66527-76-2; **4b**, 66527-81-9; **5**, 22771-44-4; **6b**, 68679-98-1; **8b**, 66527-84-2; **9b**, 66527-83-1; **11**, 68582-81-0; **12**, 66527-86-4; **13**, 66527-87-5; **14**, 66561-70-4; **15**, 66527-88-6; **16**, 66527-91-1; **17**, 60788-14-9; 17 ethyl ester, 68582-82-1; **18a** (n = 0), 68582-83-2; **18a** (n = 1, R = H), 68582-84-3; **18b** (n = 1), 68582-85-4; **19**, 68582-86-5; 1′-hydroxy-Δ^9-THC (isomer A), 66527-89-7; 1′-hydroxy-Δ^9-THC (isomer B), 66527-90-0; 2′-hydroxy-Δ^9-THC, 65372-82-9; 2′-oxo-Δ^9-THC *tert*-butyldimethylsilyl ether, 68582-87-6; 2′-oxo-Δ^9-THC, 68582-88-7; 3′-hydroxy-Δ^9-THC, 58434-44-9; 3′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether, 68582-89-8; 4′-hydroxy-Δ^9-THC, 58434-43-8; 4′-hydroxy-Δ^9-THC bis(*tert*-butyldimethylsilyl) ether, 68582-90-1; 3-carbethoxy-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran-1-ol *tert*-butyldimethylsilyl ether, 68582-91-2; Δ^9-THC, 1972-08-3; Δ^9-THC *tert*-butyldimethylsilyl ether, 61919-31-1; 1′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (isomer A), 68582-92-3; methyl 3,5-dihydroxybenzoate, 2150-44-9; 3,5-dihydroxybenzaldehyde, 26153-38-8; propane-1,3-dithiol, 109-80-8; 1′-hydroxy-Δ^9-THC *tert*-butyldimethylsilyl ether (isomer B), 68582-93-4; *tert*-butyldimethylsilyl chloride, 18162-48-6; butyryl chloride, 141-75-3; 1,2-epoxybutane, 106-88-7; 3-(*tert*-butyldimethylsilyloxy)butyl bromide, 65566-22-5; 3,5-dihydroxybenzyl alcohol, 29654-55-5.

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Pentacyclic Steroids. 5. Total Synthesis of 4,6β-Ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol and 4,6α-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one

Anil C. Ghosh,* Braja G. Hazra, Ivan Karup-Nielsen, Michael J. Kane, and David Hawke

SISA Incorporated and Sheehan Institute for Research, Incorporated, Cambride, Massachusetts 02138

William L. Duax and Charles M. Weeks

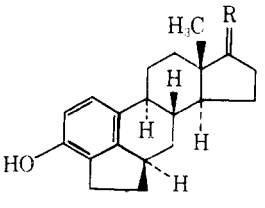
Medical Foundation of Buffalo, Buffalo, New York 14203

Received October 5, 1978

Total synthesis of the novel pentacyclic steroids 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (**5**) and 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**20**) is described. 7-Methoxy-1-tetralone (**6**) was converted in several steps into the key intermediate 8-methoxy-2a,3,4,5-tetrahydro-5-acenaphthenone (**14**). The latter ketone was converted into 4,6-ethano-3-methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (**17**) via the isothiouronium acetate (**16**). Ring cyclization of **17** led to a mixture of the stereoisomers 4,6β-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**19**) and 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**20**). The major isomer **19** was converted in four steps to the 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (**5**). The relative configuration of **5** was confirmed by an X-ray crystallographic study of the racemic mixture. The minor isomer **20** was converted into 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (**23**).

Introduction of a methyl group in the steroidal skeleton at position C-6 has led to useful oral contraceptives such as Provera (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione) and megesterol acetate.[2,3] Recently, we have described[1,4-6] the synthesis of a new series of pentacyclic steroids containing an ethano bridge across C-4 and C-6. Our studies on 4,6β-ethanoestradiol (**1**) and 4,6β-ethanoestrone (**2**) have revealed that the fusion of the ethano bridge at positions C-4 and C-6 from the β face forces the B ring to assume a highly distorted conformation. This has been confirmed by X-ray crystallographic studies on the 17-*p*-bromobenzoate of 4,6β-ethanoestradiol (**3**).[4,5]

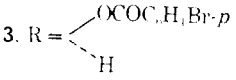
Studies with Drieding models show that the unusual strain on the B ring in 4,6β-ethanoestradiol could be somewhat relieved if the stereochemistry at C-6 or C-8 was reversed. We



4

1. R = 

2. R = O

3. R = 

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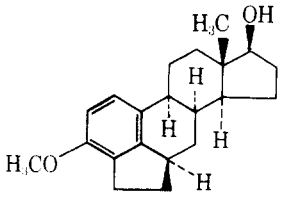


5

have recently described[6] the synthesis of one of these compounds, 4,6α-ethanoestradiol (**4**), by a partial synthesis from estrone. However, synthesis of a compound such as 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (**5**), having an 8α configuration, presents a more challenging problem. It would be difficult to prepare such unnatural steroids from estrone, since this would involve epimerization at C-8.

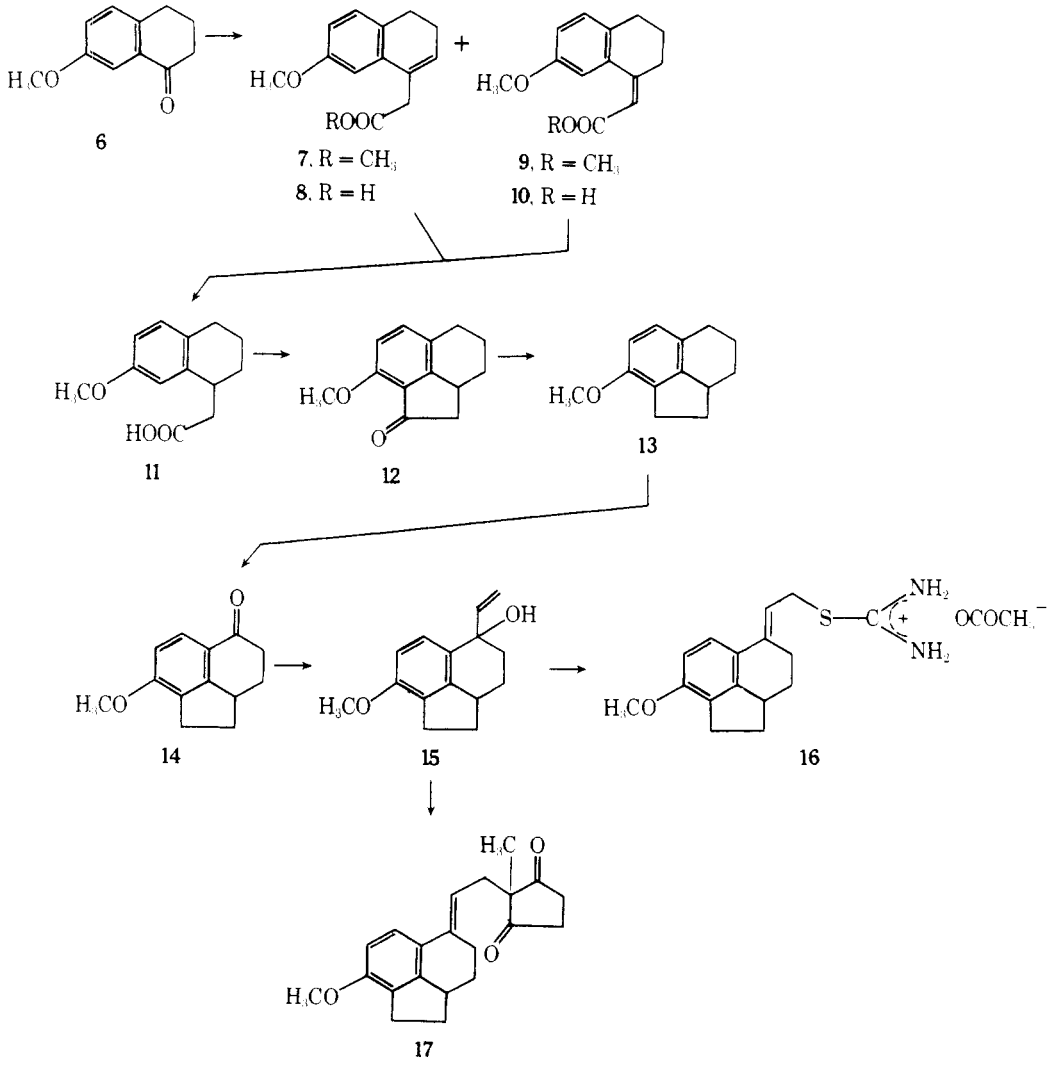
In this paper, we describe the preparation of compound **5**, from 7-methoxytetralone (**6**), by a total synthesis route. These studies have also led to the synthesis of 4,6α-ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (**20**), in which the ethano bridge across C-4 and C-6 is fused from the α face of the steroidal skeleton.

Reformatsky reaction[7,8] of 7-methoxy-1-tetralone (**6**) with methyl bromoacetate followed by treatment with 90% formic acid and saponification yielded a mixture of the acids **8** and **10** in the ratio of about 90:10, as evidenced by NMR spectra (Scheme I). Catalytic reduction of the mixture over 10% Pd/C afforded **11** in nearly quantitative yield. This was followed by cyclization with hydrogen fluoride to give the tricyclic ketone **12**. Clemmensen reduction on this latter compound afforded **13** in 85% yield. Oxidation of **13** with CrO_3 provided the tricyclic ketone **14**. The overall yield of **14** from 7-methoxy-1-tetralone (**6**) was about 45%.

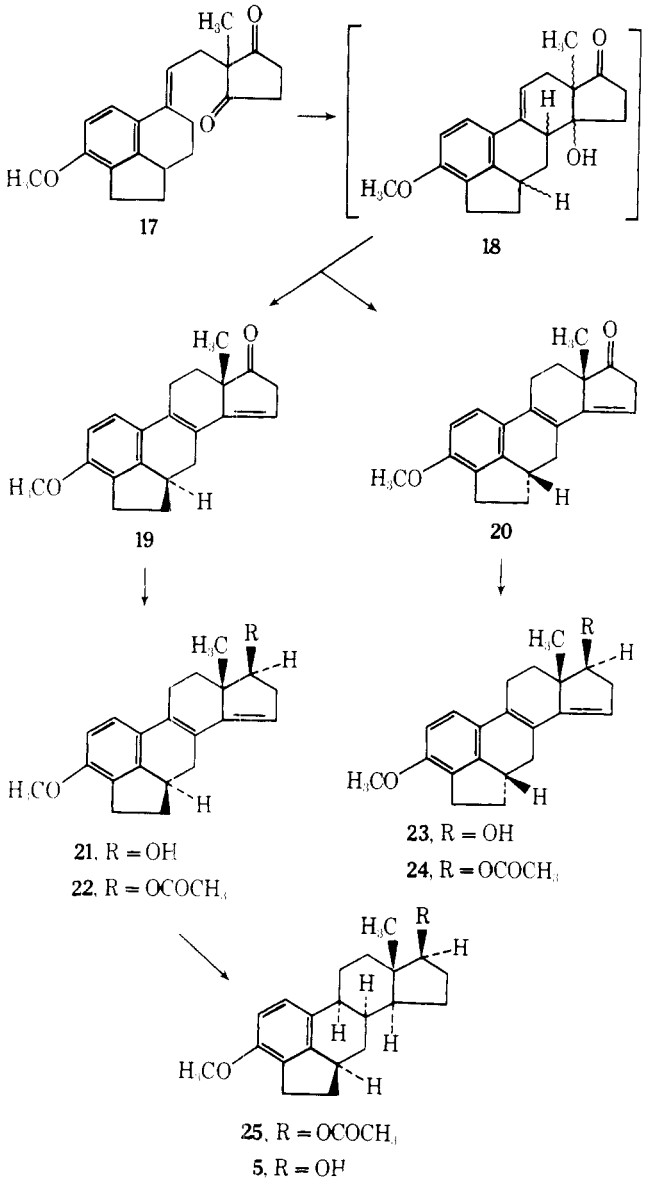
Conversion of the key intermediate **14** into the pentacyclic steroidal system was achieved via two different routes, each involving the versatile Torgov reaction.[9] Treatment of **14** with vinylmagnesium bromide in ether–tetrahydrofuran at 0 °C yielded the allylic alcohol **15**. Without further purification, this was treated with thiourea in acetic acid to provide the crystalline isothiouronium salt **16** in 60% yield. Treatment of **16** with 2-methylcyclopentane-1,3-dione in water–ether–benzene furnished the diketone **17**. The latter compound was also obtained by refluxing **15** with 2-methylcyclopentane-1,3-dione in the presence of Triton B.

It is interesting to note that during the synthesis of the dione **17** from **6**, no special stereochemical problem is encountered. However, the formation of the pentacyclic steroid system by ring closure of **17** would be accompanied by the creation of two chiral centers in the molecule. Thus, cyclodehydration of the dione **17** under normal Torgov reaction conditions[9] would lead to two possible steroidal pentaenes **19** and **20** (Scheme II). Indeed, when **17** was treated with *p*-toluenesulfonic acid, a mixture of two stereoisomers was obtained. The resulting product showed a single spot in thin-layer chromatography. However, the NMR spectrum exhibited two singlets for the C-13 methyl groups at 1.10 (major)

Scheme I



Scheme II



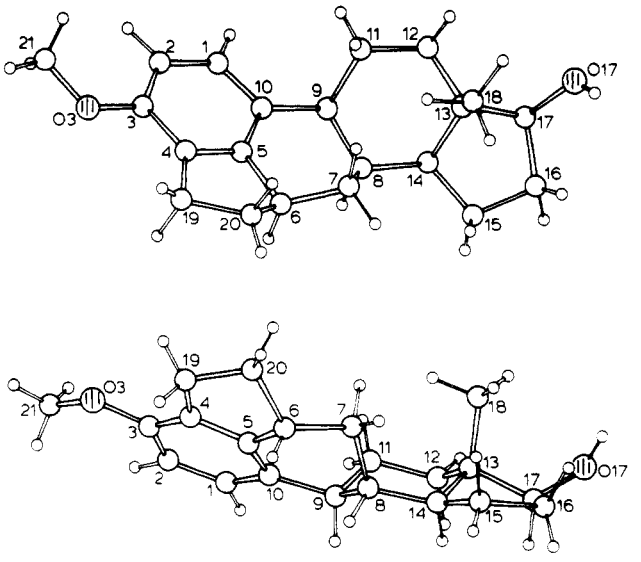


Figure 1. Two views of the conformation of 4,6β-ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol.

and 1.17 ppm (minor), indicating presence of a mixture of the stereoisomers **19** and **20**. In addition, the signals in the vinylic as well as low field half of the aromatic regions indicated that the product was a mixture, while the methoxy group showed up as a singlet. Attempts to separate these isomers by column chromatography, gas–liquid chromatography, and high-pressure liquid chromatography were unsuccessful. Purification of the isomers was further complicated by the intense violet color of the crude reaction product. Finally, after several fractional crystallizations, the major isomer of the ketone was isolated in the pure state, mp 173–175 °C. This purified isomer exhibited a C–CH_3 signal in its NMR spectrum at 1.10 ppm and its mass spectrum showed molecular ion at M^+ 306. However, since there was no precedence in literature for this type of steroid,[9] it was impossible to assign any definite structure (**19** or **20**) to the isolated major isomer of the ketone.

Since recovery of the purified major isomer of the pentaene ketone via recrystallization was poor, the mixture of the two ketones (**19** and **20**) was reduced with sodium borohydride. NMR of the product showed it to be a mixture of alcohols **21** and **23**. The ratio of the major and minor isomers was estimated to be 81:19, on the basis of NMR signals of the C–CH_3 group (signals at 0.94 and 1.00 ppm, respectively). After a series of fractional crystallizations (seven times) from methanol–chloroform mixture, the minor isomer of the alcohol was obtained in the pure state, mp 210–212 °C. The combined mother liquors were evaporated to dryness and the residual solid was recrystallized from ether–petroleum ether to afford the pure major isomer of the alcohol, mp 172–173 °C.

Once again, spectral and analytical data of the two isomers of the pentaene alcohols were found to be inadequate for making definite stereochemical assignments of the two structures **21** and **23**.

In the next stage of these studies, the crude mixture of the 17-alcohols was acetylated with acetic anhydride in pyridine to give a mixture of the two isomeric acetates **22** and **24**. The ratio of the major and minor isomers in the acetates was essentially unchanged from that found in the parent alcohol and the ketone, as evidenced by NMR spectra. The major isomer of the acetate was isolated as a colorless solid (mp 183–184 °C) by fractional recrystallization. The NMR spectrum of this compound showed a sharp singlet at 0.95 ppm (C–CH_3). The structure was further confirmed by its mass spectrum (M^+ at 350), IR (ν_{max} 1735 cm^{-1}, acetate), and elemental analysis. It was also found that the best stage for separation of the major isomer was the fractional crystallization of the pentane acetate mixture (**22** and **24**). The purified major isomer of the pentaene acetates was next subjected to catalytic hydrogenation, using Pd–$CaCO_3$ as the catalyst and 2 mol of hydrogen. Hydrolysis of the resulting triene acetate yielded the corresponding alcohol.

Although the spectroscopic and analytical data obtained from the major isomers of the pentaene ketones, alcohols, and acetates clearly established the gross molecular structures of these compounds, the relative configurations at C-6 and C-13 remained to be unequivocally assigned. Finally, the relative configuration of the major isomer of the triene alcohol **5** was determined by X-ray crystallographic studies of the racemic mixture.

Single crystals of the hemihydrate of **5** were grown by evaporation of an acetone–ethanol solution. The crystal data are: space group $C2/c$, a = 22.742 Å, b = 7.3936 Å, c = 41.772 Å, β = 101.64°, Vol = 6879.3 $Å^3$. The intensities of 6119 diffraction spectra were measured of which 4132 had intensities greater than twice the background. The crystal structure was solved by direct methods.[10,11] The structure was refined by full-matrix least-squares techniques and all hydrogen atoms were located in Fourier difference synthesis. The final reliability index (R) was 6.4%. The unit cell contained eight d–l pairs including two crystallographically distinct molecules.

Table I

reagent	solvent	time, h	temp, °C	yield of crude mixture of 19 and 20	approx isomer ratio (19:20)
p-$CH_3C_6H_4SO_3H$	C_6H_6	0.75	reflux	71	70:30
BF_3·etherate	CH_2Cl_2	17	0	90	82:18
BF_3·etherate[a]	CH_2Cl_2	138	−20	30	83:17
CF_3COOH[b]	$CDCl_3$	72	25		80:20
CH_3COOH	xylene	2	reflux	30	

[a] The intermediate product 18 was isolated from the mixture. [b] Experiment done in an NMR tube.

The relative configurations of the asymmetric centers are illustrated on the 13β-methyl isomer shown in Figure 1. The two crystallographically distinct molecules in the unit cell have nearly identical conformations. The greatest difference between them is in the D ring where two torsion angles differ by 3° each. The ring conformations are unexceptional. The B-ring confirmations are midway between 7β-sofa and 7β,8α-half-chair. The D-ring conformations are midway between C(13)-envelope and C(13),C(14)-half-chair. The additional rings have perfect envelope conformations in which the ethano carbon attached to C(6) is displaced from the plane of the other atoms toward the β face.

The relative configuration of the major isomer of the 1,3,5(10)-triene alcohol having been established at **5**, it was clear that the major isomer of the initial pentacyclic pentaene ketone had the structure **19**. The minor isomer therefore could be attributed to the 6β-H structure **20**. Also the structures **21** and **22** could be assigned to the major isomers and **23** and **24** to the corresponding minor isomers of the 17β-ol and the 17β-acetates, respectively.

In the next phase of our studies, a number of reagents were used for the cyclodehydration of **17**, in order to optimize the yield of the major isomer **19**. The results are summarized in Table I.

When the cyclization was carried out with BF_3·etherate at −20 °C the intermediate **18** was isolated. Structural assignment of **18** was based upon spectral data [δ ($CDCl_3$) 6.20 (m, 1 H, vinylic); IR ν_{max} (KBr) 3400 cm^{-1}]. Similar intermediate compounds have been previously isolated by Ananchenko and Torgov.[12] Upon increasing the temperature of the reaction mixture from −20 °C to room temperature, **18** was rapidly converted to a mixture of **19** and **20**.

In an alternate method, a mixture of **19** and **20** was obtained in 30% yield by a direct reaction between **15** and 2-methylcyclopentane-1,3-dione in refluxing xylene and acetic acid. Although the overall yield by this second route is comparable to the first one, it was found more convenient to prepare the ketones **19** and **20** via the crystalline isothiourium salt **16**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer infrared spectrophotometer 700. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU 6L and a CEC 110 mass spectrometer. Proton nuclear magnetic resonance spectra (NMR) were recorded on a Varian T-60 spectrometer, using tetramethylsilane as the internal standard. Thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F254, EM reagents). Microanalyses were carried out by Spang Microanalytical Laboratories, Eagle Harbor, Mich. Gas–liquid chromatography (GLC) was carried out with a Varian Aerograph Model 4000 instrument. High-pressure liquid chromatography (LC) was carried out using a Water Associates Model ALC 202 instrument.

7-Methoxy-3,4-dihydro-1-naphthaleneacetic Acid (8). Following the procedure of Johnson and co-workers,[7] 132 g (0.75 mol) of 7-methoxy-1-tetralone (**6**) was converted to 182 g (97%) of methyl 1-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetate: IR (neat) ν_{max} 3525 (OH), 1730 (ester >C=O) cm^{-1}; NMR ($CDCl_3$) δ 1.64–2.20 (m, 4 H), 2.6–2.7 (m, 2 H), 2.77 (s, 2 H), 3.66 (s, 3 H, OCH_3), 3.73 (s, 3 H, $COOCH_3$), 3.9 (s, 1 H), 6.63–7.13 (m, 3 H, ArH).

A solution of this hydroxy ester (182 g) and 90% formic acid (265 mL) was heated under reflux for 2 h. Formic acid was evaporated under reduced pressure to afford methyl 7-methoxy-3,4-dihydro-1-naphthaleneacetate (**7**) and its Δ^{exo} isomer **9** as a crude brown oil (164 g, 97%): IR (neat) ν_{max} 1732 (saturated ester >C=O), 1720 cm^{-1} (unsaturated ester >C=O).

To the crude methyl 7-methoxy-3,4-dihydro-1-naphthaleneacetate (**7**) and its isomer **9** (177 g, 0.76 mol) was added 20% methanolic potassium hydroxide (300 mL). The mixture was heated under reflux for 6.5 h and the methanol was removed under pressure. Water (750 mL) was added and the mixture was extracted with ether (3 × 250 mL) to remove any unsaponified material. The aqueous layer was treated with Norit (5 g), filtered through celite, and acidified with 10% HCl (350 mL) to give the unsaturated acids **8** and **10** (147 g, 89%): mp 124–135 °C (lit.[7] mp 122–138.5 °C); NMR ($CDCl_3$) δ 2.07–2.94 (m, 4 H), 3.43 (s, 2 H), 3.77 (s, 3 H), 6.03 (m, olefinic proton of compound **8**), and 6.33 (m, olefinic proton of compound **10**), 6.63–7.13 (m, 3 H).

7-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid (11). A solution of the compound **8** and its isomer **10** (113.5 g, 0.52 mol) in ethyl acetate (600 mL) was hydrogenated at room temperature and atmospheric pressure using 10% Pd/C (11.5 g). Filtration through celite and evaporation under reduced pressure yielded crude 7-methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic acid (**11**), mp 80–86 °C (102.2 g). Recrystallization of a 30.0-g sample from hexane gave 25.9 g of pure **11**, mp 88–90 °C (lit.[7] mp 88.5–89.5 °C), as white crystals: NMR ($CDCl_3$) δ 1.53–1.94 (m, 4 H), 2.53–2.9 (m, 4 H), 3.1–3.46 (m, 1 H), 3.75 (s, 3 H, OCH_3), 6.6–7.05 (m, 3 H, ArH).

8-Methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone (12). Liquid HF (1500 mL) was added to 127 g (0.58 mol) of **11** in lightly capped polyethylene bottles. The mixture was stirred at room temperature for 48 h. Then the cap was removed and stirring continued for five days to remove the HF. Addition of water (50 mL), 5% Na_2CO_3 (100 mL), and benzene (250 mL) followed by extraction of the benzene layer with 5% Na_2CO_3 (5 × 100 mL) and water (2 × 100 mL) yielded, after drying ($MgSO_4$) and concentration under reduced pressure, 108 g (93%) of 8-methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone (**12**), mp 95–97 °C. Recrystallization from benzene and petroleum ether (40–60 °C) gave pure **12**, mp 97–98 °C (lit.[7] mp 98–99.5 °C): NMR ($CDCl_3$) δ 1.88–3.27 (m, 9 H), 3.9 (s, 3 H, OCH_3), 6.7 (d, 1 H), 7.3 (d, 1 H); MS *m/e* 202 (M^+).

8-Methoxy-2a,3,4,5-tetrahydroacenaphthene (13). To mossy zinc (336 g) was added a 10% HgCL solution (300 mL) followed by addition of concentrated hydrochloric acid (15 mL) and the mixture was shaken for 5 min. The aqueous solution was decanted. The amalgamated zinc was covered with water (280 mL) and concentrated hydrochloric acid (500 mL). A solution of the ketone **12** (141 g, 0.698 mol) in toluene (300 mL) was added and the mixture was heated under reflux. After 18 h of reflux, concentrated hydrochloric acid (100 mL) was added and heating was continued for an additional 10 h. The reaction mixture was cooled and the organic phase was separated. The water layer was extracted twice with toluene (2 × 100 mL). The combined extracts were washed twice with 5% Na_2CO_3 (2 × 50 mL) and dried over $MgSO_4$. After filtration, the solution was concentrated in vacuo to afford 127 g of the crude **13**. It was vacuum distilled, bp 85 °C (0.01 mm), to furnish 110.5 g (85%) of **13** as a colorless oil: NMR ($CDCl_3$) δ 1.0–2.33 (m, 6 H), 2.33–3.23 (m, 5 H), 3.77 (s, 3 H, OCH_3, 6.6 (d, 1 H), 6.88 (d, 1 H); MS *m/e* 188 (M^+).

8-Methoxy-2a,3,4,5-tetrahydro-5-acenaphthenone (14). A solution of 13.0 g (0.13 mol) of CrO_3 in 50 mL of acetic acid–water (4:1) was added dropwise to a stirred and cooled (ice bath) solution of 10.2 g (0.054 mol) of 8-methoxy-2a,3,4,5-tetrahydroacenaphthene (**13**) over a period of 1 h. Cooling and stirring were continued for another 16 h and the reaction mixture was poured into ice water (500 mL). After addition of concentrated HCl (20 mL) the solution was extracted with chloroform. The organic layer was washed with 5% Na_2CO_3 solution (4 × 50 mL) and then with water (50 mL). Drying ($MgSO_4$) and evaporation of the solvent in vacuo yielded 8.2 g (75%) of **14** as a yellow brown oil, which solidified on standing. This was crystallized from a mixture of ether and petroleum ether to give pure **14**: mp 80–81 °C; NMR ($CDCl_3$) δ 1.0–3.40 (m, 9 H), 3.9 (s, 3 H, OCH_3), 6.77 (d, 1 H), 7.75 (d, 1 H); IR (KBr) ν_{max} 1665 cm^{-1}; MS *m/e* 202 (M^+).

Anal. Calcd for $C_{13}H_{14}O_2$ (mol wt 202): C, 77.20; H, 6.98. Found: C, 77.27; H, 6.9.

8-Methoxy-2a,3,4,5-tetrahydro-5-vinyl-5-acenaphthenol (15). A solution of 4.6 g (0.023 mol) of the ketone **14** in tetrahydrofuran (10 mL) and ether (15 mL) was added dropwise under nitrogen over 30

min to a stirred and cooled (NaCl, ice bath) solution of vinylmagnesium bromide prepared from 1.2 g (0.05 mol) of magnesium and 6.4 g (0.06 mol) of vinyl bromide in tetrahydrofuran–ether (10 + 10 mL). Stirring under cooling was continued for 2 h and the reaction mixture was left at room temperature overnight. The solution was then refluxed for 2 h and the Grignard complex was decomposed with 10% NH_4Cl solution (25 mL). After addition of water (200 mL), the organic layer was extracted with 5 × 50 mL of chloroform. Drying ($MgSO_4$) and evaporation of the solvent in vacuo yielded 5.1 g (97%) of **15** as a brown oil: IR (neat) ν_{max} 3400 cm^{-1} (OH); NMR ($CDCl_3$) δ 3.80 (s, 3 H, OCH_3), 5.0 (m 2 H, vinylic), 6.05 (m, 1 H, vinylic), 6.69 (d, 1 H), 7.12 (d, 1 H).

2-(8-Methoxy-2a,3,4,5-tetrahydro-5-acenapththylidenyl)-ethylisothiouronium Acetate (16). A solution of **15** (5 g, 0.0217 mol) and thiourea (1.65 g, 0.0217 mol) in acetic acid (17.5 mL) was stirred for 30 min at room temperature. After standing at room temperature for 18 h ether (115 mL) was added under stirring. The precipitate was filtered, washed with ether, and dried in vacuo to yield 3.11 g of **16** as a light yellow crystalline product. The combined filtrate and washings were concentrated in vacuo to yield a brown oil, which on trituration with 50 mL of benzene–ether 1:1 afforded a crystalline material. Filtration, washing, and drying yielded an additional 1.42 g for a total of 4.53 g (60%) of **16.** This on recrystallization from acetic acid–ether furnished analytically pure material: mp 136–137 °C; NMR (Me_2SO-d_6 with Me_2SO-d_5 at 2.50 as internal standard) 1.79 (s, 3 H, C–CH_3), 3.78 (s, 3 H, OCH_3), 6.75 and 7.45 (AB, 2 H, Ar–H).

Anal. Calcd for $C_{18}H_{24}N_2O_3S$ (mol wt 348.46): C, 62.04; H, 6.94; N, 8.04; S, 9.20. Found: C, 61.83; H, 7.14; N, 8.06; S, 9.14.

4,6-Ethano-3-methoxy-8(14)-seco-1,3,5(10),9(11)-estratetraene-14,17-dione (17) Method A. To a mixture of water (80 mL), ether (40 mL), and benzene (40 mL) was added 4.4 g (0.013 mol) of **16** and 2-methylcyclopentane-1,3-dione (1.7 g, 0.016 mol) and the mixture was stirred at room temperature for 18 h. A small amount of a gummy material was filtered off and 125 mL of water and 60 mL of benzene–ether (1:1) were added. The organic phase was separated and the aqueous layer was extracted with benzene–ether (1:1, 2 × 50 mL). The combined organic layers were next washed with saturated $NaHCO_3$ and saturated NaCl solution, respectively. Drying ($MgSO_4$) and evaporation of the solvent yielded 2.64 g (65%) of **17** as a crystalline product. This on recrystallization from a mixture of methanol and water afforded pure **17,** mp 89–90 °C: NMR ($CDCl_3$) δ 1.13 (s, 3 H, C–CH_3), 2.67 (s, 4 H, –$COCH_2CH_2CO$–), 3.81 (s, 3 H, OCH_3), 5.80 (m, 1 H, vinylic), 6.60 (d, 1 H), and 7.27 (d, 1 H); IR (KBr) ν_{max} 1718 cm^{-1}; MS *m/e* 324 (M^+), 213 (M − 111), 185 (M − 139).

Anal. Calcd for $C_{21}H_{24}O_3$ (mol wt 324.42): C, 77.75; H, 7.46. Found: C, 77.99; H, 7.12.

Method B. A 40% solution of Triton B in methanol (10 mL) was stirred with dry xylene (25 mL) and the alcohol was distilled off along with xylene by heating in an oil bath under vacuum. Xylene (40 mL) and 2-methylcyclopentane-1,3-dione (8.9 g, 0.08 mol) were then added and the mixture was refluxed in an atmosphere of nitrogen. A solution of the alcohol **15** (12.6 g, 0.055 mol) in xylene (75 mL) was slowly introduced during 1.5 h with stirring and refluxing. Refluxing was continued for an additional 2 h. Ether (200 mL) was added to the cooled mixture and the unchanged 2-methylcyclopentane-1,3-dione, which precipitated out, was filtered. The filtrate was washed with 5% KOH, followed by H_2O. The organic layer was dried and evaporated to furnish the crude material. This was chromatographed over alumina and the purified material was further recrystallized from dilute methanol to give the pure secosteroid **17,** mp 89–90 °C (yield 7 g, 40%).

4,6β-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (19) and 4,6α-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17-one (20). Method A. To a solution of the secosteroid **17** (3 g, 0.0093 mol) in benzene (30 mL) was added *p*-toluenesulfonic acid (0.15 g) and the mixture was refluxed for a period of 45 min using a Dean Stark apparatus. The reaction mixture was cooled and diluted with more benzene (100 mL). The benzene solution was washed successively with water and saturated sodium bicarbonate solution and finally with water. After drying over anhydrous Na_2SO_4 and filtration, the solution was concentrated to furnish 3 g of the crude ketone. This was crystallized from a mixture of methanol, acetone, chloroform, and petroleum ether to give 2 g (71%) of a pure mixture of isomers **19** and **20,** mp 185–186 °C dec. High-pressure liquid chromatography of the product showed a single peak; capacity factor K' = 1.8; 8 ft × ⅛ in. Corasil II, solvent system, cyclohexane–ethyl acetate (98:2): NMR ($CDCl_3$) δ 1.10 (s) and 1.17 (s, 3 H, ratio 70:30, C–CH_3), 3.83 (s, 3 H, OCH_3), 5.87 (m, 1 H, vinylic), 6.63 and 7.07 (AB, 2 H, ArH); IR (KBr) ν_{max} 1745 cm^{-1}; MS *m/e* 306 (M^+), (67), 278 (M − 28, 100), 263 (22), 249, 235, and 139.

Anal. Calcd for $C_{21}H_{22}O_2$ (mol wt 306.41): C, 82.32; H, 7.24. Found: C, 82.31; H, 7.22.

Method B. To a solution of 3.24 g (0.01 mol) of **17** in 100 mL of methylene chloride was added boron trifluoride etherate (0.13 mL) under stirring and cooling in an ice bath. The reaction was followed by TLC (ether–petroleum ether 1:1 on silica gel); the starting material **17** (R_f 0.4) was consumed within 2 h to give increasing amounts of an intermediate **18** (R_f 0.3) and the products **19** and **20** (R_f 0.8). A third compound (R_f 0.5), which was not further investigated, was formed in a very small amount. During the next 15 h all of the intermediate was converted into products.

After a total of 17 h at 0 °C, a saturated solution of $NaHCO_3$ (100 mL) was added whereby the dark green color of the reaction mixture slowly turned brown. The two layers were separated and the aqueous layer was extracted four times with 25 mL of methylene chloride. The combined organic layer was washed twice with 50 mL of water. Drying over magnesium sulfate and evaporation of the solvent in vacuo yielded 2.75 g (90%) of a mixture of **19** and **20** as a violet, crystalline compound. The isomer ratio of the products was found to be 82:18, as calculated from the heights of the two C–CH_3 signals in the NMR spectrum.

Method C. To a solution of **17** (0.075 g) in deuteriochloroform (0.3 mL) in an NMR tube was added trifluoracetic acid (3 μL). The reaction was followed by NMR at ambient temperature (normal probe temperature). As the reaction proceeded, at least two intermediates were clearly seen emerging and disappearing before the spectrum finally (after 72 h) was identical with that of a mixture of **19** and **20.** Diketone **17:** δ 5.80 (m, 1 H, vinylic). Intermediate **18:** δ 6.20 (m, 1 H, vinylic).

Mixture of 19 and 20: δ 5.87 (t, J = 2 Hz, 1 H, vinylic). The isomer ratio of the product was found to be 80:20 as calculated from the heights of the 13β-methyl peaks. The reaction mixture was not worked up.

Method D. To a stirred solution of **15** (2.3 g, 0.01 mol) in xylene (20 mL) was added 2-methylcyclopentane-1,3-dione (1.68 g, 0.015 mol) and acetic acid (10 mL). The mixture was refluxed under nitrogen for 2 h and after concentration to a small volume ether–benzene (1:1) was added. The precipitated unreacted 2-methylcyclopentane-1,3-dione was recovered by filtration and washed with ether. The combined filtrates were extracted with 5% $NaHCO_3$ followed by saturated NaCl solution, dried (Na_2SO_4), and filtered. Concentration of the filtrate under vacuum afforded the crude material. Crystallization from a mixture of methanol, acetone, chloroform, and petroleum ether furnished 0.91 g (30%) of crystalline material, which was a mixture of **19** and **20.**

Isolation of Pure 4,6β-Ethano-3-methoxyestra-1,3,5(10),-8,14-pentaen-17-one (19). A mixture of **19** and **20** (0.565 g) which had been purified by preparative TLC was recrystallized three times from mixtures of methanol–methylene chloride–benzene, ethanol–ethyl acetate–methylene chloride, and methanol–methylene chloride, respectively. NMR spectra revealed that the mother liquor was enriched in the major isomer. Combination and concentration of the mother liquors gave 400 mg of a crystalline product. This was purified by preparative TLC to give 0.18 g of product, which was again recrystallized from methanol–methylene chloride. Further concentration of the mother liquor, followed by recrystallization, provided **19** (0.12 g) as a strongly violet, crystalline compound: mp 173–175 °C; NMR ($CDCl_3$) δ 1.10 (s, 3 H, C–CH_3), 5.90 (t, J = 3 Hz, 1 H, vinyl), 6.69 and 7.10 (AB, J = 8 Hz, 2Ar–H); IR (KBr) ν_{max} 1745 cm^{-1}; MS *m/e* 306 (M^+).

Isolation of Intermediate 18 from the Cyclization of 17. To a solution of **17** (4.86 g, 0.015 mol) in methylene chloride (150 mL) was added boron trifluoride etherate (0.37 mL) under stirring and cooling (−20 °C) in a sodium chloride–ice bath. A TLC analysis after 138 h at −20 °C showed the presence of product and an intermediate, while all starting material had been consumed. The mixture was worked up as described earlier to give a crystalline product (4.7 g). The NMR spectrum showed the presence of the steroidal ketone and the intermediate **18** in about equal amounts. A part of this product (0.4 g) was purified by preparative TLC using silica gel plates and ether–petroleum ether–methylene chloride (1:1:1) as the solvent system. This resulted in the isolation of two fractions. The faster moving fraction (R_f 0.8, yield 0.115 g) was identified as a mixture of **19** and **20.** The second fraction (R_f 0.3) yielded a crystalline compound: mp 78–86 °C; IR (KBr) ν_{max} 3400, 2950, 2860, 1720, 1600, 1495, 1455, 1265, 1100, 1065, 1040, 795 cm^{-1}; NMR ($CDCl_3$) δ 1.13 (s, 3 H, C–CH_3), 3.83 (s, 3 H, OCH_3), 6.20 (m, 1 H, vinylic), 6.69 and 7.36 (AB, 2 H, Ar–H); MS *m/e* (M^+), 306 (M − 18). The compound was *tentatively* assigned the structure 4,6-ethano-14-hydroxy-3-methoxyestra-1,3,5(10),9(11)-tetraen-17-one (**18**).

The rest of the mixture (4.3 g) was treated with boron trifluoride etherate in methylene chloride solution at room temperature for 12 h. After workup in the usual manner, the mixture **19** and **20** was obtained as a dark crystalline product (3.5 g). An attempted purification by column chromatography on neutral alumina using benzene as the solvent led mainly to decomposition. The first fractions gave 900 mg of the mixture **19** and **20** as a violet, crystalline product. Further elution with benzene–chloroform (95:5) gave ca. 1 g of a dark blue, crystalline mixture of compounds, which did not contain either **19** or **20** and which was not further analyzed or identified.

4,6β-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (21) and 4,6α-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol (23). To a solution of 1 g of the ketone mixture **19** and **20** in tetrahydrofuran (20 mL) was added a solution of sodium borohydride (0.37 g) in ethanol (15 mL) dropwise during 15 min. It was then stirred for 2 h at room temperature. The reaction mixture was then cooled and acidified with acetic acid (1 mL). The solvent was evaporated under reduced pressure and the reaction mixture was diluted with water and extracted with a mixture of ether and ethyl acetate. The organic layer was washed successively with water and sodium bicarbonate and finally with water. The solvent was dried and evaporated to furnish 1 g of the crude alcohol. High-pressure liquid chromatography of the product showed a single peak; capacity factor $K' = 2.07$; 8 in. × ⅛ in. Corasil II; solvent system; cyclohexane–EtOAc (7:1). NMR of the crude alcohol showed it to be a mixture of **21** and **23** (ratio 81:19). Repeated recrystallization (seven times) from a mixture of methanol and chloroform furnished a constant melting material, the minor isomer of **23**: mp 210–212 °C; MS *m/e* 308 (M^+); NMR ($CDCl_3$) δ 1.00 (s, 3 H, C–CH_3), 3.85 (s, 3 H, OCH_3), 6.66 and 7.13 (2 H, Ar–H).

Anal. Calcd for $C_{21}H_{24}O_2$ (mol wt 308.4): C, 81.78; H, 7.84. Found: C, 81.74; H, 7.71.

The mother liquor of the above crystallization was evaporated to dryness and the residue was recrystallized three times from a mixture of ether and petroleum ether to furnish pure major isomer **21**: mp 172–173 °C; NMR ($CDCl_3$) δ 0.94 (s, 3 H, C–CH_3), 3.8 (s, 3 H, OCH_3), 6.63 and 7.03 (2 H, Ar–H); MS *m/e* 308 (M^+).

Anal. Calcd for $C_{21}H_{24}O_2$ (mol wt 308.4): C, 81.78; H, 7.84. Found: C, 81.77; H, 7.78.

4,6β-Ethano-3-methoxyestra-1,3,5(10),8,14-pentaen-17β-ol Acetate (22). To a solution of pentaene alcohols **21** and **23** (3 g) in pyridine (20 mL) was added acetic anhydride (8 mL) and the mixture was stirred at room temperature for 48 h. The reaction mixture was treated with ice water and the material was extracted with ether. The ethereal extract was washed successively with water and dilute hydrochloric acid and finally with water. The solvent was dried (Na_2SO_4) and evaporated to furnish the crude acetate (3 g). High-pressure liquid chromatography of the product showed a single peak; capacity factor $K'' = 2.2$; 8 in. × ⅛ in. Corasil II; solvent system, *n*-hexane–ethyl acetate (99:1). NMR spectra of this material showed the presence of two isomers **22** and **24**, C–CH_3 signals appearing at δ 0.95 (major) and 1.05 (minor). Mass spectrum showed the molecular ion at 350. It was crystallized four times from a mixture of methanol and chloroform to furnish the major isomer **22**: mp 183–184 °C; NMR ($CDCl_3$) δ 0.95 (s, 3H, C–CH_3), 2.10 (s, 3 H, CO–CH_3), 3.85 (s, 3 H, OCH_3), 5.05 (t, $J = 8.5$ Hz, CH_3 at position 17), 5.53 (m, 1 vinylic H), 6.67 and 7.09 (AB, 2 H, Ar–H); IR (KBr) ν_{max} 2950, 2860, 1735, 1595, 1495, 1450, 1375, 1250, 1200, 1100, 1055, 1035, 810 cm^{-1}; MS *m/e* 350 (M^+, 12), 290 (100), 275 (12), 165 (5).

Anal. Calcd for $C_{23}H_{26}O_3$ (mol wt 350.46): C, 78.82; H, 7.48. Found: C, 78.92; H, 7.31.

NMR spectra of the mother liquor indicated that it was enriched in the minor isomer **24** (C–CH_3 at δ 1.05). Attempts to isolate this isomer in the pure form were not successful.

4,6β-Ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol Acetate (25). A solution of the acetate **22** (0.175 g) in tetrahydrafuran (200 mL) was hydrogenated in the presence of 5% Pd–$CaCO_3$ (175 mg) at room temperature, using 2 mol of hydrogen. The product was filtered through celite, and the solvent was removed under reduced pressure. The white crystalline product (0.176 g) (99%) was recrystallized from 95% ethanol–$CHCl_3$ to give **25** as a colorless solid: mp 201–202 °C; NMR ($CDCl_3$) δ 0.87 (C–CH_3), 2.03 (acetate >C=O), 3.8 (OCH_3), 6.63 and 6.96 (2 H, ArH); IR (KBr) ν_{max} 1732 cm^{-1} (acetate >C=O); MS *m/e* 354 (M^+).

Anal. Calcd for $C_{23}H_{30}O_3 \cdot \frac{1}{2}H_2O$: C, 75.99; H, 8.59. Found: C, 75.93; H, 8.43.

4,6β-Ethano-3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (5). To a suspension of **25** (0.105 g, 0.0003 mol) in 15 mL of methanol–acetone–water (9:5:1) was added one pellet of 85% KOH (0.1 g). Gentle reflux for 1 h gave a homogeneous solution. The product was concentrated in vacuo and next treated with water. The alkaline solution was made slightly acidic with 10% hydrochloric acid and extracted with ether (3 × 10 mL). The organic layer was separated and washed with water, 5% $NaHCO_3$ solution, and again with water. After drying ($MgSO_4$) and filtration, the solution was concentrated to afford 0.10 g of crude **5**. This was purified by preparative TLC (methylene chloride–ether, 1:1) to give 0.08 g of **5** as a colorless oil. Recrystallization from ethanol–water provided pure **5**: mp 166–167 °C (softening at 140 °C); NMR ($CDCl_3$) δ 0.80 (s, 3 H, C–CH_3), 1.2–3.0 (m, 18 H, alkyl H), 3.61 (t, $J = 8$ Hz, 1 H, CHOH), 3.78 (s, 3 H, OCH_3), 6.64 and 6.96 (AB, 2 H, ArH). LC of the compound showed a single peak (*n*-hexane–ethyl acetate, 7:1); IR (KBr) ν_{max} 3390 cm^{-1} (OH); MS M^+ at 312.

For X-ray crystallographic studies, single crystals of the hemihydrate of **5** were grown by evaporation of an acetone–ethanol solution.

Acknowledgment. The authors would like to express their sincere thanks to Professor J. C. Sheehan and Drs. R. K. Razdan, H. C. Dalzell, and H. G. Pars for valuable suggestions throughout the period of this research. This work was supported by a contract from NICHD, NIH, Bethesda, MD (NO1-HD-3-2733). The X-ray work was supported in part by Grant CA 10906, awarded by the National Cancer Institute, DHEW. We gratefully acknowledge the help of Dr. C. Costello of the Massachusetts Institute of Technology for recording the mass spectra.

Registry No.—**5**, 68779-46-4; **6**, 6836-19-7; **7**, 68707-29-9; **8**, 27533-69-3; **9**, 68707-30-2; **10**, 63319-95-9; **11**, 68707-31-3; **12**, 68707-32-4; **13**, 68707-33-5; **14**, 68707-34-6; **15**, 68707-35-7; **16**, 68707-37-9; **17**, 68707-38-0; **18**, 68707-39-1; **19**, 68707-40-4; **20**, 68715-82-2; **21**, 68707-41-5; **22**, 68707-42-6; **23**, 68779-47-5; **24**, 68779-48-6; **25**, 68707-43-7; methyl 1-hydroxy-7-methoxy-1,2,3,4-tetrahydro-1-naphthalene acetate, 68707-44-8; vinyl bromide, 593-60-2; 2-methylcyclopentane-1,3-dione, 765-69-5.

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