Rachlin for guidance and assistance. Particular thanks go to Mr. L. A. Dolan and members of the Kilo Laboratory, Hoffmann-La Roche Inc., Nutley, N.J., for the preparation of large quantities of intermediates, which helped to expedite this project. We are also obligated to the personnel of the Physical Chemisty Department, Hoffmann-La Roche Inc., Nutley, N.J., under the direction of Dr. P. Bommer, for carrying out many of the spectral, microanalytical, and polarimetric determinations required in this work. Finally, we wish to express our appreciation for the valuable technical assistance provided by Mr. F. Bizzarro and Mr. R. Vass.

Registry No.—**1a,** 734-32-7; **1b,** 21800-83-9; **2a,** 25112-78-1; **2b,** 34927-33-8; **3b,** 35544-89-9; **4a,** 17553-86-5; **4b,** 33878-95-4; **5a,** 16271-49-1; **5b,** 53016-43-6; **6a,** 41878-38-0; **6b,** 53078-16-3; **7a,** 31944-51-1; **7b,** 53702-05-9; **8a,** 53702-06-0; **8b,** 53662-91-2; **9a,** 53702-07-1; **9b,** 53052-91-8; **10a,** 53662-92-3; **11a,** 53662-93-4; **12,** 53662-94-5; **12** corresponding alcohol, 50302-16-4; **13,** 53662-95-6; **14,** 13505-34-5; **15,** 15580-05-9; **17,** 27428-41-7; **20a,** 24157-07-1; **20b,** 53662-96-7; **21b,** 53662-97-8; **22a,** 434-22-0; **22b,** 793-55-5; diketene, 674-82-8; formaldehyde, 50-00-0.

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(24) If the pH is greater than 7.5, dione **14** starts to be liberated.
(25) Assayed by uv analysis: analytically pure **17** shows uv max (0.1 *N* $NaOCH_3$) 273 nm (ε 12500).

Novel Total Syntheses of (+)-Estrone 3-Methyl Ether, (+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one, and (+)-Equilenin 3-Methyl Ether

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Conjugate addition of *m*-methoxybenzylmagnesium chloride to the optically active enones **1a** and **1b** in the presence of cuprous salts gives the key tricyclic ketones **2a** and **2b,** respectively, in good yields. Cyclization of the latter materials produces the 9,11-dehydro compounds **4a** and **4b** which can be converted into the target steroids **7a** and **7b** efficiently *via* the intermediates **5a,b** and **6a,b.** Treatment of **4a** with trifluoroacetic acid leads to disproportionation as well as *tert*-butyl ether cleavage and the formation of estrapentaene **8a** oxidation of which yields (+)-equilenin 3-methyl ether (**10a**). In contrast, exposure of **4a** to *p*-toluenesulfonic acid gives the mixture of estratetraenols **11a** and **12a.**

The homologous, optically active α-methylene ketones **1a** and **1b** are readily available intermediates of great utility in the total synthesis of 19-norsteroids[1] and androstanes.[2] In the previous work,[1,2] β-keto ester intermediates containing the carbon atoms destined to become rings A and B of the steroid nucleus were added in a Michael reaction to the enones **1.** It occurred to us that these unsaturated ketones should also be valuable for the production of estrone and related compounds[3] *via* a short and potentially efficient scheme involving, as the key transformation, conjugate addition of *m*-methoxybenzyl Grignard reagents or derived organocopper species[4] to the enone system producing the tricyclic ketones **2.** We have investigated this approach and report the results herein.

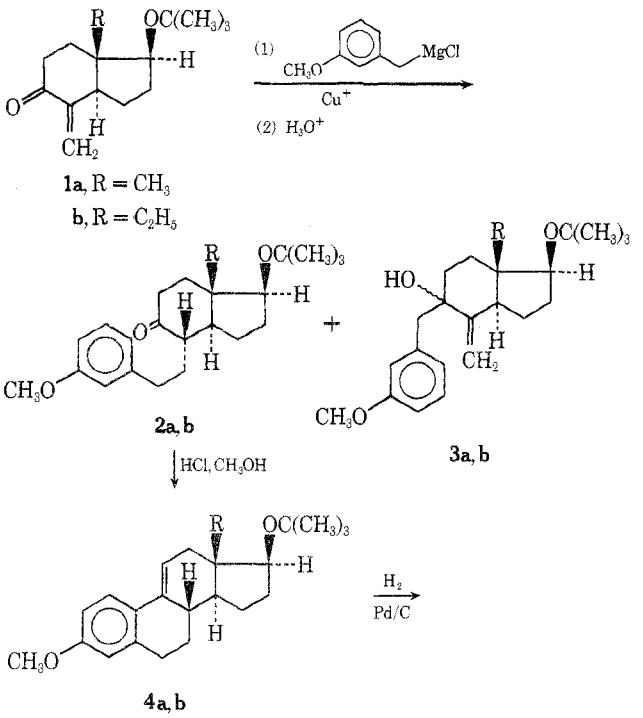
Results

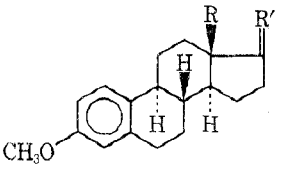
The reaction of *m*-methoxybenzylmagnesium chloride with enone **1a** was found to be regioselective, in the desired mode, when carried out in the presence of cuprous ion. Under these conditions, it was possible to obtain the 1,4 adduct **2a** in 80–90% yield after chromatographic purification, the 1,2 adduct **3a** being formed in only minor amounts. In

contrast, when this reaction was carried out in the absence of cuprous ion, only the 1,2 adduct was obtained.[5] Repetition of the copper-catalyzed procedure using the homologous enone **1b** yielded the adduct **2b** in over 60% yield.

The adducts **2a** and **2b** obtained were preponderantly the stable epimers shown having the equatorial arylethyl 4 substituent. In one experiment, a small amount of the 4-axial epimer of **2b** was isolated during chromatographic purification. Treatment of this material with methanolic sodium hydroxide readily and quantitatively converted it into the stable epimer.

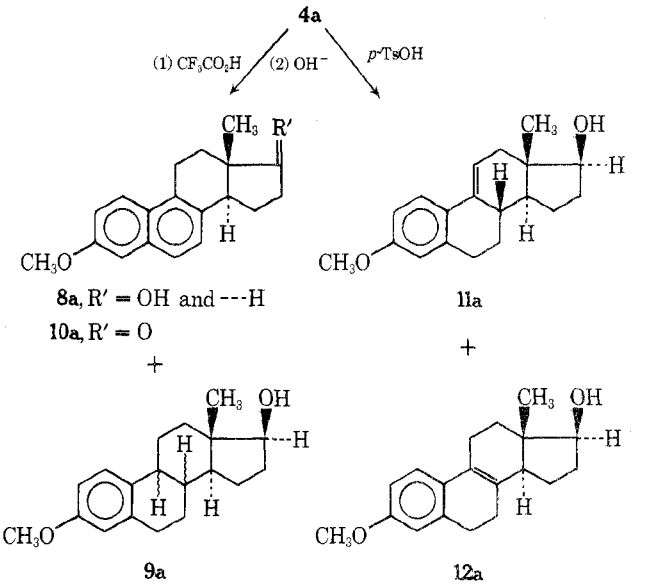
Cyclization of the tricyclic ketones **2a** and **2b** was effected at room temperature with methanolic hydrochloric acid[8] giving the crystalline tetraenes **4a** and **4b** in 77 and 85% yields, respectively. Under these conditions, essentially no cleavage of the *tert*-butyl ether moiety was observed.[9] Isolation of the intermediates **2** was unnecessary. Thus, for example, the crude product from addition of *m*-methoxybenzylmagnesium chloride to enone **1a** as described above could be directly cyclized affording pure **4a** in 71% overall yield.





Catalytic hydrogenation of **4a** over palladium on carbon was stereoselective and produced mainly the estratriene **5a** (54%[10]). Cleavage of the *tert*-butyl protecting group by treatment of **5a** with trifluoroacetic acid[9] then afforded estradiol 3-methyl ether (**6a**) which was directly oxidized[11] to estrone 3-methyl ether (**7a**). Repetition of this sequence without purification of **5a** allowed isolation of **7a** in 62% overall yield. In a similar manner, hydrogenation of **4b** gave the gonatriene **5b** (67%[10]) which was treated with *p*-toluenesulfonic acid[9] producing **6b**.[12,13] Oxidation of the latter material then yielded (+)-13β-ethyl-3-methoxygona-1,3,5(10)-trien-17-one (**7b**).[13,14] Since the chirality present in the starting enones **1** is introduced *via* a highly efficient asymmetric synthesis,[3f,15] the above scheme provides a direct route to optically active estranes and gonanes without the requirement of and disadvantages associated with classical resolutions[3c,12] or microbiological transformations.[13,14]

When cleavage of the *tert*-butyl ether in **4a** was carried out in trifluoroacetic acid at 0°,[9] disproportionation of the styrene system occurred concomitantly leading, after alkaline hydrolysis, to a product containing approximately equal parts (gc, uv analysis) of the estrapentaene **8a**[16] and a mixture of estratriene isomers **9a**.[17] Although separation of this mixture was preparatively difficult, column chromatography afforded a pure sample of **8a** which was shown to be identical with material produced from *d*-equilenin.[16] Oxidation[11] of the crude mixture of **8a** and **9a** gave *d*-(+)-equilenin 3-methyl ether (**10a**)[19,20] in low yield after purification using a combination of preparative thin layer chromatography and recrystallization. In contrast to the behavior of **4a** in trifluoroacetic acid, treatment of this substance with *p*-toluenesulfonic acid in refluxing benzene[9] allowed *tert*-butyl ether cleavage with essentially no disproportionation and produced a mixture consisting mainly of the estratetraenols **11a**[21] (major) and **12a**[12] (minor).



Experimental Section

Unless otherwise noted, work-up procedures involve three extractions with the specified solvent. Organic solutions were then combined, washed with brine, dried over anhydrous sodium or magnesium sulfate, filtered, and concentrated under water aspirator pressure at 40–50° on a rotary evaporator. The crude products were then dried under high vacuum to constant weight. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. All reactions except hydrogenations were carried out under an inert atmosphere of either argon or nitrogen. Column chromatography was performed using Merck (Darmstadt) silica gel, 0.063–0.2 mm. Thin layer chromatography was carried out using Merck (Darmstadt) silica gel 60 F-254 plates. Plates were developed with the following solvent systems: (a) 1:1 hexane–ether; (b) 19:1 hexane–ether; (c) 19:1 benzene–ethyl acetate; (d) 1:1 benzene–ethyl acetate. Spots were detected with uv light and phosphomolybdic acid spray followed by heating. Tetrahydrofuran (THF) was dried over molecular seives and slurried over Woelm grade I neutral alumina just prior to use. A 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche and Co., AG, Basle, Switzerland and designated AK-4 was employed for the hydrogenations. Varian A-60 and HA-100 or Jeolco C-60H spectrometers were used to obtain the pmr spectra ($CDCl_3$ solution). Chemical shifts are reported relative to TMS. Infrared spectra ($CHCl_3$

solution) were recorded on Beckman IR-9 or Perkin-Elmer 621 spectrophotometers. The uv spectra (95% ethanol solution) were recorded on a Cary model 14M spectrophotometer. Low-resolution mass spectra were obtained on CEC 21-110 or JMS-01SG instruments. Optical rotations were measured on a Perkin-Elmer Model 141 polarimeter and, unless otherwise noted, in 1% chloroform solutions. Gas chromatographic analyses were carried out on samples trimethylsilylated with Regisil (Regis Chem. Co.-BSTFA containing 1% TMCS) using a Becker 409 instrument. A 3 ft × 0.25 in. column of 10% OV 101 on GC-Q 100–120, at 250°, with a nitrogen carrier gas flow of 30 ml/min was employed.

(1*S*, 3a*R*, 4*S*, 7a*S*)-(+)-1-*tert*-Butoxy-4-[2-(3-methoxyphenyl)ethyl]-7a-methyl-3a,4,7,7a-tetrahydro-5(6*H*)-indanone (2a). A solution of 19.5 g (0.125 mol) of *m*-methoxybenzyl chloride[22] dissolved in 118 ml of anhydrous THF was added dropwise over 45 min to a stirred suspension of 6.25 g (0.25 mol) of magnesium turnings in 25 ml of anhydrous THF at reflux temperature. The mixture was then stirred for an additional 30 min under reflux. After cooling to room temperature, 250 ml of anhydrous THF and 11.9 g (0.062 mol) of cuprous iodide were added and the mixture was stirred for 5 min, then cooled to −20° and stirred at this temperature for 5 hr. A solution of 4.5 g (0.019 mol) of methylene ketone **1a**[1a] in 50 ml of anhydrous THF was then added with stirring at −15° over a 30-min period. When the addition was complete, the resulting suspension was poured into a stirred mixture of ice and saturated NH_4Cl. After stirring for 20 min, the solids were filtered and washed with ether. The filtrate was worked up with ether in the usual manner gaving 19.97 g of viscous, oily product. This material was chromatographed on 200 parts of silica gel. Elution with 50:1 benzene–ethyl acetate gave first bis(*m*-methoxybibenzyl) and then 6.025 g (88%) of the keto ether **2a** as a viscous oil [tlc: R_f 0.5 (system c); 0.1 (system b)].

In another run, an analytical sample of **2a** was obtained by preparative thin layer chromatography (system c) followed by evaporative distillation giving a pale-yellow oil: bp 190–200° (bath) (0.01 mm); $[\alpha]^{25}D$ +27.46°; uv max 216 nm (ε 8200), 271 (2075), 278 (1875); ir 1705 (C=O), 1610, 1595 (anisole), 1390, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.16 (m, 1, aromatic), 6.72 (m, 3, aromatic), 3.75 (s, 3, CH_3O), 3.45 (m, 1, C_1–H), 1.12 (s, 9, O-*t*-C_4H_9), 1.00 ppm (s, 3, C_{7a}–CH_3); mass spectrum *m/e* 358 (M^+).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.73; H, 9.73.

The 1,2 adduct **3a** [tlc: R_f 0.28 (system c)] was isolated as a viscous oil, by column chromatography, from fractions eluted after those containing **2a** and showed the following spectral properties: uv max 220 nm (ε 13010), 272 (2110), 280 (2020); ir 3600 (OH), 1650 (C=CH_2), 1395, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.16 (m, 1, aromatic), 6.72 (m, 3, aromatic), 4.85 (m, 1, HC=), 4.60 (m, 1, HC=), 3.75 (s, 3, CH_3O), 3.62 (m, 1, C_1–H), 2.90 (m, 2, $ArCH_2$), 1.15 (s, 9, O-*t*-C_4H_9), 0.67 ppm (s, 3, C_{7a}–CH_3); mass spectrum *m/e* 358 (M^+). This material was the sole product when no cuprous salt was employed.

(+)-17β-*tert*-Butoxy-3-methoxyestra-1,3,5(10),9(11)-tetraene (4a). A. From 2a. A solution of 1.21 g (3.34 mmol) of keto ether **2a** in 100 ml of methanol was stirred at room temperature while 20 ml of 10 *N* aqueous HCl[8] was added dropwise over a 15-min period. The addition caused a mild exotherm and a precipitate appeared toward the end of the addition period. The resulting slurry was stirred at room temperature for 5.5 hr then kept at 0° for 16 hr. The colorless solid was filtered with suction and washed with water then dried under high vacuum giving 0.876 g (77.2%) of **4a**, mp 129–131°. Tlc analysis (system b) showed a single spot, R_f 0.35. Recrystallization of a sample prepared in this way from methanol gave colorless needles: mp 133–134°; $[\alpha]^{25}D$ +101.27°; uv max 264 nm (ε 19700), infl 290–300 (ε 3550); ir 1630 (C=C), 1610, 1580 (anisole), 1393, 1365 cm^{-1} (*t*-C_4H_9); nmr δ 7.48 (d, 1, *J* = 8 Hz, C_1–H), 6.58 (m, 2, C_2–H, C_4–H), 6.07 (m, 1, C_{11}–H), 3.74 (s, 3, OCH_3), 3.52 (m, 1, C_{17}–H), 2.78 (m, 2, C_6–H), 1.15 (s, 9, O-*t*-C_4H_9), 0.77 ppm (s, 3, C_{13}–CH_3); mass spectrum *m/e* 340 (M^+). A portion of this material was sublimed prior to combustion analysis at 115–120° (0.02 mm) giving colorless solid, mp 132–133°.

Anal. Calcd for $C_{23}H_{32}O_2$: C, 81.13; H, 9.47. Found: C, 81.01; H, 9.38.

B. From 1a Without Isolation of 2a. A solution of 78 g (0.5 mol) of *m*-methoxybenzyl chloride dissolved in 430 ml of anhydrous THF was added dropwise over a period of 55 min to a stirred suspension of 24.3 g (1 mol) of magnesium turnings in 100 ml of anhydrous THF at reflux temperature. The mixture was stirred for 30 min at reflux temperature then cooled to room temperature whereupon 2000 ml of anhydrous THF and 15.85 g (0.16 mol) of cuprous chloride were added and the mixture was stirred for 30 min at room temperature. A solution of 23.6 g (0.1 mol) of enone **1a** in 200 ml of anhydrous THF was then added with stirring over a 15-min period. When the addition was complete, the resulting suspension was poured into a stirred mixture of 1 *N* aqueous H_2SO_4 and ice. After stirring for 5 min, the mixture was worked up with ether. The resulting crude, oily product was then dissolved in 3000 ml of ethanol. Within 15 min, 600 ml of 10 *N* aqueous hydrochloric acid were added with stirring and cooling, the temperature not exceeding 20°. The faintly turbid solution was stirred at 20° for 4 hr and then allowed to stand at 0° for 12 hr. The solid was filtered with suction, washed with water, and dried at 80° (15 mm). Recrystallization from ethanol–ether gave 24.15 g (71%) of **4a**, mp 131–132°.

(1*S*, 3a*R*, 4*S*, 7a*S*)-(+)-1-*tert*-Butoxy-4-[2-(3-methoxyphenyl)ethyl]-7a-ethyl-3a,4,7,7a-tetrahydro-5(6*H*)-indanone (2b). Crude enone **1b**[1a] (5.01 g; 0.02 mol) was reacted with *m*-methoxybenzylmagnesium chloride using the procedure described in part B of the preceding experiment. The crude product (17.2 g) was chromatographed on 400 g of silica gel. Elution with 19:1 hexane–ether gave fractions yielding 9.4 g of an oil which was composed mainly of *m*-methylanisole and bis(*m*-methoxybibenzyl). The early fractions eluted with 9:1 hexane–ether afforded 3.16 g (42.5%) of the stable epimer **2b** [tlc: R_f 0.54 (system a); 0.10 (system b)] in essentially pure form as a viscous oil. A sample of this material was rechromatographed on silica gel and evaporatively distilled giving the analytical specimen as a viscous, pale-yellow oil: bp 160–180° (bath temperature) (0.2 mm); $[\alpha]^{25}D$ +11.93°; ir 1705 (C=O), 1600, 1585 cm^{-1} (anisole); uv max 217 nm (ε 7946), 272 (1980), 278 (1860); nmr δ 7.15 (m, 1, aromatic), 6.72 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 3.48 (t, 1, *J* = 8 Hz, C_1–H), 1.12 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.25; H, 9.85.

The later fractions eluted with 9:1 hexane–ether yielded 1.4 g (18.8%) of a mixture of **2b** (minor) and the 4*R* epimer of **2b** [major; tlc: R_f 0.45 (system a)]. This material was rechromatographed on silica gel. Later fractions eluted with 9:1 hexane–ether furnished 0.51 g of the essentially pure (tlc) 4*R* epimer of **2b** as a viscous, colorless oil: $[\alpha]^{25}D$ +17.96°; uv max 215 nm (ε 7970), 273 (1990), 279 (1870); ir 1700 (C=O), 1600, 1585 cm^{-1} (anisole); nmr δ 7.15 (m, 1, aromatic), 6.70 (m, 3, aromatic), 3.75 (s, 3, OCH_3), 3.43 (m, 1, C_1–H), 1.10 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 372 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.53; H, 9.84.

A 54-mg sample of the 4*R* (axial) epimer was treated with 5 ml of a solution prepared by diluting 5 ml of 1 *N* aqueous NaOH to 50 ml with methanol. The mixture was heated for 5 min on a steam bath in order to effect solution. After cooling to room temperature, tlc analysis indicated that epimerization was complete as evidenced by the essential absence of the spot due to the more polar, 4-axial epimer. After standing at room temperature for 1.25 hr, the solution was diluted with dichloromethane and toluene then dried, filtered, and concentrated *in vacuo*. There was obtained 54 mg of colorless oil the tlc mobility of which was identical to that of **2b**. The latter substance was unchanged by alkali treatment.

(+)-17β-*tert*-Butoxy-13β-ethyl-3-methoxygona-1,3,5(10),9-(11)-tetraene (4b). A 7.28 g (19.6 mmol) sample of keto ether **2b** was cyclized using the procedure described above for the preparation of **4a**. There was obtained 5.86 g (84.5%) of colorless solid, mp 116–119° [tlc: one spot, R_f 0.34 (system b)]. A 1-g sample of this material was recrystallized from ethanol giving 0.91 g of colorless needles: mp 120–121°; $[\alpha]^{25}D$ +97.13°; uv max 263 nm (ε 19780), 298 (3150), infl 310 (2120); ir 1640 (C=C), 1615, 1580 (anisole), 1375 cm^{-1} (*t*-C_4H_9); nmr δ 7.45 (d, 1, *J* = 8 Hz, C_1–H), 6.63 (m, 2, C_2–H, C_4–H), 6.06 (m, 1, C_{11}–H), 3.73 (s, 3, OCH_3), 3.58 (m, 1, C_{17}–H), 1.14 ppm (s, O-*t*-C_4H_9); mass spectrum *m/e* 354 (M^+).

Anal. Calcd for $C_{24}H_{34}O_2$: C, 81.31; H, 9.67. Found: C, 81.37; H, 9.66.

(+)-17β-*tert*-Butoxy-3-methoxyestra-1,3,5(10)-triene (5a). A mixture of 0.8 g (2.35 mmol) of estratetraene **4a**, 0.25 g of 5% palladium on carbon, and 30 ml of ethyl acetate was stirred in an atmosphere of hydrogen for 1.33 hr. At the end of this time, 61 ml of hydrogen had been absorbed (59 ml theory). The catalyst was filtered with suction on Celite and the filter cake was washed with ethyl acetate. The filtrate and washes were combined and concentrated *in vacuo* giving 0.831 g of colorless oil which crystallized on standing at 0°. Recrystallization from ethanol yielded 0.433 g (54.2%) of **5a** as colorless crystals: mp 91–92.5°; ir 1610, 1580 (anisole), 1360 cm^{-1} (*t*-C_4H_9); uv max 277 nm (ε 2030), 285 (1900); nmr

δ 7.20 (d, 1, J = 8 Hz, C_1–H), 6.63 (m, 2, C_2–H, C_4–H), 3.73 (s, 3, OCH_3), 3.43 (t, 1, J = 8 Hz, C_{17}–H), 1.15 (s, O-t-C_4H_9), 0.75 ppm (s, 3, C_{13}–CH_3); mass spectrum m/e 342 (M^+). A sample of this material was sublimed at 110–120° (0.15 mm) prior to combustion analysis giving colorless solid: mp 90–92°; $[\alpha]^{25}D$ +62.20°.

Anal. Calcd for $C_{23}H_{34}O_2$: C, 80.65; H, 10.00. Found: C, 80.88; H, 9.91.

Tlc analysis (system b) of the mother liquor from the above recrystallization indicated an approximately 1:1 mixture of **5a** (R_f 0.39) and its 9β epimer (R_f 0.42).

(+)-17β-*tert*-Butoxy-13β-ethyl-3-methoxygona-1,3,5(10)-triene (5b). A 1-g (2.82 mmol) sample of gonatetraene **4b** was hydrogenated as in the preceding experiment. The crude product was chromatographed on 50 g of silica gel. Elution with 19:1 hexane–ether gave 0.925 g of colorless solid which was recrystallized from ethanol. This afforded 0.67 g (67%) of colorless plates: mp 121–123°; $[\alpha]^{25}D$ +44.69°; uv max 278 nm (ε 2020), 287 (1860); ir 1610, 1580 (anisole), 1360 cm^{-1} (t-C_4H_9); nmr δ 7.18 (d, 1, J = 9 Hz, C_1–H), 6.68 (m, 2, C_2–H, C_4–H), 3.74 (s, 3, OCH_3), 3.51 (t, 1, J = 8 Hz, C_{17}H), 1.15 ppm (s, O-t-C_4H_9); mass spectrum m/e 356 (M^+).

Anal. Calcd for $C_{24}H_{36}O_2$: C, 80.85; H, 10.18. Found: C, 80.71; H, 10.17.

(+)-3-Methoxyestra-1,3,5(10)-trien-17-one [(+)-Estrone 3-Methyl Ether] (7a). The crude product (**5a**) from hydrogenation (as described above) of 0.679 g (2 mmol) of estratetraene **4a** was dissolved in 10 ml of ice-cold trifluoroacetic acid.[9] The resulting yellow solution was kept at 0° for 20 hr then concentrated *in vacuo*. The residue was made alkaline with 0.5 N aqueous $KHCO_3$ solution (135 ml) and stirred at room temperature for 3 hr after the addition of 20 ml of tetrahydrofuran. Work-up with methylene chloride gave 0.773 g of 17-trifluoroacetoxy derivative which crystallized on standing: ir 1780 cm^{-1} (ester C=O). This product was dissolved in a mixture of 20 ml of methanol and 5 ml of 10% aqueous NaOH. The resulting solution was stirred at room temperature for 1 hr whereupon an additional 5 ml of 10% NaOH and 10 ml of methanol were added and stirring was continued for 1.75 hr. The mixture was then treated with brine and worked up with dichloromethane giving 0.567 g of crude estradiol 3-methyl ether (**6a**) as a pale-yellow foam: ir 3400 cm^{-1} (OH). Without purification, this material was dissolved in 20 ml of acetone and the solution was stirred with ice bath cooling while 0.65 ml of standard Jones reagent[11] was added over 3 min. After stirring for 5 min with ice bath cooling, the excess oxidant was decomposed by the addition of 2-propanol followed by ice–water. The acetone was removed at aspirator pressure and the residue was worked up with dichloromethane giving 0.537 g of crude **7a** as a yellow solid. Chromatography on 50 g of silica gel afforded 0.065 g of a more mobile impurity (colorless solid; eluted with 9:1 and 4:1 hexane–ether) followed by 0.35 g (61.7%) of essentially pure estrone 3-methyl ether (off-white solid; eluted with 4:1 and 2:1 hexane–ether). Recrystallization from acetonitrile gave colorless solid: mp 164–167°; $[\alpha]^{25}D$ +153.98° (c 1, dioxane); mmp with authentic (+)-estrone 3-methyl ether [$[\alpha]^{25}D$ +159.26° (c 1, dioxane)] 164–167.5°. The ir, uv, pmr, and mass spectra and tlc mobility (R_f 0.45; system d) were essentially identical with those of authentic (+)-estrone 3-methyl ether.

(+)-13β-Ethyl-3-methoxygona-1,3,5(10)-trien-17-one (7b). A solution of 0.4 g (1.12 mmol) of pure **5b** and 0.1 g of p-toluenesulfonic acid monohydrate[9] in 10 ml of toluene was stirred and heated at reflux for 1 hr. The resulting solution was cooled and treated with saturated aqueous sodium bicarbonate solution then worked up with ether giving 0.348 g of (+)-17β-hydroxy-13β-ethyl-3-methoxygona-1,3,5(10)-triene (**6b**)[12,13] as a colorless solid.

This material was dissolved in 10 ml of acetone and the resulting solution was stirred with ice-bath cooling while 0.4 ml of Jones reagent[11] was added dropwise from a syringe over a 5-min period. After stirring at 0–5° for 2 min, the red mixture was decomposed by the addition of 10% aqueous $NaHSO_3$ solution. The resulting green mixture was diluted with water and worked up with ether giving 0.334 g of crude **7b** as a tan solid. This material was chromatographed on 20 g of silica gel. Fractions eluted with 4:1 hexane–ether afforded 0.274 g (82.3%) of colorless crystalline **7b**. Recrystallization from 1:1 cyclohexane–ethyl acetate furnished 0.207 g (62%) of colorless plates: mp 148.5–150°; $[\alpha]^{25}D$ +102.37° (c 1, $CHCl_3$), +102.82° (c 1, 1:1 $CHCl_3$–CH_3OH) [lit.[14] mp 147–149°; $[\alpha]D$ +110.9° ($CHCl_3$)] [lit.[13] mp 146–147°; $[\alpha]^{20}D$ +104° (c 1, 1:1 $CHCl_3$–CH_3OH)].

(+)-17β-Hydroxy-3-methoxyestra-1,3,5(10),6,8-pentaene (8a). A 1-g (2.94 mmol) sample of estratetraene **4a** was added to 10 ml of stirred, ice-cold trifluoroacetic acid. The resulting mixture was stirred with ice-bath cooling until the solid had completely dissolved then the green-brown solution was kept at 0° for 21.5 hr. The trifluoroacetic acid was removed under reduced pressure and the residue was treated with 40 ml of methanol and 10 ml of 10% aqueous NaOH. The alkaline mixture was warmed briefly on the steam bath then stirred at room temperature for 1.5 hr during which time a white precipitate formed. After removal of the methanol *in vacuo*, the mixture was diluted with water and worked up with ether giving 0.835 g of a yellow, semicrystalline residue: uv max 229 nm (ε 31410), 268 (3170), 277 (3750), 288 (2860), 309 (820), 323 (1170), 331 (1070), 338 (1320); mass spectrum m/e 282 (M^+ **8a**), 286 (M^+ **9a**). Tlc analysis (system a) showed two spots of approximately equal intensity R_f 0.15 (**9a**) and 0.10 (**8a**; R_f identical with that of authentic **8a**[16] prepared from d-equilenin). Gc analysis showed the elution of six components: retention time 9.4 (30.4%), 13.0 (9.9%), 14.5 (1.6%), 17.9 (56.6%), 21.7 (0.8%), and 24.9 min (0.7%). The peak with retention time of 13.0 min was shown to be identical with that exhibited by authentic estradiol 3-methyl ether by coinjection. The peak with retention time of 17.9 min was shown to be identical with that exhibited by authentic estrapentaene **8a**[16] by coinjection.

In another run, the crude alcohol mixture was chromatographed on 50 parts of silica gel. Elution with 9:1 benzene–ether gave material rich in **8a** which was recrystallized from methanol. This process yielded pure **8a** as colorless solid: mp 143–146°; $[\alpha]^{25}D$ +40.16° (c 1, dioxane) (lit.[16] mp 149–150°). The ir, pmr, and uv spectra were identical with those of an authentic sample of **8a** [mp 149–150° from methanol; $[\alpha]^{25}D$ +41.74° (c 1, dioxane)] prepared from d-equilenin by methylation followed by reduction with $LiAlH_4$.[16] The nmr spectra of both samples showed solvation by methanol. Tlc comparison of these samples showed identical R_f values of 0.35 (system d).

(+)-3-Methoxyestra-1,3,5(10),6,8-pentaen-17-one [(+)-Equilenin 3-Methyl Ether] (10a). The crude mixture of **8a** and **9a** obtained from 0.34 g (1 mmol) of estratetraene **4a** as described in the previous experiment was dissolved in 10 ml of acetone and the resulting solution was stirred and cooled in an ice bath while 0.5 ml of Jones reagent[11] was added dropwise. After stirring for 5 min the excess oxidant was decomposed with 2-propanol. The resulting mixture was treated with ice–water and most of the acetone was evaporated at reduced pressure. Work-up with chloroform (the chloroform extracts were additionally washed with saturated, aqueous $NaHCO_3$) gave 0.262 g of semicrystalline product. A combination of preparative thin layer chromatography (system c) and recrystallization from methanol gave 77.5 mg (27.6%) of colorless needles: mp 192–194°; the ir, uv, pmr, and mass spectra of which were identical with those of authentic (+)- equilenin 3-methyl ether [mp 195–196°; $[\alpha]^{25}D$ +82.64° (c 1, dioxane); prepared by methylation of d-equilenin[19]. Another recrystallization from methanol gave colorless solid: mp 195–196°; $[\alpha]^{25}D$ +88.72° (c 0.86, dioxane) [lit.[16] mp 196–197°; lit.[19] mp 194–194.5°; lit.[20] mp 197–199°; $[\alpha]^{25}D$ +64° (c 1, $CHCl_3$)].

Mixture of Estratetraenols 11a and 12a. A solution of 1g (2.94 mmol) of estratetraene **4a** and 0.67 g (3.53 mmoles) of p-toluenesulfonic acid monohydrate in 80 ml of benzene was stirred and heated at reflux[9] for 1 hr. The reaction mixture was cooled, treated with saturated aqueous $NaHCO_3$, and worked up with ether giving 0.89 g of product as a yellow foam. This material was chromatographed on 50 g of silica gel. Elution with 1:1 hexane–ether furnished 0.698 g (83.6%) of a pale-yellow solid composed mainly of the mixture of **11a** and **12a** (approximately 5:3, respectively by nmr analysis); uv max 264 nm (ε 15750); infl 213 (19500), 272 (14000), 309 (2500), 322 (500); ir 3600 (OH), 1600 cm^{-1} (anisole); nmr δ 7.53 [d, J = 9 Hz, C_1–H of **11a** (major)], 7.13 [d, J = 9 Hz, C_1–H of **12a** (minor)], 6.66 (m, 2, C_2–H, C_4–H), 6.11 [m, ~ 0.65, C_{11}–H (**11a**)], 3.77 (s, OCH_3), 0.80 [s, C_{13}–CH_3 of **11a** (major)], 0.77 ppm [s, C_{13}–CH_3 of **12a** (minor)]; mass spectrum m/e 284 (M^+). Six peaks were eluted on gc analysis: retention time 9.8 (0.9%), 12.2 (8.7%), 14.7 (83.6%), 17.9 (2.6%), 19.0 (2.6%), 24.0 min (1.6%). The peak with retention time of 17.9 min was shown to be due to estrapentaene **8a** by coinjection. The peak with retention time of 14.7 min was due to the mixture of estratetraenes **11a** and **12a** which was not resolved. The remaining peaks were not identified.

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Registry No.—**1a,** 53052-87-2; **1b,** 53052-91-8; **2a,** 53016-36-7; **2b,** 53052-90-7; **2b** 4*R*-epimer, 53052-89-4; **3a,** 53684-32-5; **4a,** 53053-33-1; **4b,** 53053-35-3; **5a,** 53053-36-4; **5a** trifluoroacetoxy derivative, 29755-34-8; **5b,** 53053-37-5; **6a,** 1035-77-4; **6b,** 3625-82-9; **7a,** 1624-62-0; **7b,** 848-04-4; **8a,** 15375-29-8; **9a,** 53776-51-5; **10a,** 3907-67-3; **11a,** 6702-61-0; **12a,** 6733-79-5; *m*-methoxybenzyl chloride, 824-98-6.

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Synthesis of 9,11-Secoestradiol 3-Methyl Ether

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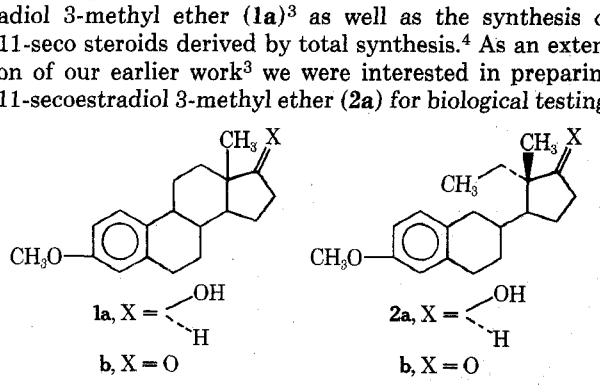
Estradiol 3-methyl ether (**1a**) is known to possess both estrogenic and antifertility activity. In an attempt to enhance the antifertility activity and/or diminish the estrogenic activity 9,11-secoestradiol 3-methyl ether (**2a**) has been prepared via a seven-step sequence starting with **1a.** Compound **2a** had weak estrogenic and antifertility activity with no appreciable separation of activities.

Several articles dealing with 9,11-seco steroids have appeared in the recent literature. Crossley and Dowell[1] reported the synthesis of 9,11-secoprogesterone in an attempt to prepare a derivative having modified progestational activity. Brain and coworkers[2] prepared a series of 9,11-seco steroids having both the A and B rings aromatic via total synthesis. We have previously reported the synthesis of optically active 9,11-seco steroids derived from estradiol 3-methyl ether (**1a**)[3] as well as the synthesis of 9,11-seco steroids derived by total synthesis.[4] As an extension of our earlier work[3] we were interested in preparing 9,11-secoestradiol 3-methyl ether (**2a**) for biological testing.



Since estradiol 3-methyl ether (**1a**) is known to possess both estrogenic[5] and antifertility[6] activity, we had hoped that cleavage of the 9,11 bond would enhance the antifertility activity, thereby leading to a greater separation of activities via the "entropy effect."[7]

The key intermediate in our previous series, 17β-hydroxy-3-methoxy-9-oxo-9,11-secoestra-1,3,5(10)-trien-11-oic acid 17-acetate (**3a**), appeared to be an ideal starting material for the synthesis of **2a.** Compound **3a** was prepared by the procedure of Cambie[8] and was purified by column chromatography. The homogeneity of **3a** was established by NMR and thin layer chromatography (TLC). The nmr spectrum of **3a** exhibited sharp singlets at δ 1.08 for the C-18[9] methyl and 1.97 for the acetoxy methyl. If compound **3a** had undergone partial epimerization at C-8 during its preparation, one would expect that the C-18 methyls and/or the acetoxy methyls of the two epimers would have different field positions in the NMR. The only resonances attributable to the C-18 methyl and the acetoxy methyl are the sharp singlets previously mentioned. The homogeneity of **3a** was further confirmed by examining the fully proton decoupled ^{13}C NMR spectrum which contained 20 sharp resonances.[10] If the compound had been a mixture of isomers, some of the carbon atoms would have been nonequivalent and more than 21 peaks would have been observed in the spectrum. Since it is highly unlikely that **3a** had undergone complete epimerization at C-8 during the ring cleavage reaction, we conclude that the stereoconfiguration at C-8 is the same as that in estradiol 3-methyl ether.

In the synthesis of 9,11-secoprogesterone,[1] the 9-keto and the 11-carboxy functions were removed concurrently by successively reducing each to the corresponding alcohol,