Tetrahedron. Vol. 31, pp. 2369 to 2377 Pergamon Press 1975. Printed in Great Britain

THE TOTAL SYNTHESIS AND ANTI-FERTILITY ACTIVITY OF 6-SILASTEROIDS

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Received in U.S.A. 24 December 1974; Received in UK for publication 13 May 1975)

Abstract—4,4-Dimethyl-6-methoxy-4-sila-1-tetralone (2) was prepared by a modified literature procedure and converted to 3-methoxy-6,6-dimethyl-6-silaestra-1,3,5(10),8,14-pentaen-17β-yl acetate (**5c**). Catalytic hydrogenation of **5c** gave 3-methoxy-6,6-dimethyl-6-silaestra-1,3,5(10),8-tetraen-17β-yl acetate (**6b**), and its 14-iso- and $\Delta^{1,3,5(10),8(14)}$ isomers, the proportions varying with the catalyst and solvent. Reduction of **6b** with lithium-liquid ammonia, and O-demethylation, gave 6,6-dimethyl-6-silaestradiol (**8b**). Reduction of the 3-methyl ether of **8b** with lithium-liquid ammonia-*t*-butanol and hydrolysis afforded 3-keto-6,6-dimethyl-6-silaestr-1(10)-en-17β-ol (**15**), which was catalytically reduced to its 1,10α-dihydro derivative **17**. The 5,6 Si-C bond of **8b**, **15** and their derivatives was cleaved by boron tribromide, aq. ethanolic hydrogen fluoride, and other reagents, providing a series of 5,6-seco-6,6-dimethyl-6-silasteroids. X-ray crystallographic analysis of **17** and the 17α-ethynyl derivative of **15** confirmed the stereochemical assignments. None of the compounds which were subjected to uterotropic, anti-uterotropic, or post-coital assays, showed significant activity. A partially completed synthesis of 6-silaestradiol (**21a**) is described.

A wide variety of aza-, oxa- and thiasteroids, isoelectronic with the natural steroidal hormones, have been synthesized in the last decade as part of an intensive search for new contraceptive agents.[1,2] In contrast, little work on silasteroids has been carried out, despite the fact that silicon is in the same periodic group as carbon and forms tetrahedral derivatives.[3] There are numerous examples of attachment of triakylsilyl groups to extra-annular sites of steroids, sometimes leading to enhanced hormonal activity,[4,5] but only one report of the replacement of an annular carbon by silicon. This single report[6] described the synthesis of 6,6 - dimethyl - 6 - silaestra - 1,3,5(10),8 - tetraen - 17β - ol (**6a**), which proved to be only weakly estrogenic. However, because of the uncertain stereochemistry at C-14 and the presence of the 8,9-double bond and the 3-OMe group in **6a**, it is not possible to draw any conclusions about the effect of the introduction of the Me_2Si group on the hormonal activity.

We have now synthesized a number of 6,6-dimethyl-6-silasteroids which are more closely related to estradiol and known contraceptive agents, established their stereochemistry, and determined their hormonal activity. Several 5,6-seco-6-silasteroids have also been synthesized, and some of the problems associated with the synthesis of 6-silasteroids with functional groups attached to silicon have been defined.

Synthetic procedures

6,6 - *Dimethyl* - 6 - *silaestra* - 1,3,5(10),8,14 - *pentaen* - 17β - *ol* (**5b**). As Barcza recognized,[6] the total synthesis of the estrane ring system pioneered by Ananchenko and Torgov,[7] and Hughes and Smith,[8,9] can be readily adapted† to 6,6-dimethyl-6-silasteroids by initiating the synthesis with the tetralone **2**.

2 was obtained by a modification of Barcza's procedure.[6] Commercially available dimethylchlorosilane was treated with *m*-methoxyphenylmagnesium bromide, to give **1a** in 86% yield. Chloroplatinic acid catalyzed addition of **1a** to acrolein diethyl acetal gave the terminal adduct **1b**, with no evidence of the non-terminal adduct **1c**. Oxidation of **1b** with Jones' reagent, followed by saponification, gave the carboxylic acid **1d** in 58% from **1a**. This yield was increased to 72% when the less expensive allyl acetate was substituted for acrolein diethyl acetal, and the adduct **1e** was saponified and oxidized with Jones' reagent. Cyclization of **1d** using phosphorus pentachloride-stannic chloride gave the silatetralone **2** in 92% yield.

The construction of the C and D rings of **5b** was then accomplished by the standard procedure,[6,‡] i.e. **2**→**3**→**4**→**5a**. The cyclization-dehydration step, **4**→**5a** was sensitive to the amount of acid used, apparently because of aryl-silicon bond cleavage,[10] and was best carried out using a catalytic amount of anhydrous p-toluenesulfonic acid in refluxing benzene.

Reduction of the 17-keto group of **5a** with sodium borohydride gave **5b** which, on acetylation, gave **5c** in 40% overall yield from **2**.

6,6-*Dimethyl-6-silaestradiol* (**8b**). The conversion of **5c** to **8b** first required reduction of the 14, 15 double bond to introduce the trans C/D ring juncture. Barcza[6] reported that this could be accomplished by hydrogenation of **5b** in the presence of 5% $Pd/CaCO_3$ in ethanol. However, his product was an oil and no proof of stereochemistry was offered. In our hands, hydrogenation of **5b** or **5c** under the same conditions gave mixtures of three dihydro products. The PMR spectrum of the mixture derived from **5c** showed C-18 Me resonances at δ 0·84, 0·90 and 0·99, in the ratio 42:33:25. These were assigned to **6b**, **7** and **6c**, respectively, after separation of **6b** and **7** as pure crystalline solids.

†Because of the inability of silicon to form stable p_π double bonds, and the ready cleavage of α- and β-silyl ketones,[10] this synthetic route cannot be used to introduce silicon in any other position of the estrane skeleton.

‡The procedures used for the preparation of compounds **2**–**5** are the same as those reported by Barcza;[6] however, since yields and spectroscopic properties have not been published, this information is included in the experimental section.

The PMR spectrum of 7 showed no olefinic protons, and the olefinic double bond must therefore be tetrasubstituted, i.e. $\Delta^{8(14)}$ or Δ^{8}. The former was preferred on the basis of a one proton triplet at δ 3·49, which was assigned to the allylic and benzylic 9α-proton coupled to the methylene protons. The structures of **6b** and **6c** were assigned on the basis of Zurcher's studies,[11] which have established that the C-18 methyl resonance of a trans C/D steroid is generally at higher field relative to the cis C/D analog.

The low yield of the trans product **6b** using 5% $Pd/CaCO_3$ prompted a search for more stereospecific hydrogenation conditions. The use of amines as co-solvents was evaluated because of the report[12] that they inhibit double bond migration and so should minimize the formation of 7. In fact the reverse effect was observed (Table 1) and **6b** was best obtained using 5% Pd on carbon in benzene (85% yield).

The next step in the synthesis was reduction of the 8,9 double bond of **6b**, to produce the trans-*anti*-trans BCD ring stereochemistry. In the synthesis of natural steroids this has been accomplished by three different methods, (1) alkali metal-ammonia reduction,[13] (2) triethylsilane/trifluoroacetic acid reduction,[14] and (3) acid catalyzed conversion to the $\Delta^{9(11)}$-isomer followed by catalytic reduction.[15] The latter two methods proved to be inapplicable to **6b**, for none of the desired product **8a** could be detected under these conditions. This result appeared to be a consequence of the sensitivity of the allyl-silicon and aryl-silicon bonds of **6a** to acid-promoted cleavage (*vide infra*). Cleavage of these carbon-silicon bonds also occurred using potassium, sodium, or lithium in liquid ammonia,[16] although with the latter metal **8a** could be isolated in 51% yield.

Hydrogenation of **6a** in the presence of 5% Pd on carbon gave no **8a**, but two different products. These were presumed to be the two possible cis-B/C isomers of **8a** produced by α- and β-face reduction of the 8,9 double bond. This supported the assigned trans B/C structure of **8a** although it did not differentiate between trans-*anti*-trans and trans-*syn*-trans BCD stereochemistry.

Conversion of **8a** to the 6,6-dimethyl-6-sila analog of estradiol (**8b**) was first attempted using boron tribromide in methylene chloride at 25°C. Surprisingly aryl-silicon bond cleavage occurred to the exclusion of O-demethylation, despite the fact that O-demethylation of an acyclic analog **9** was effected without such a complication. Partial aryl-silicon bond cleavage also occurred to some extent using pyridine hydrochloride (200°, 2 hr), while lithium iodide-collidine accomplished neither O-demethylation nor aryl-silicon cleavage. However, **8b** could be obtained in excellent yield by treatment of **8a** with methylmagnesium iodide (180°, 2 hr).[17]

The 6,6-dimethyl-6-sila analog of mestranol (**10b**), a potent oral contraceptive agent, was obtained from **8a** in 56% yield by Oppenauer oxidation to the 17-ketone **10a** and ethynylation with the ethylenediamine complex of lithium acetylide.

6,6-Dimethyl-6-sila analogs of 3-keto steroids. Birch reduction of **6b** with lithium in liquid ammonia in the presence of t-butanol gave the $\Delta^{1(10),3}$-dien-3-ol ether **11** as the major product. The structure of **11**, which is isomeric with the $\Delta^{2,5(10)}$-dien-3-ol-ether produced by Birch reduction of estradiol 3-methyl ether, was unequivocally established by its PMR spectrum which showed two olefinic protons at δ4·57 (d, J = 4 Hz, 4-CH) and 5·38 (t, J = 3 Hz, 1-CH). This change from the normal stereochemistry of Birch reduction of the aromatic A ring is not surprising in view of the report that reduction of *p*-bis(trimethylsilyl)benzene affords a diene **12** which is isomeric with the diene **13** obtained from *p*-xylene.[18] This change in the stereochemistry has been attributed to stabilization of the alternate radical anion by silicon d-orbital conjugation.[18]

Compound **11** proved susceptible to rearomatization, and approximately 50% conversion to **8a** occurred after 24 hr at room temperature. When 5% palladium on carbon or platinum[19] were added to promote this aromatization, at least two other products were observed in addition to **8a**. These by-products probably arose from silicon-carbon cleavage during the aromatization process. Rearomatization, along with oxidation of the 17-OH group, could also be accomplished with chromium trioxide-pyridine. In this case, isolation of the silanol **14a** as a by-product confirmed that some silicon-carbon cleavage had occurred.

Hydrolysis of **11** with oxalic acid in aq. methanol gave

Table 1. Catalytic hydrogenation of 14,15-double bond of 5c

CATALYST	SOLVENT	TIME	% PRODUCT COMPOSITION		
			6b (trans)	6c (cis)	7
5% $Pd/CaCO_3$	Ethanol	10 min	42	25	33
5% $Pd/SrCO_3$	Ethanol	30 min	41	13	46
5% Pd/C	Ethanol	30 min	55	0	45
5% Pd/C	Benzene	10 min	85	0	15
5% Pd/C	Ethanol/0.2% Piperidine	45 min	36	5	59
5% Pd/C	Ethanol/2% Piperidine	1 hr	38	2	60
5% Pd/C	Ethanol/20% Piperidine	3 hr	45	2	53
5% Pd/C	Ethanol/2% Pyridine	7 hr	34	7	59
5% Pd/C	Pyridine		NO REACTION		
5% Pd/C	Ethanol/2% Triethylamine	3.5 hr	33	16	51
5% Pd/C	Ethanol/2% Pyrrolidine	1 hr	40	3	57
PtO_2	Ethanol	5 hr	13	27	60
PtO_2	Ethanol/2% Pyridine	24 hr	NO REACTION		
PtO_2	Acetic Acid	3 hr	0	0	100
$(Ph_3P)_3RhCl$	EtOH	24 hr	NO REACTION		

the expected β,γ-unsaturated ketone **15**. Surprisingly, all attempts to isomerize **15** to the conjugated Δ^1-3-ketone using acidic or basic catalysts were unsuccessful; either **15** remained unchanged or complex mixtures were obtained. The 17α-ethynyl derivative of **15** was obtained by conversion of **11** to the 3,3-dimethoxy ketal with methanol/*p*-toluenesulfonic acid, Oppenauer oxidation to the 17-ketone, and treatment with lithium acetylide ethylenediamine. Regeneration of the 3-keto group with oxalic acid in aq. tetrahydrofuran then gave **16**.

The unknown stereochemistry of the A/B ring juncture of **11**, **15** and **16** was determined by X-ray crystallographic analysis of **16**. This showed the 5 proton was alfa, and also confirmed the stereochemical assignments of the other ring junctures in the skeleton.[20]

Hydrogenation of **15** using 5% Pd on carbon in ethyl acetate gave a dihydro product **17**, and X-ray crystallographic analysis[20] established that this was A/B cis isomer derived from α-face reduction of the 1,10 double bond. This stereochemistry appeared to be dictated by the distorted conformation of the B ring of **15** which leads to shielding of the β-face by the Me_2Si group. A discussion of the effects of the 6,6-dimethyl-6-sila group on the conformation of the tetracyclic steroid skeleton will be presented elsewhere.[20]

The *cis* A/B ring juncture of **17** suggested that the Δ^3-enol would be preferentially formed on enolization of the 3-keto group[21] and, consequently, dehydrogenation with dichlorodicyanoquinone[22] or palladium chloride[23] would provide a route to the Δ^4-3-keto functionality of the natural steroids. However, while evidence of α,β-unsaturated ketone formation (ν_{max} 1670 cm^{-1}) was obtained, both reagents gave inseparable mixtures of products.

5,6-Seco-6,6-dimethyl-6-silasteroids. It has recently been reported that seco steroids can exhibit significant estrogenic activity.[24] This report, coupled with the lability of the 5,6 bond of the 6-silasteroid system, prompted the synthesis of a number of 5,6-seco derivatives.

The silanol **14a**, which was formed during oxidation of **11** with chromium trioxide-pyridine, was obtained in much better yield by treatment of **10a** with boron tribromide. The fluorosilane **14b** was initially obtained by treatment of **14a** (or the corresponding disiloxane) with aq, ethanolic hydrogen fluoride.[25] It was then found that this compound could be obtained directly and in quantitative yield by ring cleavage of **10a** with aq. ethanolic hydrogen fluoride at 50° for 18 hr.

Employing this direct method, the fluorosilanes **18a**, **18b** and **19** were prepared from **8b**, **10b** and **15**, respectively.

Since acyclic arylsilanes (e.g. **9**) are inert to ethanolic hydrogen fluoride, the reactivity of the above 6-silasteroids must be related to their cyclic structure. Eaborn *et al.*[26] have measured rates of perchloric acid cleavage of acyclic and cyclic arylsilanes and reported that the rate of cleavage of **20** was 87 times greater than that of phenyltrimethylsilane. This result was discussed in terms of relief of ring strain in the transition state. Presumably this effect is responsible for the exceptional reactivity of the 6-silasteroids towards hydrofluoric acid, boron tribromide, and other reagents noted in this paper.

Biological activity of 6,6-dimethyl-6-silasteroids. Compounds **5c**, **6b**, **7**, **8b**, **10b**, **14a**, **14b**, **16**, **18a**, **18b** and **19** were screened for estrogenic, antiestrogenic, and post-coital activity. No significant estrogenic or anti-estrogenic activity was observed using doses 10^2–10^3 times that of an estradiol standard. Compounds **8b** and **18b** exhibited post-coital activity in rat, but only at 10 mg/kg. Compound **19** showed only weak androgenic activity.

This lack of significant hormonal activity might be attributed to any of a number of factors, including (1) rapid metabolic degradation, (2) steric inhibition of complexation with the uterine receptor protein(s) due either to the gem-dimethyl substituents on silicon or to conformational changes in the total steroid skeleton resulting from the longer Si–C bonds (1·84–1·88 Å) in ring B, and (3) the electronic effect of the silicon atom on ring A functional groups.

The binding affinities of **8b**, **18a** and **19**, for the estrogen specific acceptor protein of the rat uterus[27] were measured *in vitro*, and found to be 0·3, 0·1 and <0·01%, respectively, relative to estradiol (100%). This suggests that a steric or an electronic effect, rather than metabolic instability, is responsible for the absence of estrogenicity in these compounds. It is relevant to note that introduction of a Me group in the 6β position of estradiol is known to drastically reduce estrogenicity,[28] although *dimethylation* of the 6-position has much less of an effect on anabolic and progestational activity, e.g. norethisterone and its 6,6-dimethyl derivative have comparable progestational activity.[29]

Recognizing the possible deleterious effect of the 6-methyl substituents on hormonal activity, the synthesis of the exact silicon analog of estradiol, i.e. **21a**, was explored. Because of the greater reactivity of the SiH_2 group,[3] relative to the CH_2 group, protection of the 6-position during the synthesis was necessary. Work in this laboratory had established that the benzyl group is an excellent silicon protecting group, stable to acids and moderate bases, and many oxidizing and reducing agents yet readily cleaved in ethanol in the presence of Pd on C and hydrogen,[30] i.e.

$$\text{>SiBz}_2 + H_2/EtOH \xrightarrow{Pd} \text{>Si(OEt)}_2 \xrightarrow{H^-} \text{>SiH}_2.$$

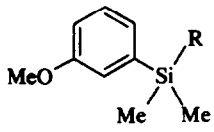
Accordingly, the synthesis of 6,6-dibenzyl-6-silaestradiol (**21b**) was initiated. Using the same sequence employed in the 6,6-dimethyl series, the synthesis of the dibenzyl analog of **5c** was accomplished. Unfortunately, lack of regiospecificity in subsequent steps, and the inability to effect purification by crystallization or elution chromatography, forced curtailment of this work.

The paucity of silicon protecting groups, plus the increased reactivity of the Si–C bond evident in the 6,6-dimethyl-6-silasteroids, create substantial synthetic obstacles.

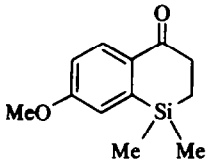
EXPERIMENTAL

M.ps were determined using a Kofler-hot-stage microscope and are uncorrected. IR spectra were measured with a Perkin-Elmer 267 Spectrophotometer. Unless otherwise mentioned, NMR spectra were recorded on a Varian Model A-100, using TMS as an internal standard; chemical shifts are expressed in δ units. Mass spectra were determined using an Associated Electrical Industries MS-902 instrument. UV absorption spectra were obtained using a Cary 14 spectrophotometer. Gas liquid chromatographic analysis was carried out using either Varian Model 1400 or Hewlett-Packard Model 700 instruments with columns containing 3% SE-30 on Variport, and 2% OV-17 on Gaschrome G, respectively. Microanalyses were carried out by Micro-Tech Laboratories, Skokie, Illinois. ChromAR was obtained from Mallinckrodt, St. Louis, Mo.

All reactions were carried out under an atmosphere of dry, oxygen-free nitrogen.



1a: R = H
b: R = $CH_2CH_2CH(OEt)_2$
c: R = $CHMe{\cdot}CH(OEt)_2$
d: R = CH_2CH_2COOH
e: R = $CH_2CH_2CH_2OAc$



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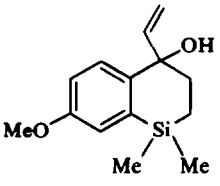

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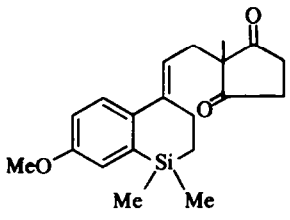

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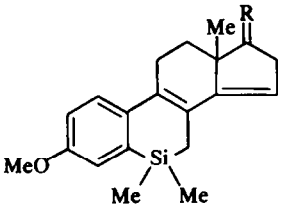
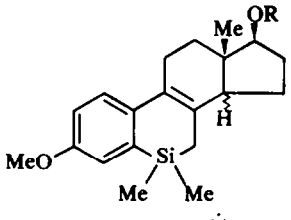
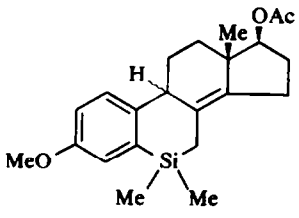


5a: R = O
b: R = β-OH, α-H
c: R = β-OAc, α-H



6a: R = H, trans C/D
b: R = Ac, trans C/D
c: R = Ac, cis C/D



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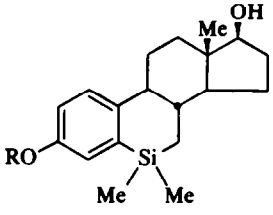
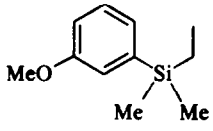


8a: R = Me
b: R = H



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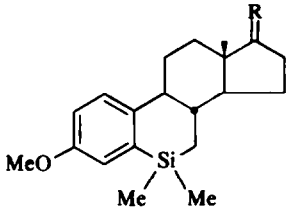
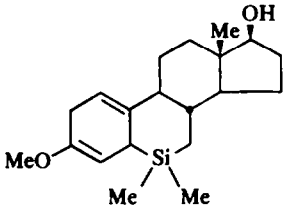


10a: R = O
b: R = α-C≡CH, β-OH



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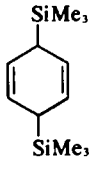

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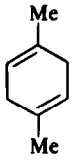

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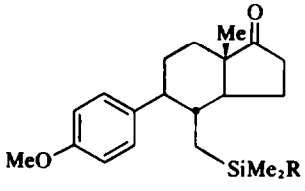
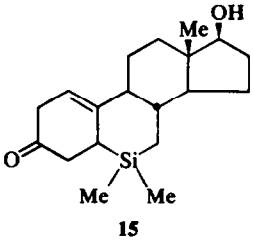


14a: R = OH
b: R = F



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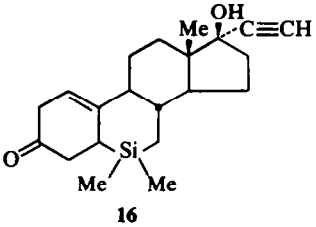

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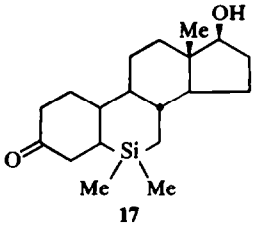

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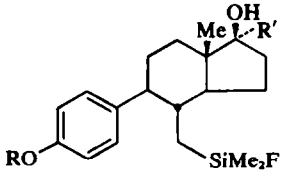
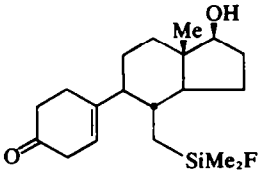


18a: R,R′ = H
b: R = Me, R′ = C≡CH



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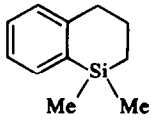
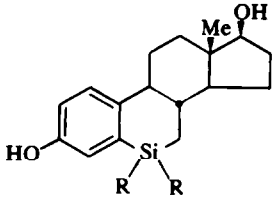


20



21a: R = H
b: R = Bz

Dimethyl-m-methoxyphenylsilane (**1a**). A soln of dimethylchlorosilane (94·0 g, 1·00 mol) in 400 ml ether was added dropwise (1 hr) to a stirred suspension of *m*-methoxyphenylmagnesium bromide (1·05 mol) in 1 l ether at room temp. After refluxing for 3 hr the mixture was cooled and hydrolyzed with 600 ml water and 1 l 1 N HCl. The two layers were separated and the aqueous layer extracted with ether (2 × 500 ml). The combined organic phases were washed with water and dried (Na_2SO_4). Distillation of the crude product *in vacuo* afforded 142 g (86%) of the silane **1a**; b.p. 102–105° (22 mm); IR (liquid film) 2115 (Si–H), 1600 (aromatic C=C) cm^{-1}; NMR ($CDCl_3$) δ 3·80 (s, 3, OCH_3), 4·42 (m, 1, $\equiv$SiH), 6·82–7·36 (m, 4, ArH). (Found *m/e*: 166·081. Required for $C_9H_{14}SiO$: *m/e* 166·081).

3-[(m-*Methoxyphenyl*)*dimethylsilyl*]*propionic acid* (**1d**). Acrolein diethyl acetal (109 g, 0·840 mol) was slowly added (1 hr) to a stirred mixture of **1a** (137 g, 0·825 mol) and chloroplatinic acid (1·3 ml, 0·1 N in isopropanol). The exothermic reaction was maintained at 25° using a water bath. After stirring for an additional 0·5 hr, the unchanged acetal was removed *in vacuo* at room temp to give 214 g of crude **1b**; IR (liquid film) 1600 (aromatic C=C) cm^{-1}; NMR ($CDCl_3$) δ 0·76 (m, 2, $\equiv SiCH_2$–CH_2–), 1·17 (t, 6, J = 8 Hz, OCH_2CH_3), 1·60 [m, 2, $-CH_2-CH_2-CH(OEt)_2$], 3·53 [q, 4, J = 8 Hz, $(OCH_2CH_3)_2$], 3·80 (s, 3, OCH_3), 4·40 (t, 1, J = 6 Hz, $-CH_2-CH(OEt)_2$], 6·80–7·36 (m, 4, ArH). The mass spectrum of **1b** showed a weak molecular ion. (Found: (M^+-15) *m/e* 281·158. Required for $C_{15}H_{25}SiO_3$ (M^+-15): *m/e* 281·157).

Jones' reagent (8 N, 600 ml, 4·80 mol) was added (2 hr) to a stirred soln of the crude **1b** (214 g, 0·723 mol) in 2 l acetone (distilled from $KMnO_4$) keeping the temp of the mixture below 5°. The excess reagent was destroyed by the dropwise addition of isopropanol (230 ml) and stirring for an additional 5 min at 0°. The mixture was concentrated to one-third its volume *in vacuo* at 0°–5°, diluted with one l of ice-water, and extracted with cold ether (3 × 1 l). The combined ether phases were shaken successively with water and NaCl aq, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* yielded a crude mixture (249 g) of ester and acid, which was saponified with KOH (1 mol) in 75% aqueous EtOH (2 l) at room temp for 2 hr. After removal of EtOH *in vacuo* the mixture was diluted with water (500 ml) and the neutral material extracted with ether. Acidification of the aqueous phase, followed by extraction with ether yielded 125 g of the acid **1d**. Distillation of the crude product *in vacuo* afforded 110 g (58%) of a low melting solid; b.p. 130–136° (0·025 mm) [reported[6] 108° (0·15 mm)]; IR (liquid film) 3600–2500 (free and bonded OH), 1705 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 1·09 (m, 2, $Si-CH_2-CH_2$), 2·12 (t, 2, J = 8 Hz, $SiCH_2CH_2COOH$), 3·79 (s, 3, OCH_3), 6·82–7·36 (m, 4, ArH), 8·56 (br s, 1, COOH). The mass spectrum of **1d** failed to show a molecular ion. (Found: (M^+-15) *m/e* 223·079. Required for $C_{11}H_{15}SiO_3$ (M^+-15): *m/e* 223·079).

In an alternative procedure, allyl acetate (58·0 g, 0·580 mol) was added dropwise to a stirred, cooled (10°) mixture of **1a** (84·3 g, 0·508 mol) and 0·5 N chloroplatinic acid in isopropanol (2 ml), and stirring was continued at room temp for 18 hr. At the end of this period more catalyst (0·1 ml) was added and the reaction was completed by heating at 50° for 3 hr. Removal of the excess allyl acetate yielded the crude **1e** (134 g, 99%), which was saponified (25°, 18 hr) with KOH (42 g) in 75% aqueous EtOH. After removal of EtOH *in vacuo*, the mixture was diluted with water and the product extracted with $CHCl_3$ (750 ml). Evaporation of the dried (Na_2SO_4) $CHCl_3$ extract gave the desired alcohol (100%) which was oxidized to the acid **1d** (72%) with Jones' reagent by the procedure described above.

6-*Methoxy*-4,4-*dimethyl*-4-*sila*-1-*tetralone* (**2**). The silatetralone **2** was prepared as a low melting solid in 92% yield following the literature procedure;[6,12] b.p. 105–107° (0·025 mm) [reported[6] 87° (0·05 mm)]; IR (liquid film) 1640 (C=O) cm^{-1}; UV (MeOH) 225 nm (ϵ 16,100), 277 (15,400); NMR ($CDCl_3$) δ 1·18 (m, 2, C-3), 2·88 (m, 2, C-2), 3·85 (s, 3, OCH_3), 6·84–6·96 (m, 2, ArH), 8·07 (d, 1, J = 10 Hz, C-8). (Found *m/e*: 220·092. Required for $C_{12}H_{16}SiO_2$: *m/e* 220·092).

1,1-*Dimethyl*-4-*hydroxy*-7-*methoxy*-4-*vinyl*-1,2,3,4-*tetrahydro*-1-*silanaphthalene* (**3**). The title compound was obtained in approximately 90% purity and immediately converted to the more stable isothiuronium salt following the literature procedure.[6]

1,1-*Dimethyl*-4-[2'-(1",3"-*dioxo*-2"-*methyl*-*cyclopenta*-2"-*yl*)*ethylidene*]-7-*methoxy*-1,2,3,4-*tetrahydro*-1-*silanaphthalene* (**4**). A mixture of the preceding crude isothiuronium acetate (0·21 mol, assuming 100% purity) and 91·8 g (0·820 mol) of 2-methylcyclopentane-1,3-dione in 1·23 l of t-BuOH and 205 ml water was refluxed for 19 hr. The oily residue (66·5 g), obtained by following the reported[6] isolation procedure, was purified by elution from silica gel (2 kg) with benzene and then 5% acetone in benzene, to give 42·7 g (61%) of **4** as an oil.

An analytical sample of **4** was prepared by preparative TLC (ChromAR 1000, 40% benzene–CCl_4) of a small sample of this oil; IR (CCl_4) 1760 (shoulder), 1725 (C=O) cm^{-1}; UV (MeOH) 259 nm (ϵ 13,500); NMR ($CDCl_3$) δ 0·90 (m, 2, C-2), 1·16 (s, 3, C-2"), 3·79 (s, 3, C-7), 5·40 (t, 1, J = 6 Hz, C-1'), 6·74–7·24 (m, 3, ArH). (Found: *m/e* 342·164. Required for $C_{20}H_{26}SiO_3$: *m/e* 342·165).

3-*Methoxy*-6,6-*dimethyl*-6-*silaestra*-1,3,5(10),8,14-*pentaene*-17β-*yl acetate* (**5c**). The title compound **5c** was prepared in three steps[6,12] from the secosteroid **4**. It was purified by crystallization from methanol in 40% yield; m.p. 137–139°; IR (CCl_4) 1740 (C=O), 1590 (aromatic C=C) cm^{-1}; UV (MeOH) 235 nm (ϵ 12,800), 307 (ϵ 22,400); NMR ($CDCl_3$) δ 1·00 (s, 3, C-18), 1·26–2·00 (m, 4, C-7, C-12), 2·08 (s, 3, $OCO-CH_3$), 2·36–2·96 (m, 4, C-11, C-16), 3·80 (s, 3, OCH_3), 5·04 (t, 1, J = 9 Hz, C-17), 5·57 (br t, 1, C-15), 6·80–7·43 (m, 3, ArH). (Found *m/e*: 368·180. Required for $C_{22}H_{28}SiO_3$: *m/e* 368·181).

Catalytic hydrogenation of **5c**. The catalytic hydrogenation of **5c** was first carried out using 10 mg of the compound, 5 mg of the catalyst and 3 ml of the solvent. In each case the composition of the reaction mixture was determined by GLC (250°, 3% SE-30 on Variport) and the structures of the products were confirmed by NMR. The results are summarized in Table 1 (*vida supra*).

(a) *Preparation of* **6b**. A soln of **5c** (5·75 g) in benzene (40 ml) was added to a suspension of 10% Pd on C (2·9 g) in the same solvent (200 ml) and stirred under a H_2 until one equiv of H_2 was absorbed (20 min). Filtration, evaporation, and crystallization from MeOH gave **6b** (3·74 g, 66%); m.p. 92–94°; IR ($CHCl_3$) 1730 (C=O), 1600 (aromatic C=C) cm^{-1}; UV (MeOH) 220 nm (sh, ϵ 15,400), 279 (13,000); NMR ($CDCl_3$) δ 0·84 (s, 3, C-18), 2·02 (s, 3, $OCO-CH_3$), 2·12–2·76 (m, 3, C-11, C-14), 3·78 (s, 3, OCH_3), 4·76 (t, 1, J = 8 Hz, C-17), 6·76–7·34 (m, 3, ArH). (Found: *m/e* 370·196. Required for $C_{22}H_{30}SiO_3$: *m/e* 370·196).

(b) *Preparation of* **7**. A soln of **5c** (250 mg) in glacial AcOH (10 ml) was added to a suspension of Pt (125 mg) in the same solvent (4 ml) under H_2 and stirred until one equiv of H_2 was absorbed (2 hr). Filtration, evaporation, and crystallization from MeOH gave **7** (183 mg, 73%); m.p. 104–106°; IR ($CHCl_3$) 1730 (C=O), 1600 (aromatic C=C) cm^{-1}; UV (MeOH) 227 nm (sh, ϵ 13,600), 284 (2200); NMR ($CDCl_3$) δ 0·90 (s, 3, C-18), 3·49 (br t, 1, J = 7 Hz, C-9), 4·69 (br t, 1, J = 8 Hz, C-17). The remainder of the NMR spectrum was identical with that of **6b**. (Found: *m/e* 370·196. Required for $C_{22}H_{30}SiO_3$: *m/e* 370·196).

(c) *Preparation of* **6c**. Attempts to prepare an analytically pure sample of **6c** were unsuccessful. The structure of **6c** was established by GC–MS and an NMR spectrum of the enriched mother liquors of crystallization of **6b** and **7**, which showed an enhancement of the C-18 methyl signal of **6c** at δ 0·98.

3-*Methoxy*-6,6-*dimethyl*-6-*silaestra*-1,3,5(10)-*trien*-17β-*ol* (**8a**). Li ribbon (40 mg, 5·7 mmole) was added to a stirred soln of **6b** (300 mg, 0·810 mmole) in dry THF (5 ml) and ammonia 20 ml) at −33°. After 10 min, the deep blue color of the mixture was discharged with sat ammonium chloride and the ammonia was evaporated with a stream of N_2. Water (*ca* 10 ml) was added, and the mixture was extracted with benzene (10 ml). The residue (268 mg) from the dried organic phase was saponified with KOH (112 mg) in 75% aqueous EtOH (4 ml) at room temp (1 hr). After removal of EtOH *in vacuo*, the mixture was diluted with water (5 ml) and extracted with $CHCl_3$ (2 × 10 ml). Crystallization of the crude product from hexane gave **8a** (139 mg, 51%); m.p. 103–107°; IR ($CHCl_3$) 3600 (OH), 1595 (aromatic C=C) cm^{-1}; UV (MeOH) 222 nm (sh, ϵ 10,000), 282 nm (3000), 290 (2700); NMR ($CDCl_3$) δ 0·72 (s, 3, C-18), 2·26 (m, 1, C-9), 3·70 (t, 1, J = 8 Hz, C-17), 3·78

(s, 3, OCH_3), 6·83 (dd, 1, J = 9, 3 Hz, C–2), 6·96 (d, 1, J = 3 Hz, C–4), 7·37 (d, 1, J = 9 Hz, C–1). (Found: *m/e* 330·202. Required for $C_{20}H_{30}SiO_2$: *m/e* 330·202).

3 - *Hydroxy* - 6,6 - *dimethyl* - 6 - *silaestra* - 1,3,5(10) - *trien* - 17β - *ol* (**8b**). Solvent was removed from an etheral soln (5 ml) of MeMgI and **8a** (250 mg, 0·757 mmol) by a stream of N_2 and the mixture was heated at 170–180° for 3 hr. It was then hydrolysed with ice-water (10 ml) and 0·5 N HCl (8 ml) and extracted with $CHCl_3$ (2 × 20 ml).

The crude product (230 mg) from the dried (Na_2SO_4) $CHCl_3$ phase was purified by preparative TLC (silica gel, 10% acetone in $CHCl_3$) to give **8b** (161 mg, 68%) as an amorphous white solid (m.p. 95–98°). Although homogeneous by TLC (silica gel, 4% MeOH in $CHCl_3$) and GLC (TMS ether), attempts to crystallize this compound were unsuccessful; IR ($CHCl_3$) 3600 (OH), 1595 (aromatic C=C) cm^{-1}; UV (MeOH) 222 nm (sh, ε 9300), 282 (2700), 291 (sh, 2400); NMR ($CDCl_3$) δ 0·74 (s, 3, C–18), 3·72 (t, 1, J = 8 Hz, C–17), 6·74 (dd, 1, $J_{C_1-C_2}$ = 6 Hz, $J_{C_2-C_4}$ = 2 Hz, C–2), 6·89 (d, 1, J = 2 Hz, C–4), 7·30 (d, 1, J = 6 Hz, C–1). (Found: C, 71·92; H, 9·13; *m/e* 316·185. Required for $C_{19}H_{28}SiO_2$: C, 72·10; H, 8·92; *m/e* 316·186).

3 - *Methoxy* - 6,6 - *dimethyl* - 6 - *silaestra* - 1,3,5(10) - *trien* - 17 - *one* (**10a**). A soln of crude **8a** (890 mg, 2·70 mmol), distilled aluminum isopropoxide (778 mg, 3·65 mmol), and cyclohexanone (3·8 ml) in dry toluene (100 ml) was refluxed for 1 hr. The mixture was cooled (50°), Rochelle salt (820 mg) in water (39 ml) added, and the resulting mixture steam distilled until the distillate was clear. The mixture was then extracted with $CHCl_3$ (2 × 100 ml), and the organic phase was dried (Na_2SO_4).

The crude product (890 mg) was purified by elution from silica gel (40 g) wity 1% acetone in CCl_4, and then 3% acetone in CCl_4, to give 500 mg (57% from **6b**) of **10a**.

An analytical sample was prepared by crystallization from hexane; m.p. 101–104°; IR ($CHCl_3$) 1730 (C=O), 1595 (aromatic C=C) cm^{-1}; UV (MeOH) 222 nm (sh, ε 9100), 283 (2400), 290 (2200); NMR ($CDCl_3$) δ 0·77 (s, 3, C–18), 2·07–2·46 (m, 3, C–9, C–16), 3·70 (s, 3, OCH_3), 6·76 (dd, 1, J = 8, 3 Hz, C–2), 6·89 (d, 1, J = 3 Hz, C–4), 7·28 (d, 1, J = 8 Hz, C–1). (Found: *m/e* 328·186. Required for $C_{20}H_{28}SiO_2$: *m/e* 328·186).

In an alternative procedure, a solution of **8a** (52 mg, 0·16 mol) in CH_2Cl_2 (2 ml) was added to a stirred mixture of CrO_3 (96 mg, 0·96 mmol) and pyridine in CH_2Cl_2 (2 ml). After stirring for 25 min at room temp, the soln was decanted from the residue and the solvent removed *in vacuo*. The residue was taken up in ether and washed with dilute aqueous base, brine and dried (Na_2SO_4).

Two products **10a** (21 mg, 40%) and **14a** (2 mg, 4%) were isolated by the preparative TLC of the crude mixture (silica gel, 5% acetone in CCl_4).

3 - *Methoxy* - 6,6 - *dimethyl* - 6 - *sila* - 17α - *ethynylestra* - 1,3,5(10) - *trien* - 17β - *ol* (**10b**). A mixture of **10a** (200 mg, 0·609 mmol) and lithium acetylide-ethylenediamine complex (1·3 g, 13 mmol) in anhyd dioxane (12 ml) was stirred vigorously at room temp (1·5 hr). The mixture was cooled to 0°, saturated ammonium chloride (2 ml) added, and then water (40 ml). The resulting mixture was extracted with $CHCl_3$ (3 × 20 ml) and the organic phase dried (Na_2SO_4) and concentrated. The crude residue (202 mg) was purified by preparative TLC (silica gel, 5% acetone in CCl_4) to give **10b** (119 mg, 56%).

An analytical sample was prepared by crystallization from hexane; m.p. 130–131°; IR ($CHCl_3$) 3595 (OH), 3300 (C≡CH), 1595 (aromatic C=C) cm^{-1}; UV (MeOH) 222 nm (sh, ε 8800), 283 (2300), 290 (2000); NMR ($CDCl_3$) δ 0·84 (s, 3, C–18), 2·15 (m, 1, C–9), 2·58 (s, 1, C≡CH), 3·78 (s, 3, OCH_3), 6·83 (dd, 1, J = 8, 3 Hz, C–2), 6·96 (d, 1, J = 3 Hz, C–4), 7·37 (d, 1, J = 8 Hz, C–1), (Found: C, 74·22; H, 8·52; *m/e* 354·202. Required for $C_{22}H_{30}SiO_2$: C, 74·55, H, 8·53; *m/e* 354·202).

3 - *Methoxy* - 6,6 - *dimethyl* - 6 - *silaestra* - 1(10),3 - *dien* - 17β - *ol* (**11**). Li ribbon (150 mg, 217 mmol) was added to a stirred soln of **6b** (500 mg, 1·35 mmol) in dry THF (5 ml), t-BuOH (5 ml), and ammonia (25 ml) at −33°. After 1 hr, the deep blue color of the mixture was discharged with saturated ammonium chloride and the ammonia was evaporated with a stream of N_2. Water (20 ml) was then added and the mixture extracted with $CHCl_3$ (2 × 20 ml). Evaporation of the dried $CHCl_3$ phase gave crude **11** (460 mg) as a foam.

A sample was purified by continuous preparative TLC (silica gel, 4% acetone in CCl_4, 3 hr). Crystallization of **11** was not successful; IR ($CHCl_3$) 3610 (OH), 1675, 1645 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 0·84 (s, 3, C–18), 2·15 (m, 1, C–9), 2·80 (m, 2, C–2), 3·52 (s, 3, OCH_3), 3·64 (t, 1, J = 8 Hz, C–17), 4·57 (d, 1, J = 4 Hz, C–4). 5·38 (t, 1, J = 3 Hz, C–1). (Found: *m/e* 332·217. Required for $C_{20}H_{32}SiO_2$: *m/e* 332·217).

6,6 - *Dimethyl* - 6 - *sila* - 17β - *hydroxy* - *estr* - 1(10)*en* - 3 - *one* (**15**). A soln of crude **11** (490 mg, 1·47 mmol) in MeOH (35 ml) was added to a cooled (ice bath) soln of oxalic acid (530 mg, 4·2 mmol) in water (7 ml). After stirring the mixture at room temp for 1 hr, it was again cooled, neutralized (saturated $NaHCO_3$) and MeOH removed *in vacuo*. The aqueous phase was extracted with EtOAc and the extract was dried (Na_2SO_4) and concentrated. The ketone **15** (218 mg, 49% from **6b**) was isolated from the residue by continuous preparative TLC (silica gel, 10% acetone in CCl_4, 2 hr), and crystallized from ether-hexane; m.p. 136–139°; IR ($CHCl_3$) 3600 (OH), 1710 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0·74 (s, 3, C–18), 2·38–2·91 (m, 5, C–2, C–4, C–9), 3·65 (t, 1, J = 8 Hz, C–17), 5·40 (t, 1, J = 3 Hz, C–1). (Found: *m/e* 318·202. Required for $C_{19}H_{30}SiO_2$: *m/e* 318·202).

3,3 - *Dimethoxy* - 6,6 - *dimethyl* - 6 - *silaestr* - 1(10) - *en* - 17β - *ol*. A soln of **11** (0·89 g, 2·8 mmol) and anhyd *p*-toluenesulfonic acid (6 mg, 0·04 mmol) in dry MeOH (50 ml) was stirred at room temp for 2 hr. The mixture was then cooled and neutralized with sat $NaHCO_3$ (1 ml). The residue obtained by the removal of solvent *in vacuo* was taken up in $CHCl_3$ (50 ml) and shaken successively with water and brine. Evaporation of the dried (Na_2SO_4) $CHCl_3$ phase gave the ketal (1·02, 100%) as a foam.

Although homogeneous by TLC (silica gel, 4% MeOH/$CHCl_3$), attempts to crystallize this compound were unsuccessful; IR ($CHCl_3$) 3600 (OH) cm^{-1}; NMR ($CDCl_3$) δ 0·74 (s, 3, C–18), 1·96–2·34 (m, 2, C–4), 3·16 (s, 3, OCH_3), 3·23 (s, 3, OCH_3), 3·64 (t, 1, J = 8 Hz, C–17), 5·31 (m, 1, C–1). (Found: *m/e* 364·244. Required for $C_{21}H_{36}SiO_3$: *m/e* 364·244).

3,3 - *Dimethoxy* - 6,6 - *dimethyl* - 6 - *silaestr* - 1(10) - *en* - 17 - *one*. A soln of the above crude ketal (1·02 g, 2·80 mmol), distilled aluminum isopropoxide (780 mg, 3·65 mol), and cyclohexanone (3·9 ml) in dry toluene (100 ml) was refluxed for 1 hr. The mixture was then cooled (50°), Rochelle salt (800 mg) in water (40 ml) added, and the resulting mixture steam distilled until the distillate was clear. It was then extracted with $CHCl_3$ (2 × 200 ml). The crude product (1·01 g) from the dried (Na_2SO_4) $CHCl_3$ phase was purified by elution from basic alumina (activity III, 120 g) with CCl_4, 50% $CHCl_3$ in CCl_4, and $CHCl_3$, to give 676 mg (67% from **11**) of the desired ketone as a foam.

Although homogeneous by TLC (silica gel, 40% MeOH/$CHCl_3$), attempts to crystallize this compound were unsuccessful; IR ($CHCl_3$) 1730 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0·86 (s, 3, C–18), 2·00–2·40 (m, 4, C–4, C–16), 3·16 (s, 3, OCH_3), 3·23 (s, 3, OCH_3), 5·32 (m, 1, C–1). (Found: *m/e* 362·227. Required for $C_{21}H_{34}SiO_3$: *m/e* 362·227).

3,3 - *Dimethoxy* - 6,6 - *dimethyl* - 6 - *sila* - 17α - *ethynylestr* - 1(10) - *en* - 17β - *ol*. A mixture of the preceding ketone (400 mg, 1·10 mmol) and lithium acetylide-ethylene diamine complex (2·4 g, 24 mmol) in anhyd dioxane (24 ml) was stirred vigorously at room temp for 2·5 hr. The mixture was cooled to 0° and the complex decomposed with sat ammonium chloride (4 ml) and water (60 ml). The resulting mixture was extracted with $CHCl_3$ (3 × 30 ml) and the organic phase dried (Na_2SO_4).

The residue (411 mg) from the organic phase was purified by elution from basic alumina (III, 40 g) with CCl_4, followed by 50% $CHCl_3$ in CCl_4, to give 210 mg (49%) of the desired ethynyl compound as a foam; IR (CCl_4) 3605 (OH), 3300 (–C≡CH) cm^{-1}; NMR ($CDCl_3$) δ 0·79 (s, 3, C–18), 2·10–2·24 (m, 2, C–4), 2·50 (s, 1, –C≡CH), 3·10 (s, 3, OCH_3), 3·18 (s, 3, OCH_3), 5·26 (m, 1, C–1). (Found: *m/e* 388·243. Required for $C_{23}H_{36}SiO_3$: *m/e* 388·243).

6,6 - *Dimethyl* - 6 - *sila* - 17α - *ethynyl* - 17β - *hydroxy* - 1(10) - *estren* - 3 - *one* (**16**). A soln of oxalic acid (231 mg, 2·57 mmol) in water (6·3 ml) was added to a cooled (ice bath) soln of the preceding ketal (210 mg, 0·541 mmol) in THF (20 ml). The mixture

was stirred at room temp for 6 hr. It was then cooled and neutralized with sat $NaHCO_3$ aq and the THF removed *in vacuo*. The aqueous phase was extracted with $CHCl_3$ (2 × 25 ml).

The residue (168 mg) from the dried (Na_2SO_4) $CHCl_3$ extracts was purified by preparative TLC (ChromAR-1000, 3% acetone in CCl_4), followed by crystallization from methylene chloride-hexane, to give **16** (71 mg, 39%); m.p. 223–226°; IR ($CHCl_3$) 3600 (OH), 3300 (C≡CH), 1710 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0·86 (s, 3, C–18), 2·56 (s, 1, C≡CH), 2·68–2·94 (m, 2, C–4), 5·41 (t, 1, J = 3 Hz, C–1). (Found: C, 73·55; H, 8·99; *m/e* 342·202. Required for $C_{21}H_{30}SiO_2$: C, 73·62; H, 8·84, *m/e* 342·202).

6,6 - *Dimethyl* - 6 - *sila* - 17β - *hydroxy* - 10 - *isoestran* - 3 - *one* (**17**). A soln of **15** (195 mg) in EtOAc (5 ml) was added to a suspension of prereduced 5% Pd on C (203 mg) in the same solvent (20 ml) and stirred under H_2 for 18 hr. The mixture was filtered through celite and the solvent evaporated *in vacuo* to give a white foam (181 mg).

Preparative TLC (ChromAR-500, 7·5% acetone in CCl_4) afforded 64 mg (33%) of pure **17** which crystallized as needles from ethyl acetate; m.p. 189–191°; IR ($CHCl_3$), 3400 (OH), 1710 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0·71 (s, 3, C–18), 3·84 (t, 1, J = 8 Hz, C–17). (Found: *m/e* 320·217. Required for $C_{19}H_{32}SiO_2$: *m/e* 320·217).

5,6 - *Seco* - 3 - *methoxy* - 6,6 - *dimethyl* - 6 - *hydroxy* - 6 - *silaestra* - 1,3,5(10) - *trien* - 17 - *one* (**14a**). A soln of 1 M boron tribromide in CH_2Cl_2 (51 μl, 0·05 mmol) was added to a cooled (dry ice) soln of **10a** (17 mg, 0·05 mmol) in the same solvent (3 ml). After 4 hr at this temp, the mixture was poured into water (10 ml) containing 2N HCl (2 ml). The aqueous phase was extracted with CH_2Cl_2 (10 ml) and the latter extract dried (Na_2SO_4) and evaporated *in vacuo* to afford 17 mg of crude **14a**.

Preparative TLC (ChromAR-500, 5% acetone in benzene) yielded pure **14a** (11 mg, 62%) as an oil; IR ($CHCl_3$) 3590, 3660 (OH), 1735 (C=O), 1610 (aromatic C=C) cm^{-1}; UV (MeOH) 223, 277, 283 nm; NMR ($CDCl_3$, CH_2Cl_2 as a reference) δ −0·085 [s, 3, ≡Si(CH_3)$_2$], −0·055 (s, 3, ≡Si(CH_3)$_2$], 1·02 (s, 3, C–18), 1·89–2·26 (m, 3, C–9, C–16), 3·78 (s, 3, OCH_3), 6·80–7·16 (m, 4, ArH). (Found: *m/e* 346·197. Required for $C_{20}H_{30}SiO_3$: *m/e* 346·197).

5,6 - *Seco* - 3 - *methoxy* - 6,6 - *dimethyl* - 6 - *fluoro* - 6 - *silaestra* - 1,3,5(10) - *trien* - 17 - *one* (**14b**). A soln of **10a** (75 mg, 0·23 mmol) in a mixture of abs EtOH (10 ml) and 50% aqueous HF (7 ml) was heated at 50° for 20 hr. The mixture was poured into ice-water (50 ml) and extracted with benzene (2 × 60 ml). The extract was dried (Na_2SO_4) and evaporated *in vacuo* to afford 71 mg (89%) of **14b** as an oil of 98% purity (GLC); IR ($CHCl_3$) 1730 (C=O), 1610 (aromatic C=C) cm^{-1}; UV (MeOH) 224 nm (ϵ 8333); NMR ($CDCl_3$, CH_2Cl_2 as a reference) δ −0·03 (m, 6, ≡Si(CH_3)$_2$], 0·65 (m, 2, C–7), 1·03 (s, 3, C–18), 3·78 (s, 3, OCH_3), 6·76–7·18 (m, 4, Ar–H). (Found: *m/e* 348·192. Required for $C_{20}H_{29}SiO_2F$: *m/e* 348·192).

5,6 - *Seco* - 3 - *hydroxy* - 6,6 - *dimethyl* - 6 - *fluoro* - 6 - *silaestra* - 1,3,5(10) - *trien* - 17β - *ol* (**18a**). A soln of **8b** (130 mg, 0·411 mmol) in EtOH (17 ml) and 50% aqueous HF (17 ml) was heated at 50° for 6 hr. It was then poured into ice-water (100 ml) and extracted with benzene (2 × 100 ml). Evaporation of the dried (Na_2SO_4) organic phase gave **18a** (126 mg, 92%) as an amorphous white solid, m.p. 168–170°.

Although homogeneous by TLC (ChromAR-500, 15% acetone in CCl_4) and GLC (TMS ether), attempts to crystallize **18a** were unsuccessful; IR (KBr) 1510, 1610 (aromatic C=C) cm^{-1}; UV (MeOH) 223 nm (ϵ 7500), 277 (1600), 285 (sh, 1400); NMR ($CDCl_3$) δ, 0·88, (s, 3, C–18), 3·72 (t, 1, J = 8 Hz, C–17), 6·72 (d, 2, J = 9 Hz, C–2, C–4), 7·02 (d, 2, J = 9 Hz, C–1, C–5). (Found: *m/e* 336·191. Required for $C_{19}H_{29}SiO_2F$: *m/e* 336·191).

5,6 - *Seco* - 3 - *methoxy* - 6,6 - *dimethyl* - 6 - *fluoro* - 6 - *sila* - 17α - *ethynylestra* - 1,3,5(10) - *trien* 17β - *ol* (**18b**). A soln of **10b** (114 mg, 0·322 mmol) in a mixture of abs EtOH (15 ml) and 50% aqueous HF (15 ml) was heated at 50° for 18 hr. The mixture was poured into ice-water (50 ml) and extracted with benzene (2 × 60 ml). The extract was dried (Na_2SO_4) and evaporated *in vacuo* to afford 120 mg (99%) of **18b** as an oil of 98% purity (GLC). IR (CCl_4) 3595 (OH), 3300 (–C≡CH), 1590 (aromatic C=C) cm^{-1}; UV (MeOH) 224 nm (ϵ 8145); NMR ($CDCl_3$) δ 0·6 (m, 2, C–7), 1·0 (s, 3, C–18), 2·6 (s, 1, –C≡CH), 3·77 (s, 3, OCH_3), 6·7–7·2 (m, 4, C–1, C–2, C–4, C–5). (Found: *m/e* 374·208. Required for $C_{22}H_{31}SiO_2F$: *m/e* 374·208).

5,6 - *Seco* - 6,6 - *dimethyl* - 6 - *fluoro* - 6 - *sila* - 17β - *hydroxy* - *estra* - 1(10) - *en* - 3 - *one* (**19**). A soln of **15** (180 mg, 0·566 mmol) in EtOH (24 ml) and 50% aqueous HF (24 ml) was allowed to stand at room temp for 0·5 hr. It was then poured into ice-water (150 ml) and extracted with benzene (2 × 150 ml). Evaporation of the dried (Na_2SO_4) organic phase gave **19** (189 mg, 98%) as an oil, homogeneous by TLC (ChromAR-500, 15% acetone in CCl_4) and GLC (TMS ether); IR (CCl_4) 3610 (OH), 1720 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0·78 (s, 3, C–18), 2·90 (d, 2, J = 2 Hz, C–2), 3·66 (t, 1, J = 7 Hz, C–17), 5·55 (t, 1, J = 3 Hz, C–1). (Found: *m/e* 338·207. Required for $C_{19}H_{31}SiO_2F$: *m/e* 338·207).

Dibenzylchlorosilane. This compound was prepared from trichlorosilane and benzylmagnesium bromide in 53% yield following a reported procedure;[33] b.p. 123–125° (0·02 mm); IR (liquid film) 2165 (Si–H), 1600, 1495 (aromatic C=C) cm^{-1}. (Found: *m/e* 246·0628. Required for $C_{14}H_{15}SiCl$: *m/e* 246·0632).

m-*Methoxyphenyldibenzylsilane.* This compound was prepared from *m*-methoxyphenylmagnesium bromide and dibenzylchlorosilane in 83% yield; b.p. 150–156° (0·025 mm); IR (liquid film) 2125 (Si–H), 1495, 1570–1600 (aromatic C=C) cm^{-1}; NMR ($CDCl_3$) δ 2·37 [d, 4, J = 4 Hz, ($C_6H_5CH_2$)$_2$Si≡], 3·68 (s, 3, OCH_3), 4·45 [t, 1, J = 4 Hz, ($C_6H_5CH_2$)$_2$SiHAr], 6·81–7·28 (m, 14, ArH). (Found: *m/e* 318·1442. Required for $C_{21}H_{22}SiO$: *m/e* 318·1440).

3 - [(m - *Methoxyphenyl*)*dibenzylsilyl*]*propanol.* A mixture of *m*-methoxyphenyldibenzylsilane (102·5 g, 0·331 mol), allyl alcohol (20·3 g, 0·35 mol), potassium acid phthalate buffer (pH5, 25 ml), chloroplatinic acid (1·92 ml, 0·5 M in iPrOH), and t-BuOH (450 ml)[34] was stirred at room temp. Additional amounts (1·92 ml, 0·5 ml) of chloroplatinic acid were added to the reaction mixture after 25 and 90 hr, respectively.

After stirring for 96 hr, t-BuOH was removed *in vacuo*. The aqueous phase was extracted with $CHCl_3$. Concentration of the dried (Na_2SO_4) $CHCl_3$ phase gave the desired alcohol (120 g) in quantitative yield as an oil homogeneous by GLC and TLC; IR (liquid film) 3580 (OH), 1600, 1490 (aromatic C=C) cm^{-1}, NMR ($CDCl_3$) δ 0·72 (m, 2, ≡SiCH_2CH_2CH_2OH), 1·48 (m, 2, ≡SiCH_2CH$_2$–CH$_2$OH), 2·37 [s, 4, ($C_6H_5CH_2$)$_2$Si≡], 3·46 (t, 2, J = 6 Hz, ≡SiCH$_2$CH$_2$CH$_2$OH), 3·70 (s, 3, OCH_3), 6·80–7·26 (m, 14, ArH). The mass spectrum of this product failed to show a molecular ion. [Found: (M–15) *m/e* 361·163. Required for $C_{23}H_{25}SiO_2$: (M–15) *m/e* 361·162].

3 - [(m - *Methoxyphenyl*)*dibenzylsilyl*]*propionic acid.* This compound was obtained as an oil in 58% yield by oxidation of the preceding alcohol with Jones' reagent. Its purity was verified by conversion to its methyl ester, followed by TLC and GLC analysis.

The desired acid was also obtained in 27 and 41% yields, respectively, by hydrosilylation of ethyl acrylate and acrolein diethyl acetal with *m*-methoxyphenyl-dibenzylsilane; IR 3600–2550 (free and bonded OH), 1705 (C=O), 1490, 1500 (aromatic C=C) cm^{-1}; NMR ($CDCl_3$) δ 1·12 (m, 2, ≡SiCH_2CH$_2$–), 2·14 (t, 2, J = 8 Hz, ≡SiCH$_2$CH_2COOH), 2·38 [s, 4, ($C_6H_5CH_2$)$_2$Si≡], 3·72 (s, 3, OCH_3), 6·82–7·34 (m, 14, ArH), 8·0 (br s, 1, COOH). The mass spectrum of this carboxylic acid failed to show a molecular ion. (Found: (M-2) *m/e* 388·149. Required for $C_{24}H_{24}SiO_3$: (M–2) *m/e* 388·149).

6 - *Methoxy* - 4,4 - *dibenzyl* - 4 - *sila* - 1 - *tetralone.* This compound was prepared in 75% yield using the procedure described for the preparation of **2**; m.p. 95–96° (ether); IR (KBr) 1655 (C=O) cm^{-1}; UV (MeOH) 224 nm (ϵ 33,300), 253 (6200), 258 (8100), 276 (13,700); NMR ($CDCl_3$) δ 1·04 (m, 2, C–3), 2·36 [m, 6, C–2 and ($C_6H_5CH_2$Si≡], 3·70 (s, 3, OCH_3), 6·72–7·24 (m, 13, ArH), 8·05 (d, 1, J = 9 Hz, C–8). (Found: *m/e* 372·154. Required for $C_{24}H_{24}SiO_2$: *m/e* 372·154.

1,1 - *Dibenzyl* - 4 - *hydroxy* - 7 - *methoxy* - 4 - *vinyl* - 1,2,3,4 - *tetrahydro* - 1 - *silanaphthalene.* This compound was obtained by treatment of the preceding tetralone with vinyl magnesium chloride. The crude product immediately was converted to its isothiuronium acetate without purification (c.f. the preparation of **3**).

1,1 - *Dibenzyl* - 4 - [2' - (1",3" - *dioxo* - 2" - *methylcyclopenta* - 2" -

yl)ethylidene - 7 - methoxy - 1,2,3,4 - tetrahydro - 1 - silanaphthalene. This compound was obtained as an oil (63% yield) by the procedure described for the preparation of **4**. An analytical sample was prepared by preparative TLC (ChromAR-1000, 1% acetone in benzene); IR ($CHCl_3$) 1760 (sh), 1720 (C=O) cm^{-1}; UV (MeOH) 218 nm (ϵ 32,600), 263 (10,900), 293 (6300); NMR ($CDCl_3$) δ 0·80 (m, 2, C-2), 1·07 (s, 3, C-2'), 3·72 (s, 3, C-7), 5·24 (t, 1, J = 6 Hz, C-1'), 6·70–7·34 (m, 13, ArH). (Found *m/e* 494·228. Required for $C_{32}H_{34}SiO_3$: *m/e* 494·228).

3 - *Methoxy - 6,6 - dibenzyl - 6 - silaestra - 1,3,5(10),8,14, - pentaene - 17β - yl acetate.* This compound was prepared from the preceding seco-steroid in three steps[6,12] (25% yield). It was purified by preparative TLC (silica gel, 20% acetone–$CHCl_3$) and obtained as an oil; IR (CH_2Cl_2) 1730 (C=O), 1600, 1490 (aromatic C=C) cm^{-1}; UV (MeOH) 220 nm (ϵ 33,800), 307 (16,900); NMR ($CDCl_3$) δ 0·93 (s, 3, C-18), 1·26–1·68 (m, 4, C-7, C-12), 2·07 (s, 3, CH_3CO_2–), 2·26 (s, 2, $C_6H_5CH_2$), 2·39 (s, 2, $C_6H_5CH_2$), 2·20–2·74 (m, 4, C-11, C-16), 3·78 (s, 3, OCH_3), 4·96 (t, 1, J = 8 Hz, C-17), 5·44 (br t, 1, C-15), 6·72–7·38 (m, 13, ArH). (Found: *m/e* 520·243. Required for $C_{34}H_{36}SiO_3$: *m/e* 520·243).

3 - *Methoxy - 6,6 - dibenzyl - 6 - silaestra - 1,3,5(10),8 - tetraene - 17β - yl acetate.* A soln of the preceding pentaene (200 mg) in EtOH (20 ml) containing 0·3% piperidine was added to a suspension of 5% Pd on C (125 mg) in the same solvent (10 ml) and stirred under H_2 until one equiv of H_2 was absorbed (2 hr). The NMR spectrum of the crude mixture indicated the presence of the desired product and its $\Delta^{8(14)}$ isomer (1:1). Partial purification (*ca* 90%) was effected by continuous TLC (silica gel, 1·5% acetone-carbon tetrachloride, 2 hr). Attempted crystallization of the oily products was unsuccessful. *$\Delta^{1,3,5(10),8}$-Tetraene*; IR (CH_2Cl_2) 1730 (C=O), 1600, 1490 (aromatic C=C) cm^{-1}; UV (MeOH) 220 nm (ϵ 30,000), 280 (10,000); NMR ($CDCl_3$) δ 0·72 (s, 3, C-18), 2·04 (s, 3, OCO–CH_3), 2·24 (s, 2, $C_6H_5CH_2$), 2·40 (s, 2, $C_6H_5CH_2$), 2·12–3·70 (m, 3, C-11, C-14), 3·77 (s, 3, OCH_3), 4·66 (t, 1, J = 8 Hz, C-17), 6·76–7·26 (m, 13, ArH). (Found: *m/e* 522·259. Required for $C_{34}H_{38}SiO_3$: *m/e* 522·259).

$\Delta^{1,3,5(10),8(14)}$-Tetraene; IR (CH_2Cl_2) 1730 (C=O), 1600, 1490 (aromatic C=C) cm^{-1}; UV (MeOH) 220 nm (ϵ 28,000), 280 (5,000); NMR ($CDCl_3$) δ 0·88 (s, 3, C-18), 2·04 (s, 3, OCO–CH_3), 2·24 (s, 2, $C_6H_5CH_2$), 2·31 (br s, 2, $C_6H_5CH_2$), 2·12–2·48 (m, 4, C-11, C-15), 3·40 (br t, J = 8 Hz, C-9), 3·62 (s, 3, OCH_3), 4·66 (br t, 1, J = 7 Hz, C-17), 6·40 (d, 1, J = 3 Hz, C-4), 6·80–7·24 (m, 13, ArH). (Found: *m/e* 522·259. Required for $C_{34}H_{38}SiO_3$: *m/e* 522·259).

Biological activity. Female Sprague-Dawley rats were employed, and the steroids in sesame oil were administered orally (*or*) and/or by subcutaneously (*sc*) injection. Estrogenicity was determined by uterotropic assay using estradiol (*sc*) or ethynylestradiol (*or*) as standards. At least three dose levels of the unknown and three dose levels of the standards (*sc*, 0·04, 0·08, 0·16 μg, *or* 0·4, 0·8, 1·6 μg) were tested simultaneously on ten animals per group. Antiestrogenicity was determined similarly, using an estradiol (0·32 μg) standard and *sc* administration. Post-coital activity was determined by *sc* administration of a fixed daily dose of the steroid to 10 animals on days 0–4 of pregnancy. Autopsy was performed on day 10.

Using these protocols, the following 6-silasteroids were screened for estrogenicity (*E*), antiestrogenicity (*AE*), and post-coital (*PC*) activity: **5c**, *E* (*sc*, *or*), *AE*; **6b**, *E* (*sc*, *or*), *PC*; **7**, *E* (*sc*, *or*), *PC*; **8b**, *E* (*sc*); **10b**, *E* (*or*), *PC*; **14a**, *E* (*sc*), *AE*; **14b**, *E* (*sc*), *AE*, *PC*; **16**, *PC*; **18a**, *E* (*or*): **18b**, *E* (*or*), *PC*; **19**, *E* (*or*). No significant activity was observed. Compound **19** showed weak androgenic activity in rat.

Acknowledgements—The financial support of this work by the Contraceptive Development Branch, Center for Population Research, NICHD, NIH, under contract No. NIH-NICHD-72-2716, and permission to use biological data obtained from the Contraceptive Development Branch, are hereby acknowledged. The authors are grateful to Dr. G. Kimmel and Ms. B. Hartwell (RTI) for determination of the estrogen binding affinities, and to Dr. A. T. McPhail and Mr. R. W. Miller (Duke University) for the X-ray crystallographic results reported herein. The authors also wish to thank Dr. D. Rosenthal and Mr. F. Williams for mass spectral data (obtained from the Research Triangle Center for Mass Spectrometry, with support from the Biotechnology Resources Branch of the Division of Research Resources, NIM, Grant No. RR-330) and Drs. M. E. Wall (RTI), S. G. Levine (N. Carolina State University), and S. Barcza (Sandoz-Wander, Inc.), for helpful discussions.

REFERENCES

[1a] H. O. Huisman, *Total Synthesis of Heterocyclic Steroidal Systems*, Steroids, Vol. 8, MTP International Review of Science, (Edited by W. F. Johns), Butterworths, London (1973); [b] H. O. Huisman, *Bull. Soc. Chim. Fr.* 13 (1968).

[2a] *Contraception: The Chemical Control of Fertility* (Edited by D. Lednicer), Marcel Dekker, New York (1969); [b] H. Singh, V. Parashar, R. B. Mathur, and R. K. Malhotra, *Ind. J. Pharm.* **34**, 1, (1972).

[3a] C. Eaborn, *Organosilicon Compounds* Butterworths, London (1960); [b] L. H. Sommer, *Stereochemistry, Mechanism and Silicon.* McGraw-Hill New York (1965); [c] E. A. V. Ebsworth, *Organometallic Compounds of the Group IV Elements* (Edited by A. G. MacDiarmid) Vol. 1, Part 1, pp. 1–104. Marcel Dekker, New York (1968).

[4] For example, see [a] E. Chang and V. K. Jain, *J. Med. Chem.* **9**, 433 (1966); [b] E. A. Brown and I. Laos, *Belg. Pat.* 668,903, *Chem. Abstr.* **65**, 7238 (1966); [c] E. A. Brown and R. A. Mikulec, *U.S. Pat.* 3,300,523, *Chem. ASbstr.* **66**, 115877 (1967); [d] E. A. Brown and I. Laos, *German Pat.* 2,216,495, *Chem. Abstr.* **78**, 30086 (1973); [e] W. Hartmann, K. Barnikol-Oettler and G. Teichmueller, *E. German Pat.* 79,012, *Chem. Abstr.* **76**, 34488 (1972).

[5] For reviews of the pharmacology of other silicon compounds, see [a] L. G. Garson and L. K. Kirchner, *J. Pharm. Sci.* **60**, 1113 (1971); [b] M. G. Voronkov and E. Lukevics, *Russ. Chem. Rev.* **38** 975 (1969); [c] R. J. Fessenden and J. S. Fessenden, *Adv. Drug Research* **4**, 95 (1967).

[6] S. Barcza and C. W. Hoffman, *Abstr.* 2nd Int. Symp. *Organosilicon Chem.* p. 12; Bordeaux, France, (1968) U.S. Pats. 3,529,005 and 3,637,782; *Chem. Abstr.* **76**, 3,637,782 (1972).

[7] S. N. Ananchenko and I. V. Torgov, *Dokl. Akad. Nauk. SSSR* **127**, 553 (1959); *Tetrahedron Letters* 1553 (1963).

[8] G. A. Hughes and H. Smith, *Proc. Chem. Soc.* **75** (1960); *Chem. Ind.* 1022 (1960).

[9] For recent reviews, see [a] R. T. Blickenstaff, A. C. Ghosh and G. C. Wolf, *Total Synthesis of Steroids.* Academic Press, New York (1974); [b] J. Weill-Raynal, *Bull. Soc. Chim. Fr* 4561 (1969).

[10] C. Eaborn and R. W. Bott, *Organometallic Compounds of the Group IV Elements* (Edited by A. G. MacDiarmid), pp. 359–436. Marcel Dekker, New York (1968).

[11a] R. F. Zurcher, *Helv. Chim. Acta* **46**, 2054 (1963); [b] C. Rufer, E. Schröder and H. Gibian, *Liebigs Ann.* **701**, 206 (1968).

[12] C. Djerassi, J. Romo and G. Rosenkranz, *J. Org. Chem.* **16**, 754 (1951).

[13] H. L. Dryden, Jr., *Reductions of Steroids by Metal-Ammonia Solutions* in *Organic Reactions in Steroid Chemistry* (Edited by J. Fried and J. A. Edwards) Vol. 1, pp. 1–60. Van Norstrand Reinhold, New York, (1972).

[14a] T. A. Serebryakova, A. V. Zakharychev, R. N. Chigir, S. N. Ananchenko, I. V. Torgov and E. G. Kryuchenko, *French Pat.* 2,100,753; *Chem. Abstr.* **78**, 30088 (1973); T. A. Serebryakova, Z. N. Parnes, A. V. Zakharychev, S. N. Anachenko and I. V. Torgov, *Bull. Acad. Sci. USSR* 662 (1969); [b] F. A. Carey and H. S. Tremper, *J. Am. Chem. Soc.*, **90**, 2578 (1968).

[15] G. H. Douglas, J. M. H. Graves, D. Hartley, G. A. Hughes, B. J. McLoughlin, J. Siddall and H. Smith, *J. Chem. Soc.*, 5072 (1963).

[16] Cleavage may be caused by the alkali metal amide; for a precedent, see C. R. Hauser and C. R. Hance, *J. Am. Chem. Soc.* **73**, 5846 (1951).

[17] For a review of this and other O-demethylating agents, see E. Haslam, *Protective Groups in Organic Chemistry* (Edited by J. F. W. McOmie), pp. 157–169. Plenum Press, New York (1973).

[18] H. Alt, E. R. Franke and H. Bock, *Angew. Chem.* Intern. Edn, **8**, 525 (1969).

[19a] E. Farkas and N. J. Bach, *J. Org. Chem.* **36**, 2715 (1971); [b] D. R. Weyenberg and L. H. Toporcer, *J. Am. Chem. Soc.* **84**, 2843 (1962).

[20] A. T. McPhail and R. W. Miller, *J. Chem. Soc.*, Perkin II, in press.

[21]R. Bucourt, *Bull. Soc. Chim. Fr.* 1262 (1963).
[22a]A. B. Turner and H. J. Ringold, *J. Chem. Soc.* C, 1720 (1967); [b]C. C. Beard, *Introduction of Double Bonds into the Steroidal System*, in *Organic Reactions in Steroid Chemistry* (Edited by J. Fried and J. A. Edwards), Vol. 1, pp. 265–374. Von Norstrand Reinhold, New York (1972).
[23]Von B. Bierling, K. Kirschke, H. Oberender and M. Schultz, *J. Prakt. Chem.* 314, 170 (1972).
[24]A. T. Neyyaraphally, R. C. Gupta, S. C. Srivastava, J. S. Bindra, P. R. Grover, B. S. Setty and Nitya Anand, *Ind. J. Chem.* 11, 325 (1973).
[25]C. Eaborn, *J. Chem. Soc.* 2846 (1952).
[26]C. Eaborn, D. R. M. Walton and M. Chan, *J. Organometal. Chem.* 9, 251 (1967).
[27]S. G. Korenman, *Endocrinology* 87, 1119 (1970); and refs therein.
[28]C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann, *J. Am. Chem. Soc.* 72, 4540 (1950).
[29]T. Miki, K. Hiraga, T. Asako, K. Yoshioka, H. Sugitiara, R. Nakayama and M. Masuoka, *Yakugaku Zasshi* 94, 238 (1974); *Chem. Abstr.* 80, 121195 (1974).
[30]Unpublished studies, C. G. Pitt, A. E. Friedman, D. Rector and M. C. Wani (1974).
[31]J. W. Jenkins, N. L. Lavery, P. R. Guenther and H. W. Post, *J. Org. Chem.* 13, 862 (1948).
[32]G. H. Barnes, *U.S. Pat.* 3,398,174 (1968).