S*)-zearalanone gave approximately the same response as (*S*)-zearalanone. This result agrees with the findings of Hurd and Shah,[6] *i.e.*, synthetic (*R,S*)-zearalanone had about the same uterotropic activity as (*S*)-zearalanone. This suggests that (*R*)-zearalanone has a synergistic effect on the uterotropic activity of (*S*)-zearalanone.



10



11

Experimental Section

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed in our laboratories. Spectra were recorded on the following instruments: uv, Bausch & Lomb Spectronic 505; ir, Perkin-Elmer Model 21 spectrophotometer; optical activity, O. C. Rudolph and Sons Model 80 polarimeter; nmr, Varian Associates A-60A spectrometer ($CDCl_3$ as the solvent and TMS as the internal standard). All the ir (**2**–**11**), uv (**11**), and nmr (**2**–**11**) spectra taken were consistent with the assigned structures.

2-[10(*S*)-Hydroxy-6-oxo-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid μ-Lactone (2). (*S*)-Zearalenone (**1**, 100 g, 0.32 mol) was dissolved in 500 ml of DMSO, benzyl chloride (110 g, 0.87 mol) and anhydrous K_2CO_3 (160 g, 1.16 mol) were added, and the mixture was heated for 7 hr on a steam bath. The mixture was cooled to room temperature, diluted with H_2O, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed several times with H_2O and dried over Na_2SO_4 and the $CHCl_3$ removed to give 194 g of residue. Crystallization twice from *i*-PrOH gave 138 g (88%) of **2** as white crystals, mp 128.5–129.5°. *Anal.* ($C_{32}H_{34}O_5$) C, H.

2-[10(*S*)-Hydroxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid μ-Lactone (3). A mixture of **2** (200 g, 0.40 mol), 400 ml of ethylene glycol, *p*-toluenesulfonic acid (2.0 g), and 3.5 l. of toluene was slowly distilled to remove the water formed in the reaction. After 45 hr, the reaction mixture gave a negative Zimmermann test for α-methylene ketones. The mixture was cooled, diluted with Et_2O, washed successively with H_2O, 5% NaOH, H_2O, saturated NaCl, and dried over Na_2SO_4, and the solvents were removed to give 218 g of residue. Chromatography of the crude product on 1 kg of Florisil using 2% MeOH–C_6H_6 gave 213 g (98%) of **3** as a colorless glass.

2-[10(*S*)-Hydroxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid (4). To a solution of **3** (37 g, 68 mmol) in 400 ml of DMSO was added 100 ml of 40% NaOH (aqueous), and the resulting solution was heated at 120° for 5 hr under N_2. The solution (red) was cooled, poured into ice H_2O, acidified with 10% H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed several times with H_2O and dried over Na_2SO_4 and the $CHCl_3$ removed to give 31 g of cream-colored solid. Recrystallization from C_6H_{14}–C_6H_6 gave 25 g (72%) of **4** as a white amorphous solid, mp 104–106°. *Anal.* ($C_{34}H_{40}O_7$) C, H.

Methyl 2-[10(*S*)-Hydroxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoate (5). To a suspension of **4** (48 g, 86 mmol) in 300 ml of C_6H_6 was added an excess of freshly prepared diazomethane (from *N*-methylnitrosourea) in 250 ml of Et_2O. After addition was complete, the solution (light yellow) was stirred for 15 min, excess diazomethane was destroyed by addition of acetic acid, and the solvents were removed to give 48.8 g of light yellow oil. Chromatography on 1250 g of SilicAR, CC-7, using $CHCl_3$ gave 41 g (84%) of **5** as a colorless oil. *Anal.* ($C_{35}H_{42}O_7$) C, H.

Methyl 2-[10(*S*)-Tosyloxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoate (6). A solution of **5** (32 g, 56 mmol) in 400 ml of anhydrous pyridine was cooled to 5°, and freshly recrystallized *p*-toluenesulfonyl chloride (12.4 g, 65 mmol) was added in several portions. The reaction mixture was stirred for 44 hr at 5°, then diluted with ice water, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, 5% HCl, and 5% $NaHCO_3$ and dried over Na_2SO_4–K_2CO_3. Removal of the chloroform at room temperature gave 36 g (89%) of crude **6**.

Methyl 2-[10(*R*)-Acetoxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoate (7). Toluenesulfonic ester **6** (36 g, 49.5 mmol) and tetraethylammonium acetate tetrahydrate (36 g, 138 mmol) were dissolved in 700 ml of methyl ethyl ketone and refluxed for 46 hr. The mixture was cooled and the solvent removed. The residue was dissolved in $CHCl_3$, washed several times with H_2O, and dried over Na_2SO_4, and the $CHCl_3$ was removed to give 26.1 g of dark brown oil. Chromatography on 1 kg of SilicAR, CC-7, using $CHCl_3$ gave 10.2 g (35%) of **7** as a light yellow oil. *Anal.* ($C_{37}H_{44}O_8$) C, H.

The remainder of the chromatography fractions contained olefinic and hydroxylic material which were the result of elimination and substitution (with water) side reactions.

2-[10(*R*)-Hydroxy-6-ethylenedioxy-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid (8). A solution of **7** (38 g, 62 mmol) in 400 ml of DMSO was heated to 120°, and 100 ml of 40% NaOH was added under N_2. The mixture was heated at 120° for 5 hr, cooled to room temperature, and diluted with H_2O. The diluted mixture was washed twice with Et_2O (discarded), then acidified

with 30% H_2SO_4, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Removal of the $CHCl_3$ gave 36 g of brown oil which was partially purified by dissolving in MeOH and treating with charcoal. Concentration gave a light yellow residue. Crystallization from C_6H_{14}–C_6H_6 gave 21 g (61%) of **8**, mp 104–106°. *Anal.* ($C_{34}H_{40}O_7$) C, H.

2-[10(*R*)-Hydroxy-6-oxo-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid (9). To a solution of **8** (20 g, 35.7 mmol) in 150 ml of THF was added, with cooling, 100 ml of 2.2 *N* $HClO_4$ and the mixture was stirred at room temperature for 6 hr. The mixture was poured into H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O and saturated NaCl and dried over Na_2SO_4. Removal of the solvents gave 17.8 g (96%) of crude **9** as an oil. Crystallization of a small portion from C_6H_{14}–C_6H_6 gave pure **9** as a white amorphous solid, mp 82–84°.

2-[10(*R*)-Hydroxy-6-oxo-*trans*-1-undecenyl]-4,6-bis(benzyloxy)benzoic Acid μ-Lactone (10). A solution of **9** (10 g, 19.4 mmol) in anhydrous C_6H_6 was cooled to 5°, trifluoroacetic anhydride (4.2 g, 20 mmol) was slowly added over a 30-min period under N_2, and the mixture was stirred at 5° for 24 hr. The reaction mixture was washed with 5% KOH (aqueous), H_2O, and saturated NaCl and dried over Na_2SO_4. Removal of the C_6H_6 gave 6.3 g of brown residue which was recrystallized several times from *i*-PrOH to give 1.8 g (19%) of pure **10** as white crystals, mp 128.5–129.5°. *Anal.* ($C_{32}H_{34}O_5$) C, H.

(*R*)-Zearalanone (11). A portion of **10** (1.0 g, 2 mmol) was dissolved in 140 ml of EtOH–EtOAc (2.5:1) and hydrogenated under atmospheric pressure and room temperature with 5% Pd/C (0.3 g). Filtration of the catalyst and removal of the solvents gave 0.60 g (94%) of white solid. Recrystallization from MeOH gave pure (*R*)-zearalanone (**11**) as white crystals: mp 190–191°; $[\alpha]^{25}D$ (MeOH) +36.8°. (The physical properties of (*S*)-zearalanone are mp 190–191°; $[\alpha]^{25}D$ (MeOH) −34°.) *Anal.* ($C_{18}H_{24}O_5$) C, H.

Uterotropic Assay. Samples were administered orally (in sesame oil) to ten adult castrate female mice for 3 days at levels of 50, 100, and 300 μg/mouse/day. On day 4 the animals were sacrificed, and the uteri were removed and weighed.

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Synthesis and Biological Properties of 17α-Furylestradiol and Dihydroequilin Derivatives

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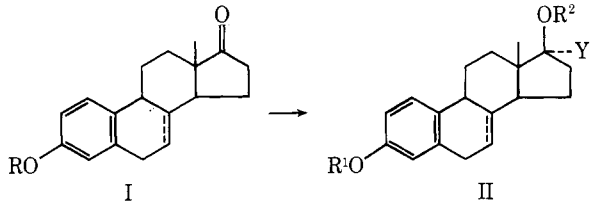
A series of 17α-furylestradiol and dihydroequilin derivatives was synthesized by reacting the appropriate 3-substituted estrone and equilin with 2- or 3-furyllithium. The oral estrogenic activity of the compounds was compared with that of mestranol. In the Allen–Doisy test, the 17α-(3-furyl) analogs were 4–19 times as potent orally as the standard in rats but they were less active in mice. Acetylation of the 17-alcohol or replacement of the 3-furyl by a 2-furyl group produced a decrease in activity. In the mouse uterotrophic assay in mice the compounds were less effective than mestranol and exhibited very shallow dose–response curves.

As part of an extensive program concerning the oxidation of furans,[1,2] a series of 17α-(3-furyl)estradiol and dihydroequilin derivatives was synthesized. As evidenced by the detailed pharmacology of estrofurate[3] [17α-(3-furyl)-estra-1,3,5(10),7-tetraene-3,17-diol 3-acetate, compound **13**], these constitute a new class of potent oral estrogens with a profile of activity in animals different from the one exhibited by mestranol. This paper deals with the synthesis and biological properties of these compounds as well as those of the related 17α-(2-furyl) and 17α-(3-tetrahydrofuryl) analogs.



I II

R = CH_3, cyclopentyl, and tetrahydropyranyl
R^1 = H, CH_3, cyclopentyl, and acetyl
R^2 = H and acetyl
Y = 2-furyl, 3-furyl, and 3-tetrahydrofuryl

Chemistry. The 17α-(3-furyl)-17-hydroxy and 17α-(2-furyl)-17-hydroxy moieties in II were introduced conventionally by reacting the appropriate estrone and equilin derivatives I with 3- and 2-furyllithium. The phenolic alcohols were usually protected as tetrahydropyranyl ethers prior to the reaction and removal of the protecting group could be achieved under mildly acidic conditions without concomitant dehydration.

Acetylation of the 3-phenols was accomplished with acetic anhydride and pyridine at room temperature. In order to acetylate the 17-alcohol, more drastic conditions were required such as heating the pyridine–acetic anhydride solution at 100° for 24 hr. The compounds prepared are listed in Table I.

Biology. 1. Methods. The oral estrogenicity of the compounds was determined in two standard assays.

(a) Allen–Doisy test[4a] with a slight modification.[4b] Cornification of the vaginal epithelial cells in ovariectomized rats or mice was the end point of the experiment. The results are expressed as the dose necessary to induce cornification in 50% of the animals (ED_{50}). The ED_{50} was calculated by using an average of 40 (20–100) animals per compound. Dose–response curves were used to determine the ED_{50} graphically.[5] There were at least four dose levels for the determination of the ED_{50} for each compound.

(b) Uterotrophic assay in immature intact mice.[6] This test was done at a minimum of five doses for each compound. Five to ten animals were used at each dose level. The results are expressed as the minimum effective dose