Compounds obtained from methods 1 and 2 were identical in ir and NMR spectra. Anal. ($C_{11}H_9NO_2$) C, H, N.

6,7-Bis(bromomethyl)quinoline-5,8-dione (5). 6,7-Dimethylquinoline-5,8-dione (10a, 0.27 g, 1.4 mmol), *N*-bromosuccinimide (0.43 g, 2.8 mmol), and catalytic amounts of benzoyl peroxide were refluxed in 25 ml of CCl_4 overnight. The mixture was filtered and the filtrate was evaporated to dryness. The yellow oily residue was crystallized from ethyl acetate and petroleum ether to give yellow microcrystals (150 mg, 30%), mp 127–129°. Anal. ($C_{11}H_7NO_2Br$) C, H, N, Br.

1′,4′-Dihydroxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (12). To a molten mixture of anhydrous $AlCl_3$ (300 g) and sodium chloride (100 g) at 180° was added, in small portions with stirring, a mixture of 2,3-dimethylhydroquinone (22 g, 0.16 mol) and glutaric acid (21 g, 0.16 mol); the temperature was not allowed to exceed 195°. The mixture was cooled and decomposed with water (1 l.) and concentrated HCl (500 ml), and the precipitate which formed was collected. Recrystallization from ethanol gave 20 g (53%) of yellow crystals, mp 82–83°. Anal. ($C_{13}H_{14}O_4$) C, H.

1′,4′-Dimethoxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (13). Ketone 12 (5 g, 0.02 mol), anhydrous potassium carbonate (6.5 g, 0.04 mol), and dimethyl sulfate (8 g, 0.06 mol) were refluxed in 50 ml of dry acetone for 8 hr. The mixture was filtered and the filtrate was evaporated to dryness. The oily residue was crystallized from ethyl acetate and ligroine to give colorless crystals (3.2 g, 61%), mp 79–81°. Anal. ($C_{15}H_{18}O_4$) C, H.

2,3-Dibromo-1,2,3,4-tetrahydro-5,8-dimethoxy-6,7-dimethyl-2,3-methylene-1,4-dioxonaphthalene (15a). Bromine (6.4 g, 0.04 mol) in 5 ml of AcOH was added slowly with stirring to benzocycloheptenedione 13 (2.62 g, 0.01 mol) in AcOH (30 ml). Stirring was continued overnight at room temperature. The yellow tetrabromo precipitate 14 was collected, washed with AcOH followed by EtOH, and dried (3.5 g). The tetrabromo derivative was dissolved in 20 ml of warm pyridine and was allowed to stand at room temperature overnight. The resulting brown suspension was added to 100 ml of diluted HBr. The precipitate which formed was collected and dissolved in 60 ml of EtOAc, filtered, and evaporated to dryness. The gummy residue was purified by column chromatography (silica gel) using as eluent EtOAc and ligroine (1:5, v/v). Recrystallization from ethanol gave pale yellow crystals (0.6 g, 14%): mp 165–166°; NMR ($CDCl_3$) δ 2.25 (s, 6), 2.33 (d, J = 4 Hz, 1), 2.70 (d, J = 4 Hz, 1), and 3.82 (s, 6); ir (KBr) 1690 cm^{-1} (–C=O). Anal. ($C_{15}H_{14}Br_2O_4$) C, H, Br.

3-Bromo-2-bromomethyl-6,7-dimethylnaphthazarin (6a). Compound 15a (0.7 g) in 20 ml of glacial AcOH which contained 3 ml of concentrated HBr was boiled for 10 min. The resulting brown mixture was poured into ice H_2O. The precipitate was collected, dried, and recrystallized from EtOAc and ligroine to give brown crystals (0.2 g, 30%), mp 205° dec. Anal. ($C_{13}H_{10}Br_2O_4$) C, H, Br.

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Studies in Antifertility Agents. 8. Seco Steroids. 2. 5,6-Secoestradiol and Some Related Compounds

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Three-ring β-secoestradiols, 2α,3β- and 2β,3β-2-ethyl-3-(*p*-hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ols, have been synthesized and some of them shown to possess significant antiimplantation activity in rats.

The relationship between estrogenic, antiestrogenic, and antifertility activity, in particular postcoital antifertility activity, has been the subject of considerable discussion.[1] A critical estrogen–progesterone balance is necessary for implantation of the blastocyst and its subsequent development, and any alteration in this balance may lead to termination of pregnancy. Compounds which are able to alter the estrogen–progesterone ratio level in the uterine milieu possess the inherent possibility of acting as postcoital antifertility agents. Thus, while estrogens are at one phase or another essential in the normal process of mating and early pregnancy, they prevent conception at practically all stages in most mammalian species. In our search for new postcoital antifertility agents secoestrones seemed of potential interest, as these could either mimic, compete with, and dis-

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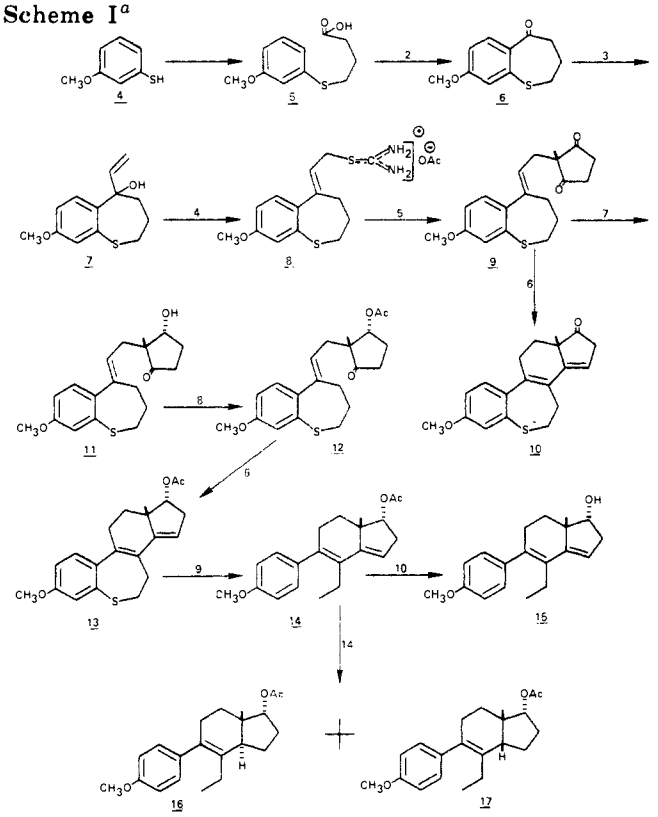
place estrogens from their possible receptors in the uterus.[2,3] The synthesis and biological evaluation of three of the four possible isomers of 2-ethyl-3-(*p*-hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ols (**26**, **27**, and **28**), which are ring B secoestradiols, are reported in this communication.

Scheme I[a]



[a]Steps: 1, γ-butyrolactone, Na; 2, PPA; 3, CH_2=$CHMgBr$; 4, $(NH_2)_2CS$, AcOH; 5, 2-methylcyclopentane-1,3-dione, KOH; 6, TsOH; 7, $LiAl(OBu^t)_3H$; 8, Ac_2O, Py; 9, Raney nickel, H_2; 10, Na_2CO_3.

Chemistry. The synthesis of 5,6-seco steroids was first investigated through thia-*B*-homo steroid intermediates. *m*-Methoxythiophenol, prepared from *m*-methoxyphenol by the method of Newman,[4] via its thiocarbamate, on condensation with γ-butyrolactone followed by PPA cyclization gave the thiapinone **6**. The vinylcarbinol **7**, obtained from **6** by condensation with vinylmagnesium bromide, when condensed as such, or better through its isothiouronium salt **8**, with 2-methylcyclopentane-1,3-dione gave the diketone **9**. Treatment of **9** with TsOH in benzene gave the required thia-*B*-homo steroid ketone **10** but in rather poor yield. The diketone **9** was, therefore, first selectively reduced with $LiA(OBu^t)_3H$ to give the hydroxy ketone **11** as the α isomer (vide infra) (NMR: br s, 1, C*H*OH). Its *O*-acetyl derivative **12** on treatment with TsOH in benzene gave a moderately good yield of the *O*-acetylthiapinol **13**, which on desulfurization by treatment with Raney nickel followed by hydrolysis gave the dienol **15**. The uv spectra of **13** and **14** showed λ max at 270 and 257 nm, respectively. This relatively low value for λ max for such a conjugated diene system is very likely due to the two double bonds in **13** and **14** not being in the same plane as the benzene ring; the higher λ max for the tetracyclic compound **13** could be due to its conformational rigidity which enables some degree of coplanarity of the double bonds with the aromatic system (see Scheme I).

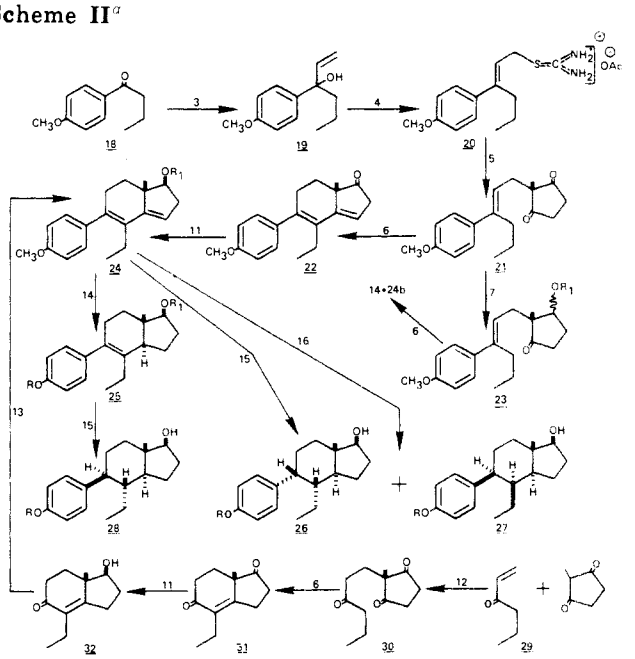
Catalytic hydrogenation of the α-acetoxy compound **14** using Pd/C until 1 mol of H_2 was absorbed gave a mixture of 1α,- and 1β, 7α-acetoxy-2-ethyl-6β-methyl-3-(*p*-methoxyphenyl)bicyclo[4.3.0]non-2-enes (**16** and **17**). The presence of 6β,7α substituents in **14** does not offer any selectivity of approach to the catalyst which would explain the formation of a mixture of 1α and 1β isomers in this reduction.

In view of the poor yield, the unstable character of the thiapinone **10**, and the lack of stereoselectivity in the reduction of the dienol acetate **14**, alternative methods for the preparation of the dienone **22** were investigated.

p-Methoxybutyrophenone (**18**), on condensation with vinylmagnesium bromide, gave the vinylcarbinol **19**, which was converted to the diketone **21** by treatment with 2-methylcyclopentane-1,3-dione. Cyclization of the diketone **21** TsOH in benzene gave the dienone **22**, which on $NaBH_4$ reduction gave the dienol **24a**. The latter was acetylated with Py and Ac_2O to the corresponding *O*-acetyl compound **24b**, which proved to be different from the dienol **15** and its *O*-acetyl derivative **14**, obtained by the thiapinone route. Since **24a** would have a 7β-hydroxyl group, the isomer **14** could be assigned 7α stereochemistry. $LiAl(OBu^t)_3H$ reduction of the diketone **21** resulted in the hydroxy ketone **23a**, which when acetylated to the 7-*O*-acetyl compound **23b** followed by chromatographic separation gave the acetoxy compounds **14** and **24b** as the major and minor products, respectively. Stereochemical assignment was based on NMR; 7-H appeared as a doublet and triplet in **14** and **24b**, respectively.

A more convenient approach to the dienol **24a** involved the condensation of 2-ethyl-6β-methyl-7β-hydroxybicyclo[4.3.0]non-1-en-3-one (**32**) with *p*-methoxyphenyllithium essentially according to the procedure of Boyce and Whitehurst.[5] The keto enol **32** was prepared by the condensation of propyl vinyl ketone with 2-methylcyclopentane-1,3-dione, followed by TsOH cyclization in benzene, and $NaBH_4$ reduction (see Scheme II).

Scheme II[a]



a, R_1 = H; **b**, R_1 = Ac; **c**, R = R_1 = H; **d**, R = CH_3, R_1 = H; **e**, R = CH_3, R_1 = Ac; **f**, R = CH_3; **g**, R = H

[a]Steps: 11, $NaBH_4$; 12, KOH; 13, *p*-$OMeC_6H_4MgBr$; 14, 10% Pd/C, 1 mol of H_2O; 15, K-NH_3; 16, 10% Pd/C, 2 mol of H_2O.

Controlled catalytic hydrogenation of the dienol **24a** in ethanol over Pd/C until 1 mol of H_2 was absorbed gave the corresponding trans-fused enol **25d**. The stereospecificity of hydrogenation can be explained by the fact that both 6-

Table I. Antiimplantation and Estrogenic Activity in Rats

Compd no.	Antiimplantation act., mg/kg	Estrogenic activity: Dose, mg/rat × 5 days	Uterine wt, mg	Vaginal cornifications[a]	Vaginal opening
Controls (distilled water)	All pregnant	Distilled water	15	0	Closed
28g	5	0.33	77	+++	Open
25c	10				
27g	20	1	50	++	Open
26g	10	1	73	+++	Open
Estrone		10 μg	65	+++	Open

[a] 0 = no cornified cell; ++ = about 75%.cornified cells; +++ = 100% cornified cells.

methyl and 7-hydroxy groups are β-oriented and would thus hinder the β-face approach to the catalyst. Such effects in controlling the stereospecificity of reduction have been reported for hydrindan and decalone systems.[6] The styryl double bond of 1α-enol **25d** was reduced with K in liquid NH_3 to yield **28**. Its stereochemistry has been assigned on the basis of the well-established mechanism of metal–ammonia reduction and by analogy with the intermediates in estrone synthesis. The position of the NMR signal at 52 Hz for the 6-CH_3 in **25d** (shown to be 54 Hz for the corresponding 1α isomer lacking the 2-ethyl group)[2] supported the stereochemistry assigned to **25d**.

Catalytic hydrogenation of **25d** or **24a** in ethanol over Pd/C yielded a mixture of two products, obviously isomers having cis–anti–trans (**26f**) and cis–syn–trans (**27f**) stereochemistry in a ratio of 40:60, which could be separated by fractional crystallization. In the NMR spectrum the isomer formed in larger proportion, **27f**, showed a highly shielded CH_3CH_2 resonance. This isomer has been assigned the cis–syn–trans stereochemistry on the basis that 1,3-steric interaction between the 6β-CH_3 and 2β-ethyl groups would force the ethyl group within the shielding cone of the phenyl group. The fact that the **27f** isomer is formed in relatively larger proportion would be due to less steric hindrance for the hydrogenation from the α face of the molecule.

The dienol **24a** on K–NH_3 reduction gave only one product which proved to be identical with **26f**, earlier obtained by catalytic hydrogenation of dienol **24a**. This would obviously be due to 1,4-hydrogen addition, followed by reduction of the $\Delta^{1(2)}$ isomer, and would explain the obtained stereochemical results.

The hydroxymethyl ethers **26f**, **27f**, and **28f** on demethylation with KOH in diethylene glycol gave the desired corresponding phenols **26g**, **27g**, and **28g**.

Antifertility Activity. Antiimplantation activity of these compounds was studied in female albino rats mated to coeval males of proven fertility as described earlier.[7] The compounds were suspended in gum acacia and administered orally to colony bred adult mated female rats (150–170 g) on days 1–7 postcoitum. The results were scored as positive only if implantations were totally absent in both uterine horns.

Estrogenic Activity. The estrogenic activity was evaluated by the immature ovariectomized rat (25–35 g) uterine weight and vaginal cornification period. The compounds were administered orally as above and assessed for their estrogenic activity.[7]

The results described in Table I show that some of the compounds have significant antiimplantation and estrogenic activity (cf. ref 1 and 7); compound **28g** which resembles estrone most closely appears to be the most active compound of this group. However, the surprising feature is the estrogenic activity of **26g** which has a cis stereochemistry corresponding to the 8,9 cis-steroid junction, suggesting that disposition of the aromatic ring with respect to rings C/D is not critical for binding to the estrogenic receptor.

Experimental Section

Melting points were taken in a sulfuric acid bath and are uncorrected. The uv spectra were measured with a Perkin-Elmer 202 spectrophotometer and ir on Infracord 337. The NMR spectra were carried out on a Varian A-60D spectrometer using Me_4Si as internal standard. The NMR spectra were taken in CCl_4, unless otherwise stated, and the values are given in hertz units. All the compounds were routinely checked for their structure by ir and NMR spectrometry, and data are presented only for compounds with some special features.

***O-m*-Methoxyphenyl Dimethylthiocarbamate (2).** NaH (25.18 g, 1.05 mol) was added in small portions to a cold and stirred solution of *m*-methoxyphenol (I, 130.2 g, 1.05 mol) in DMF (750 ml). After hydrogen evolution ceased the solution was maintained at 10° and dimethylthiocarbamoyl chloride (175 g, 1.40 mol) was added to it all at once, when the temperature rose to 30°. The reaction mixture was stirred for 1 hr at 50–60°, an excess of 1% KOH solution added, the mixture extracted with a mixture of benzene and petroleum ether, and the organic phase washed successively with NaCl, 5% KOH solution, and saturated NaCl solution, dried (Na_2SO_4), and concentrated. The residue was distilled to give 166 g (74.9%) of **2**: bp 160–162° (4 × 10^{-2} mm). Anal. ($C_{10}H_{13}O_2NS$) C, H, N.

***S-m*-Methoxyphenyl Dimethylthiocarbamate (3).** *O-m*-Methoxyphenyl dimethylthiocarbamate (**2**, 166 g, 0.79 mol) was heated to 280° for 45 min. The reaction product was then distilled to give 140.4 g (84.6%) of **3**: bp 162–164° (3 × 10^{-2} mm). Anal. ($C_{10}H_{13}O_2NS$) C, H, N.

***m*-Methoxythiophenol (4).** A mixture of the *S*-aryl compound **3** (136.3 g, 0.65 mol), MeOH (700 ml), and NaOH solution (10%, 450 ml) was refluxed for 10–12 hr under N_2 atmosphere. The solution was concentrated under reduced pressure, acidified with HCl, saturated with NaCl, and extracted with benzene. The benzene layer was washed with water, dried (Na_2SO_4), and concentrated. The residual oil was distilled to give 70 g (77.4%) of **4**: bp 79° (2 × 10^{-2} mm).

γ-(*m*-Methoxyphenyl)mercaptobutyric Acid (5). γ-Butyrolactone (44.7 g, 0.52 mol) was added in one lot to a solution of the Na salt of *m*-methoxythiophenol, prepared from Na (12.5, 0.54 g-atom), absolute EtOH (200 ml), and the thiophenol **4** (70 g, 0.5 mol). The reaction mixture was refluxed for 4 hr and then EtOH distilled off. The resultant waxy mass was dissolved in water, dried (Na_2SO_4), and concentrated. Distillation of the residue gave 76.6 g (67.8%) of acid **5**: bp 165–167° (10^{-2} mm); crystallized from ether–petroleum ether, mp 46–48°. Anal. ($C_{11}H_{14}O_3S$) C, H.

8-Methoxy-5-oxo-2,3,4-5-tetrahydrobenzo[*b*]thiepin (6). Polyphosphoric acid (1600 g) was heated on a water bath and the mercaptobutyric acid **5** (76.6 g, 0.34 mol) added to it in small lots in 30 min. The reaction mixture was heated for a further 15 min with constant shaking; the hot syrup was poured onto crushed ice and extracted with ether. The ether solution was washed succes-

sively with water, 10% $NaHCO_3$ solution, and water, dried (Na_2SO_4), and concentrated. The residue on distillation gave 58.3 g (82.7%) of ketone **6**: bp 147–149° (10^{-2} mm). Anal. ($C_{11}H_{12}O_2S$) C, H.

5-Hydroxy-5-vinyl-8-methoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepin (7). The ketone **6** (32.0 g, 0.15 mol) in a mixture of dry THF (60 ml) and ether (200 ml) was added in 0.5–1 hr to a stirred solution of vinylmagnesium bromide (prepared from 13.52 g, 0.56 g-atom, of Mg, 60 ml of vinyl bromide) at −10°. Stirring was continued for 3 hr below −10° and the mixture allowed to stand overnight at room temperature. It was then refluxed for another 2 hr, cooled, and poured onto a mixture of crushed ice and NH_4Cl. The organic layer was separated, the aqueous phase extracted with ether, the combined ether layer washed with small portions of water, dried (Na_2SO_4), and concentrated, and the residue was distilled to give 31.7 g (87.3%) of **7**: bp 152–153° (5×10^{-3} mm). Anal. ($C_{17}H_{16}O_2S$) C, H.

8-Methoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepinylindeneethylisothiouronium Acetate (8). A mixture of the vinylcarbinol **7** (11.8 g, 0.05 mol), thiourea (3.8 g, 0.05 mol), and AcOH (50 ml) was stirred at 25° for 4 hr. The reaction mixture was diluted with ether (300 ml) and cooled to below 15°. The precipitated isothiouronium salt was filtered and washed with a little cold ether to give 13 g (73.4%) of **8**: mp 165–166°. Anal. ($C_{16}H_{22}O_3N_2S_2$) C, H.

2-(8-Methoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepinylindeneethyl)-2-methylcyclopentane-1,3-dione (9). (A) From Vinylcarbinol 7. A mixture of **7** (31.7 g, 0.13 mol), 2-methylcyclopentane-1,3-dione (19.58 g, 0.63 mol), and KOH (0.2 g) in 2-propanol (210 ml) was refluxed for 10–12 hr on a steam bath. The solvent was removed under reduced pressure, the residue was cooled and triturated with ether (100 ml), and the unreacted methylcyclopentanedione (9.1 g) was filtered and washed with ether and a little benzene. The combined filtrate was washed with $NaHCO_3$ (10%) and water, dried (Na_2SO_4), and concentrated, and the residue was crystallized from methanol: 22.5 g (50.2%); mp 99–100°. Anal. ($C_{19}H_{22}O_3S$) C, H.

(B) From the Isothiouronium Salt 8. A mixture of **8** (8.85 g, 25 mmol) and 2-methylcyclopentene-1,3-dione (5.61 g, 50 mmol) in aqueous EtOH (50 per cent, 225 ml) was stirred for 4 hr at room temperature. The reaction mixture was concentrated, cooled to room temperature, diluted with saturated NaCl solution, and extracted with ethyl acetate. The organic layer was washed with 10% $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), and concentrated and the residue crystallized from methanol: 6.25 g (76%); mp 98–99°.

3-Methoxy-*B*-homo-5a-thia-1,3,5(10),8,14-estrapentaen-17-one (10). A solution of the dione **9** (165 mg, 0.50 mmol) and TsOH (86 mg, 0.50 mmol) in benzene (30 ml) was refluxed using a Dean-Stark water separator for 30 min. The reaction mixture was cooled and filtered to remove the precipitated TsOH monohydrate, the benzene solution was washed with 5% $NaHCO_3$ and NaCl solution, dried (Na_2SO_4), and concentrated, and the residue was chromatographed on a silica gel (10 g) column using benzene–petroleum ether as eluent to give 38 mg (24.3%) of **10** as a light red-brown oil, which on keeping turned reddish violet. Anal. ($C_{19}H_{20}O_2S$) C, H.

1α-Hydroxy-2-(8-methoxy-2,4,5-tetrahydrobenzo[*b*]thiepinylindeneethyl)-2-methylcyclopentan-3-one (11). A solution of $LiAl(OBu^t)_3H$ (23.4 g, 92 mmol) in dry THF (800 ml) was added during 1 hr to a stirred solution of the dione **9** (24.8 g, 75 mmol) in THF (700 ml) at 0°. The reaction mixture was left stirring overnight at room temperature, then cooled to 0°, and this was added to a saturated solution of Na_2SO_4 (1 l.). The inorganic salts were filtered off, the cake was washed with benzene and ether, the mixed organic layer was washed with saturated NaCl solution and dried (Na_2SO_4), and solvent was removed. The residue was crystallized from MeOH to yield 17 g (68.1%) of **11**: mp 116–118°. Anal. ($C_{19}H_{24}O_3S$) C, H.

1α-Acetoxy-2-(8-methoxy-2,3,4,5-tetrahydrobenzo[*b*]thiepinylindeneethyl)-2-methylcyclopentan-3-one (12). A mixture of the hydroxy compound **11** (9.9 g, 29.8 mmol), Ac_2O (6 ml), and dry pyridine (24 ml) was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in ether, washed successively with dilute AcOH, water, 10% $NaHCO_3$, and water, and dried (Na_2SO_4), and the solvent was removed to give 10.5 g (97.7%) of **12** as an oil. Anal. ($C_{21}H_{26}O_4$) C, H.

3-Methoxy-*B*-homo-5a-thia-1,3,5(10),8,14-estrapentaen-17α-ol Acetate (13). The keto ester **12** (12.3 g, 32.8 mmol) was added to a suspension of TsOH (4.5 g, 26.2 mmol) in dry benzene (400 ml); the mixture was refluxed for 50 min through a Dean-Stark water separator and worked up as described in **10**. The crude product was purified by chromatography on silica gel (400 g) using benzene–petroleum ether as eluent to give 8.5 g (72.6%) of **13** as an oil. Anal. ($C_{21}H_{24}O_3S$) C, H.

7α-Acetoxy-2-ethyl-6β-methyl-3-(*p*-methoxyphenyl)bicyclo[4.3.0]nona-2,9-diene (14). A solution of the acetoxy compound **13** (10.8 g, 30.3 mmol) in dioxane (500 ml) was hydrogenated in the presence of Raney nickel at atmospheric pressure and at 60–65° until desulfurization was complete (monitored by TLC and uv), the catalyst was filtered off, and the solvent removed. Crystallization of the residue from MeOH gave 4.0 g (40.4%) of **14**: mp 90–92°; NMR 304 (d, 1, H-7, J = 5 Hz). Anal. ($C_{21}H_{26}O_3$) C, H.

2-Ethyl-6β-methyl-3-(*p*-methoxyphenyl)bicyclo[4.3.0]nona-2,9-dien-7α-ol (15). A mixture of the acetoxy compound **14** (3.2 g, 10.1 mmol), Na_2CO_3 (10 g), H_2O (15 ml), and MeOH (100 ml) was refluxed for 8 hr on a steam bath. The reaction mixture was filtered, the filtrate concentrated, and the residue diluted with water and extracted with ether. The ether solution was washed with water and dried (Na_2SO_4) and the solvent removed. The residue was crystallized from petroleum ether to yield 1.92 g (67.2%) of **15**: mp 96–98°. Anal. ($C_{19}H_{24}O_2$) C, H.

3-Hydroxy-3-(*p*-methoxyphenyl)-1-hexene (19). This was prepared from *p*-methoxybutyrophenone (26.7 g, 0.15 mol), Mg (10.5 g, 0.53 g-atom), and vinyl bromide (53 ml) as described for **7**: yield 29.1 g (94.1%); bp 101–103° (2×10^{-2} mm). Anal. ($C_{13}H_{18}O_2$) C, H.

***S*-[3-(*p*-Methoxyphenyl)-2-hexenyl]thiouronium Acetate (20).** It was obtained from the carbinol **19** (32.8 g, 0.16 mol) by treatment with thiourea (12.12 g, 0.16 mol) in AcOH (130 ml) as described for **8** and crystallized from benzene–petroleum ether: yield 38.6 g (74.9%); mp 151–153°. Anal. ($C_{16}H_{24}O_3N_2S$) C, H, N.

2-Methyl-2-[3-(*p*-methoxyphenyl)-2-hexenyl]cyclopentane-1,3-dione (21). (A) From the Vinylcarbinol 19. A mixture of the carbinol **19** (12.03 g, 58.3 mmol), 2-methylcyclopentane-1,3-dione (8.5 g, 76 mmol), and a trace of solid KOH in *i*-PrOH (75 ml) on heating gave 4.7 g (26.8%) of the dione **21**: bp 164–166° (2×10^{-3} mm). Anal. ($C_{19}H_{24}O_3$) C, H.

(B) From the Isothiouronium Salt 20. Treatment of the isothiouronium salt **20** (24.3 g, 75 mmol) with 2-methylcyclopentane-1,3-dione (16.8 g, 150 mmol) in aqueous EtOH as described for **9** gave **20**: yield 19.3 g (85.8%).

2-Ethyl-6β-methyl-3-(*p*-methoxyphenyl)bicyclo[4.3.0]nona-2,9-dien-7-one (22). The diketone **21** (13.05 g, 50.1 mmol) was cyclized by treatment with TsOH (6.45 g, 37.5 mmol) in dry benzene (700 ml) using a Dean-Stark water separator, when the dienone **22** was obtained. This was purified by chromatography on a silica gel (300 g) column using benzene–petroleum ether as eluent: obtained as an oil, 4.7 g (33.2%). Anal. ($C_{19}H_{22}O_2$) C, H.

2-Ethyl-6β-methyl-3-(*p*-methoxyphenyl)bicyclo[4.3.0]nona-2,9-dien-7β-ol (24a). $NaBH_4$ (2.4 g, 63.5 mol) was added to a solution of the dienone **22** (4.7 g, 16.64 mmol) in EtOH (325 ml) at −15° and the reaction mixture was stirred for another 1 hr at −15°. A few drops of AcOH were added to decompose unreacted $NaBH_4$; the solution was diluted with water and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and concentrated and the residue crystallized from ether–petroleum ether: 4.6 g (97.2%); mp 81–82°. Anal. ($C_{19}H_{24}O_2$) C, H.

In an alternative method the keto enol **32** (9.7 g, 0.05 mol) in ether (100 ml) was added to a solution of *p*-methoxyphenyllithium, prepared from butyllithium (14.4 g, 0.225 mol) and *p*-methoxybromobenzene (29.9 g, 0.16 mol), in ether (400 ml) at −30 to −40° under an oxygen-free nitrogen atmosphere. Sufficient THF was added to dissolve the separated complex. The reaction mixture was stirred at this temperature for 1 hr, the temperature was then allowed to come to 10° in about 1–1.5 hr, and the mixture was allowed to stand at this temperature overnight. The complex was decomposed by adding a saturated solution of NaCl (100 ml); the ether layer was separated, washed with saturated NaCl solution, and dried ($MgSO_4$). The solvent was removed and residual thick oil was distilled to give 11.1 g (73.55%) of **24a**, mp 83°.

1-Hydroxy-2-methyl-2-[3-(*p*-methoxyphenyl)-2-hexenyl]cyclopentan-3-one (23a). The diketone **21** (10 g, 33.3 mmol) in dry THF (250 ml) was reduced by treatment with $LiAl(OBu^t)_3H$ (10.2 g, 40.1 mmol) in THF (300 ml) as described for **11** to give 9.8 g (97.3%) of the hydroxy compound **23a** as an oil. Anal. ($C_{19}H_{26}O_3$) C, H.

1-Acetoxy-2-methyl-2-[3-(*p*-methoxyphenyl)-2-hexenyl]cyclopentan-3-one (23b). This was obtained by acetylation of the hydroxy compound **23a** (10.23 g, 33.8 mmol) with Ac_2O (5

ml) and pyridine (20 ml) as described for **12**: yield 10.8 g (92.7%); an oil. Anal. ($C_{21}H_{28}O_4$) C, H.

Cyclization of 1-Acetoxy-2-methyl-2-[3-(*p*-methoxyphenyl)-2-hexenyl]cyclopentan-3-one (14 and 24b). The acetoxy compound **23b** (3.6 g, 10.5 mmol) was cyclized by treatment with TsOH (1.35 g, 7.8 mmol) in dry benzene (150 ml) as described for **13**. The crude reaction product (3.42 g) was crystallized from EtOH to give 770 mg of the α-acetoxy compound **14**.

The mother liquor was concentrated under reduced pressure and the residue (2.5 g) was chromatographed on silica gel (100 g) using petroleum ether–benzene as eluent. From the earlier fractions, 200 mg of the β-acetoxy compound **24b** was obtained. The latter fractions gave a further 700 mg of α-acetoxy compound **14**. The overall yields of the α- and β-acetoxy epimers were 43.1 and 5.9%, respectively.

The β-acetoxy compound **24b** was also obtained by acetylation of the dienol **24a** (500 mg, 1.76 mmol) with Ac_2O (0.3 ml) and pyridine (1.2 ml) by the same procedure as described for **12**: yield 380 mg (66.2%); crystallized from MeOH, mp 94–96°; NMR 298 (t, 1, H-7, J = 8.5 Hz). Anal. ($C_{21}H_{26}O_3$) C, H.

2-Methyl-2-(3-oxohexyl)cyclopentane-1,3-dione (30). A mixture of 2-methylcyclopentane-1,3-dione (11.2 g, 0.1 mol), propyl vinyl ketone (**29**, 12.25 g, 0.125 mol), KOH (500 mg), and dry MeOH (80 ml) was refluxed for 5 hr. The solvent was removed under reduced pressure. The residue was taken up in $CHCl_3$, washed with water, dried (Na_2SO_4), and concentrated to give 16 g (76.1%) of **33** as an oil: ir (neat) 1730 cm^{-1} (C=O). The crude compound **30** was used directly for the next step without further purification.

2-Ethyl-6-methylbicyclo[4.3.0]non-1-ene-3,7-dione (31). A mixture of **30** (21 g, 0.1 mol), TsOH (1 g), and dry benzene (100 ml) was refluxed through a Dean-Stark water separator; after 3 hr an additional quantity of TsOH (1 g) was added. The required amount of water was collected in 5–6 hr. The reaction mixture was cooled and washed with water, the benzene layer was dried (Na_2SO_4) and concentrated and the residual oil was distilled to give 16.3 g (84.9%) of **31**: bp 125° (0.03 mm). Anal. ($C_{12}H_{16}O_2$) C, H.

2-Ethyl-7β-hydroxy-6β-methylbicyclo[4.3.0]non-1-en-3-one (32). A solution of $NaBH_4$ (1.02 g, 0.0268 mol) in *i*-PrOH (100 ml) and EtOH (100 ml) was added dropwise to a stirred solution of the diketone **31** (19.2 g, 0.1 mol) in EtOH (50 ml) kept at 0°. The reaction mixture was further stirred at this temperature for 0.5 hr and allowed to come to room temperature, and the stirring was continued at room temperature for another 45 min. A few drops of AcOH were then added to decompose excess of $NaBH_4$ and the solvent was removed under reduced pressure. The residual oil was taken up in $CHCl_3$, washed with water, dried ($MgSO_4$), and concentrated and the oil was distilled to give 17 g (87.6%) of **32**: bp 125° (0.006 mm). Anal. ($C_{12}H_{18}O_2$) C, H.

2-Ethyl-6β-methyl-3-(*p*-methoxyphenyl)-*trans*-bicyclo[4.3.0]non-2-en-7β-ol (25d). The dienol **24a** (2.2 g, 7.2 mmol) in EtOH (125 ml) was hydrogenated over 10% Pd/C (0.75 g) until 1 mol of H_2 had been absorbed. The catalyst was removed by filtration and the filtrate concentrated to give 2 g (96.9%) of the enol **25d** as an oil.

2-Ethyl-6β-methyl-3-(*p*-methoxyphenyl)-7β-acetoxy-*trans*-bicyclo[4.3.0]non-2-ene (25e). This was obtained by acetylation of the enol **25d** (500 mg, 1.75 mmol) with Ac_2O (0.3 ml) and pyridine (1.2 ml) as described for **12**: yield 400 mg (69.7%). Anal. ($C_{21}H_{28}O_3$) C, H.

2α-Ethyl-3β-(*p*-methoxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol (28f). K metal (4.5 g, 0.115 g-atom) was added to a solution of the enol **25d** (2.946 g, 10.28 mmol) in a mixture of dry dioxane (150 ml), dry ether (270 ml), and liquid NH_3 (450 ml) kept at −50°. After stirring for 2 hr, solid NH_4Cl was added to destroy excess of K and then NH_3 was allowed to evaporate. The residue was shaken with water (1.5 l.) and extracted with ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (100 g) using benzene as eluent to give 2.3 g (77.6%) of **28f** as an oil. Anal. ($C_{19}H_{28}O_2$) C, H.

2β-Ethyl-3β-(*p*-methoxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol and 2α-Ethyl-3α-(*p*-methoxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol (27f and 26f). (A) The dienol **24a** (2 g, 0.007 mol) in EtOH (100 ml) was hydrogenated at atmospheric temperature and pressure over 10% Pd/C (200 mg) until 2 mol of H_2 had been absorbed. The catalyst was removed by filtration, the filtrate concentrated, and the residue crystallized from ether–petroleum ether to give 1.1 g (54.24%) of **27f**: mp 109°; NMR 50 (s, 3, ang CH_3), 12 (t, 3, $-CH_2CH_3$). Anal. ($C_{19}H_{28}O_2$) C, H.

The filtrate after removal of **27f** was concentrated to give 0.7 g (34.5%) of **26f** as an oil: NMR 61 (s, 3, ang CH_3), 43 (t, 3, $-CH_2CH_3$). Anal. ($C_{19}H_{28}O_2$) C, H.

(B) In an alternate method isomer **26f** was prepared by K–liquid NH_3 reduction of the dienol **24a** as described for **28f**: yield 60%.

From the Enol 25a. The enol **25d** (2 g, 0.007 mol) in EtOH (100 ml) was hydrogenated at atmospheric temperature and pressure over 10% Pd/C (200 mg) until 1 mol of H_2 had been absorbed. The catalyst was removed by filtration and the solution was concentrated to give 1.1 g (54.24%) of **27f** and 0.7 g (34.5%) of **26f**.

2-Ethyl-6β-methyl-3-(*p*-hydroxyphenyl)-*trans*-bicyclo[4.3.0]non-2-en-7β-ol (25c). A mixture of the methoxy compound **25d** (800 mg, 2.79 mmol), KOH (7.5 g), and hydrazine hydrate (0.5 ml) in diethylene glycol (40 ml) was heated under N_2 atmosphere for 1.5 hr. The cooled solution was diluted with water and treated with sodium dithionite (1 g), and CO_2 was passed through the solution. The separated semisolid was extracted with ether, the ether layer washed with water, dried (Na_2SO_4), and concentrated, and the residue crystallized from benzene–petroleum ether to give 440 mg (57.8%) of **25c**: mp 198–200°. Anal. ($C_{18}H_{24}O_2$) C, H.

2α-Ethyl-3β-(*p*-hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol (28g). This was obtained by demethylation of **28f** (860 mg, 2.99 mmol) with KOH (8 g) in diethylene glycol (45 ml), as described for **25c**: yield 300 mg (36.7%); mp 154–156°. Anal. ($C_{18}H_{26}O_2$) C, H.

2α-Ethyl-3α-(*p*-hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol (26g). Demethylation of **26f** (860 mg, 2.99 mmol) with KOH (8 g) in diethylene glycol (45 ml) as in **25c** gave 480 mg of **26g** as an oil. Anal. ($C_{18}H_{26}O_2$) C, H.

2β,3β-(*p*-Hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ol (27g). This was obtained by demethylation of **27f** (860 mg, 2.99 mmol) with KOH (8 g) in diethylene glycol (45 ml) as described for **25c**: yield 500 mg; mp 170°. Anal. ($C_{18}H_{26}O_2$) C, H.

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