Reduction of (3*RS*,4*RS*)-4-Methyl-1,5-dioxaspiro[2.5]octane (19). Following the procedure for **12**, 31 mg (0.24 mmol) of **19** was reduced with 15 mg (0.4 mmol) of $LiAlH_4$. Work-up gave 25 mg (80%) of the alcohol **24** as a colorless liquid: ir (neat) 3450 cm^{-1} (–OH); NMR ($CDCl_3$) δ 4.07–3.45 (2 H, m, methylene at C_6), 3.28 (1 H, q, methine at C_3, J = 13 Hz), 1.70 (4 H, m, methylene at C_4 and C_5), 1.21 (3 H, s, methyl at C_3), 1.17 (3 H, d, methyl at C_2, J = 5.5 Hz). GLC analysis (5% FFAP, 80 °C) showed one peak at the retention time of 6.2 min.

Reduction of (3*SR*,4*RS*)-4-Methyl-1,5-dioxaspiro[2.5]octane (20). Following the procedure for **12**, 30 mg (0.24 mmol) of **20** was reduced with 15 mg (0.4 mmol) of $LiAlH_4$. Work-up gave 20 mg (76%) of the alcohol **23** as a colorless liquid: ir (neat) 3450 cm^{-1} (–OH); NMR ($CDCl_3$) δ 4.15–3.43 (2 H, m, methylene at C_6), 6.72 (1 H, q, methine at C_2, J = 13 Hz), 2.20 (1 H, broad, –OH), 1.17 (3 H, d, methyl at C_2, J = 5.5 Hz), 1.11 (3 H, s, methyl at C_2). GLC (5% FFAP, 80 °C) showed the presence of one component at the retention time of 2.7 min, identical with the major product of methyllithium addition to **18**.

Acknowledgment. We are indebted to Professor Robert Vince and Dr. Philip Lyon for assistance in the P388 tests; to Professor Chester J. Mirocha and his associates, Mr. S. Pathre, Mr. Tom Robison, and Mr. J. C. Behrens, of the University of Minnesota Department of Plant Pathology for a sample of T-2 toxin and for screening the spirooxiranes for skin irritant activity; and to the University of Minnesota Graduate School and College of Pharmacy for financial support. The assistance of Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, Ohio State University, Columbus, is also noted with appreciation.

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Steroidal 3,5-Dienes

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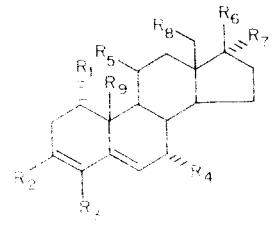
A series of $\Delta^{3,5}$-androstadienes, estradienes, and gonadienes was prepared and evaluated as claudogenic agents. Claudogenic activity was limited to relatively few members of the series, but three compounds—**12**, **14**, and **15**—were very potent.

The function of the carbonyl moiety at C-3 of steroid hormones in eliciting biological responses has been the subject of some study in this[1] and other laboratories.[2,3] In the course of our search for claudogenic steroids, we needed to prepare estr-4-ene-3α,17β-diol by reduction of 19-nortestosterone with $LiAlH_4$. Purification of the crude product gave estr-4-ene-3β,17β-diol and estra-3,5-dien-17β-ol (**1**). Routine screening of the latter compound, which presumably comes from dehydration of the 3α-alcohol, showed marked claudogenic activity.

Searching the literature, we were impressed by a related family of steroidal 3-aryl-$\Delta^{3,5}$-dienes **2** which were purported to "... share with estrone the capacity to inhibit uterine response to progesterone."[4] Based on the reported

Table I. Steroidal 3,5-Dienes



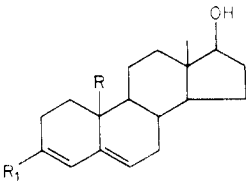
No.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8	R_9	Mp, °C	Lit. mp, °C	Yield, %	Formula	Analyses
1	H	H	H	H	H	OH	H	H	H	106-109	112-113[a,b]	29.1		
6	H	H	H	H	H	$OCOCH_3$	H	H	H	109-112	107-108[c]	13.3		
7	H	H	H	H	H	O		H	H	214-218		47.8	$C_{18}H_{24}O$	H; C[d]
8	H	CH_3	H	H	H	$OCOCH_3$	H	H	H	157-164		37.3	$C_{21}H_{30}O$	C, H
9	H	C_6H_5	H	H	H	OH	H	H	H	145-150	128-132[d]	44.5		
10	H	C_6H_5	H	H	H	$OCOCH_3$	H	H	H	152-154	158-159[d]			
11	H	C_6H_5	H	H	H	O		H	H	190-193		27.1	$C_{24}H_{28}O$	C, H
12	H	H	H	CH_3	H	OH	H	H	H	102-106			$C_{19}H_{28}O \cdot 0.25H_2O$	C, H
13	H	H	H	CH_3	H	$OCOCH_3$	H	H	H	80-81			$C_{21}H_{30}O_2$	C, H
14	H	CH_3	H	CH_3	H	OH	H	H	H	82-91			$C_{20}H_{30}O$	C, H
15	H	CH_3	H	CH_3	H	$OCOCH_3$	H	H	H	114-115		30.1	$C_{22}H_{32}O_2$	C, H
16	H	C_6H_5	H	CH_3	H	OH	H	H	H	145-148		59.2	$C_{25}H_{32}O$	C, H
17	H	H	H	H	H	$OCOCH_3$	H	CH_3	H	124-127		74	$C_{21}H_{30}O_2$	C, H
18	H	CH_3	H	H	H	$OCOCH_3$	H	CH_3	H	130-134		61	$C_{22}H_{32}O_2$	C, H
19	H	H	H	CH_3	H	$OCOCH_3$	H	CH_3	H	124-127		34	$C_{22}H_{32}O_2$	C, H
20	H	CH_3	H	CH_3	H	$OCOCH_3$	H	CH_3	H	104-107		82	$C_{23}H_{34}O_2$	C, H
21	H	H	H	H	H	OH	H	H	CH_3	153-155	98-100[e]	47.8	$C_{19}H_{28}O$	C, H
22	H	CH_3	H	H	H	OH	H	H	CH_3	128-131	134-136[f,g]	43.7		
23	H	H	CH_3	H	H	OH	H	H	CH_3	146-150		31.7	$C_{20}H_{30}O$	C, H
24	H	H	H	CH_3	H	OH	H	H	CH_3	142-144		77	$C_{20}H_{30}O$	C, H
25	H	H	H	CH_3[g]	H	OH	H	H	CH_3	159-162		52.5	$C_{20}H_{30}O$	C, H
26	CH_3	H	H	CH_3[g]	H	OH	H	H	CH_3	148-150		56.2	$C_{20}H_{32}O$	C, H
27	H	CH_3	CH_3	H	H	OH	H	H	CH_3	186-190		40.2	$C_{21}H_{32}O$	C, H
28	H	CH_3	H	CH_3	H	OH	H	H	CH_3	170-172		68.4	$C_{21}H_{32}O$	C, H
29	H	CH_3	H	CH_3[g]	H	OH	H	H	CH_3	132-134		49	$C_{20}H_{32}O$	C, H
30	CH_3	CH_3	H	CH_3	H	OH	H	H	CH_3	161-165		47.3	$C_{22}H_{34}O$	C, H
31	H	CH_3	CH_3	CH_3	H	OH	H	H	CH_3	155-160		53.3	$C_{22}H_{34}O$	H; C[u]
32	H	C_4H_9	H	H	H	OH	H	H	CH_3	94-97			$C_{23}H_{36}O \cdot 0.5H_2O$	H; C[x]
33	H	C_4H_9	H	CH_3	H	OH	H	H	CH_3	121-124		37.9	$C_{24}H_{38}O$	C, H
34	H	C_6H_5	H	H	H	OH	H	H	CH_3	162-164	154-156[h,q]	45.8	$C_{25}H_{32}O$	C, H
35	H	C_6H_5	H	H	H	$OCOCH_3$	H	H	CH_3	170-173			$C_{27}H_{34}O_2$	C, H
36	H	C_6H_5	H	CH_3	H	OH	H	H	CH_3	161-162		57.8	$C_{26}H_{34}O$	C, H
37	H	H	H	H	OH	OH	H	H	CH_3	178-180[r]	150-151[i]		$C_{19}H_{28}O_2 \cdot 0.5H_2O$	C, H
38	H	CH_3	H	H	OH	O		H	CH_3	164-166		4.1	$C_{20}H_{28}O_2$	C, H

39	H	CH_3	H	H	OH	OH	H	H	CH_3	149-152		43.2	$C_{20}H_{30}O_2 \cdot 0.25H_2O$	C, H
40	H	CH_3	H	H	OH	OH	CH_3	H	CH_3	202-208		32.9	$C_{21}H_{32}O_2 \cdot 0.25H_2O$	C, H
41	H	H	H	CH_3	OH	OH	H	H	CH_3	178-180		13.1	$C_{20}H_{32}O_2 \cdot 0.25H_2O$	C, H
42	H	H	H	CH_3[g]	OH	OH	H	H	CH_3	134-145		30.6	$C_{20}H_{30}O_2$	H; C[v]
43	H	CH_3	H	CH_3	OH	OH	H	H	CH_3	199-203		29.4	$C_{21}H_{32}O_2$	C, H
44	H	H	H	H	H	OH	H	H	CH_2OH	143-147		25.5	$C_{19}H_{28}O_2$	C, H
45	H	H	H	H	H	$OCOCH_3$	H	H	CH_2OCOCH_3	97-98		60.2	$C_{23}H_{32}O_4$	C, H
46	H	CH_3	H	H	H	O		H	CH_3	127-131		55	$C_{20}H_{28}O$	C, H
47	H	C_4H_9	H	H	H	O		H	CH_3	91-93		44.3	$C_{23}H_{34}O$	C, H
48	H	C_6H_5	H	H	H	O		H	CH_3	207-209	206-207[h]	35.9		
49	H	CH_3	H	CH_3	H	O		H	CH_3	149-152		62.8	$C_{21}H_{30}O$	C, H
50	H	H	H	H	H	OH	CH_3	H	H	143-145	140-141[a,b]	53.5		
51	H	C_6H_5	H	H	H	OH	CH_3	H	H	168-170		36.2	$C_{25}H_{32}O$	C, H
52	H	H	H	H	H	OH	CH_3	H	CH_3	136-140	160-162[j]	22		
53	H	CH_3	H	H	H	OH	CH_3	H	CH_3	151-153	153-154[k,s]	34		
54	H	H	H	CH_3	H	OH	CH_3	H	CH_3	145-147		30	$C_{21}H_{32}O$	C, H
55	H	CH_3	H	CH_3	H	OH	CH_3	H	CH_3	118-121		54.2	$C_{22}H_{34}O$	C, H
56	H	H	H	O	H	OH	H	H	CH_3	170-172[l]		65.3		
57	H[w]	H	H	O	H	$OCOCH_3$	H	H	CH_3	168-170	171-173[m]	54.3		
58	H	H	H	O	H	O		H	CH_3	164-166	164[n]	77.5		
59	H	CH_3	H	CH_2OH	H	OH	H	H	CH_3	171-175		63.7	$C_{20}H_{30}O_2$	C, H
60	H	CH_3	H	$COCH_3$	H	OH	H	H	CH_3	224-227		17.4	$C_{22}H_{32}O_2$	C, H
61	H	CH_3	H	$C(NH)CH_3$	H	OH	H	H	CH_3	150-152		4.3	$C_{22}H_{33}NO$	C, H, N
62	H	Cl	H	H	H	OH	H	H	CH_3	140-142	146-148[o]	66.2		
63	H	Br	H	H	H	OH	H	H	CH_3	143-145		55.9	$C_{19}H_{27}BrO$	C, H, Br
64	H	Br	H	H	H	$OCOCH_3$	H	H	CH_3	175-177	162-168[p]	64.8		
65	H	Cl	H	H	H	$OCOCH_3$	H	H	H	115-117		34	$C_{20}H_{27}ClO_2$	C, H, Cl
66	H	Cl	H	CH_3	H	OH	H	H	CH_3	178-180		45.2	$C_{20}H_{29}ClO$	C, H, Cl
67	H	Cl	H	CH_3	H	$OCOCH_3$	H	H	CH_3	178-180		21.6	$C_{22}H_{31}ClO_2$	C, H, Cl
68	H	$HOCH_2CH_2O$	H	O	H	$OCOCH_3$	H	H	CH_3	178-180		22.5	$C_{23}H_{32}O_5$	C, H
69	H	CH_3O	H	CH_3	H	$OCOCH_3$	H	H	CH_3	174-179		71.9	$C_{23}H_{34}O_3$	C, H
70	H	CH_3O	H	CH_3	O	O		H	CH_3	207-210		75.4	$C_{21}H_{28}O_3$	C, H
71	H	CH_3O	H	CH_3[g]	O	O		H	CH_3	160-169		9.2	$C_{21}H_{28}O_3$	C, H
72	H	$(C_2H_5O)PO_2$	H	H	H	OH	H	H	H	121-127			$C_{22}H_{35}O_5P$	C, H
73	H	$(C_2H_5O)_2PO_2$	H	H	H	OH	H	H	CH_3	102-114			$C_{23}H_{37}O_5P$	C, H

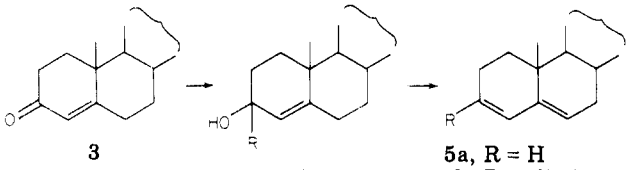
[a] J. A. Szpilfogel, Dutch Patent 90 744 (1959); *Chem. Abstr.*, 54, 13178 (1960). [b] Organon Laboratories Ltd., British Patent 841 411 (1960); *Chem. Abstr.*, 55, 9475 (1961). [c] Isolated from preparation of 1: P. N. Rao and H. R. Gollberg, *Chem. Ind. (London)*, 1317 (1961). [d] L. J. Chinn, U.S. Patent 3 246 022 (1966); *Chem. Abstr.*, 64, 19726 (1966). [e] R. I. Dorfman, E. Caspi, and P. K. Grover, *Proc. Soc. Exp. Biol. Med.*, 110, 750 (1962); E. Caspi, P. K. Grover, N. Grover, E. J. Lynde, and T. Nussbaumer, *J. Chem. Soc.*, 1710 (1962). [f] F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, 79, 5029 (1957). [g] β isomer. [h] M. Douek and G. Just, *Can. J. Chem.*, 44, 2233 (1966). [i] W. R. Slaunwhite, Jr., L. Neely, and A. A. Sandberg, *Steroids*, 3, 391 (1964). [j] B. Pelc, *Collect. Czech. Chem. Commun.*, 25, 309 (1960). [k] B. Pelc, *ibid.*, 25, 1624 (1960). [l] A. Butenandt, E. Hausmann, and J. Paland, *Chem. Ber.*, 71, 1316 (1938). [m] H. J. Siemann, W. Pohnert, and S. Schwarz, East German Patent 39 210 (1965); *Chem. Abstr.*, 63, 18222 (1965). [n] J. R. Billeter and K. Miescher, *Helv. Chim. Acta*, 31, 629 (1948). [o] G. W. Moresch and W. A. Neuklis, *Can. J. Chem.*, 41, 1627 (1963); F. Galinovsky, E. Kerschbaum, and H. Janisch, *Monatsh. Chem.*, 84, 193 (1953). [p] J. A. Ross and M. D. Martz, *J. Org. Chem.*, 29, 2784 (1964); mp 178-179.5 °C in an evacuated capillary. [q] Compound 35 is mentioned in this paper; however, the melting point and analytical data given for it correspond instead for the 17β-ol 34. [r] This material is the hemihydrate while the previously reported material is anhydrous. [s] B. Pelc, Czech Patent 96 125 (1960); *Chem. Abstr.*, 55, 15551 (1961). [t] C: calcd, 84.32; found, 83.72. [u] C: calcd, 84.02; found, 83.45. [v] C: calcd, 79.42; found, 78.93. [w] 6-Chloro. [x] C: calcd, 82.01; found, 81.48.

biological profile of **2** and the claudogenic activity of **1**, we prepared and studied a number of estra-3,5-dienes, androsta-3,5-dienes, and gona-3,5-dienes hoping to find an effective claudogen preferably having an antiprogestational mechanism of action.

Chemistry. Two convenient methods for preparation of $\Delta^{3,5}$-dienes were available from readily obtained Δ^4-3-ketones **3**. The first method was to reduce **3** to the corresponding alcohol **4a**, followed by dehydration. The second method was to add an organometallic reagent to **3**, followed by dehydration of the resulting alcohol. A



1, R = R_1 = H
2, R = H, CH_3; R_1 = aryl



3 **4** **5a**, R = H; **b**, R = alkyl, aryl

representative number of androsta-3,5-dienes were prepared as shown in Table I. The estra-3,5-dienes listed in Table I were also prepared by these methods; however, some difficulty was encountered in purifying 3-alkylestra-3,5-dien-17β-ols. These products were sensitive to air oxidation as evidenced by continually changing elemental analyses. Surprisingly, this problem was solved with 3,7α-dimethylestra-3,5-dien-17β-ol by purification of its acetate derivative.

Preparation of a small number of $\Delta^{3,5}$-dienes with substituents other than alkyl or aryl at C-3 was accomplished by standard methods. Thus, the 3-methoxy-$\Delta^{3,5}$-dienes were prepared from the corresponding Δ^4-3-ketones and trimethyl orthoformate. The 3-halides were also prepared from the corresponding Δ^4-3-ketones using $POCl_3$ or $POBr_3$.

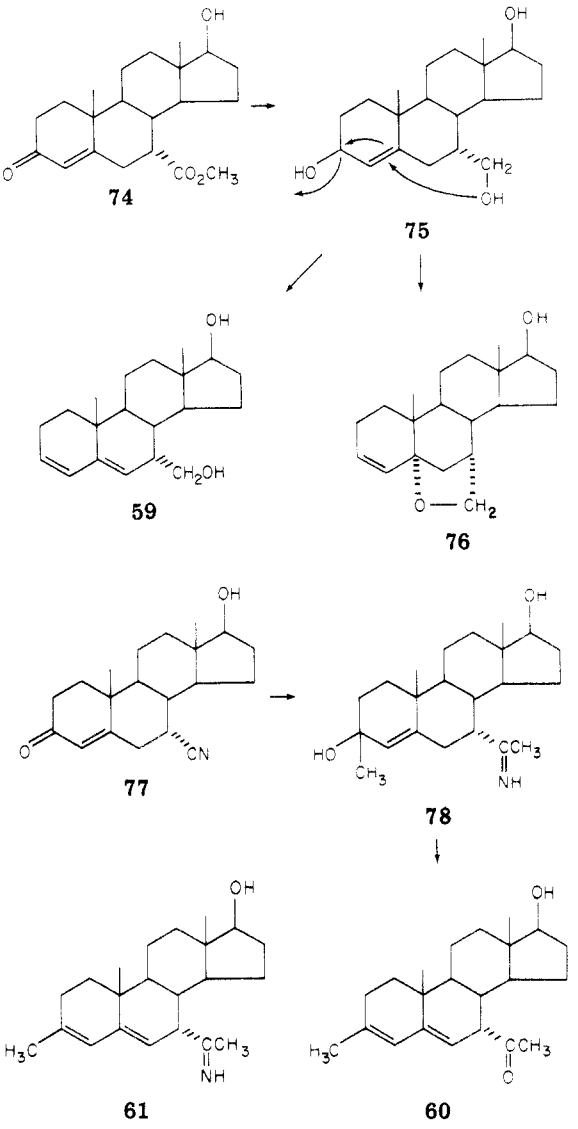
Reduction of methyl 17β-hydroxy-3-oxoandrost-4-ene-7α-carboxylate (**74**) with lithium aluminum hydride, followed by acid-catalyzed dehydration of the resulting triol **75**, gave the 7α-hydroxymethyl derivative **59**. The sample of **59** is most likely a mixture of **59** and the isomeric ether **76** since the uv extinction value of 8290 found for **59** is less than half that expected for the *trans*-diene system. The ether **76** could arise from the allylic alcohol **75** as shown by the arrows.

Reaction of 7α-cyanotestosterone (**77**) with an excess of methyllithium gave, after the usual acidic work-up, the 7α-acetyl compound **60** and a second compound **61**. Elemental analyses for **61** correspond to the formula $C_{22}H_{33}NO$. The NMR spectrum of **61** showed clearly the C-18 and C-19 methyl groups at 0.79 and 0.97 ppm, respectively. The C-3 methyl appeared at 1.73 ppm, while a sharp singlet at 2.00 ppm is attributed to a *C*-methylimine [$-C(CH_3)=N-$]. The NMR is similar to the NMR spectrum of **60**. The uv spectrum has maxima at 232 nm (ϵ 14 800), 237 sh (14 300), and 251 (12 600) which are similar to the $\Delta^{3,5}$-diene's absorption, but the shape of the curve is different and also different from **60**. The ir shows absorption at 3400, 3240, 1650, and 1625 cm^{-1}. Overall, the spectral and analytical data indicate **61** is the iminodiene shown below.

Table II. Claudogenic Activity

No.	ED_{50}, mg/kg	No.	ED_{50}, mg/kg
1	10	21	10
6	30	24	10
7	30	28	30
12	3	30	30
14	3	40	30
15	10[a]		

[a] ED_{100}.



74 **75** **59** **76** **77** **78** **61** **60**

Biological Results. Primary claudogenic screening of the compounds listed in Table I, using a hamster model, showed a fairly restricted SAR. Only the compounds listed in Table II showed an ED_{50} of 30 mg/kg or less, which we arbitrarily set as the minimum value for activity. The estradienes possessed the highest order of activity. Acetylation (**6**) of the parent **1** or oxidation of the 17-hydroxy (**7**) gave compounds of diminished activity. Introduction of a 7α-methyl group (**12**) greatly enhanced activity. Surprisingly, acetylation of this compound led to loss of activity. Introduction of a 3-methyl group alone gave no activity but introduction of both a 3- and a 7α-methyl group (**14**) gave high activity. In this case, acetylation (**15**) did not diminish the activity. The ED_{100} of the latter compound was 10 mg/kg.

In the androstadiene series, the parent **21** was about as

active as 1. Introduction of a 7α-methyl group (**24**) did not change the activity. Introduction of methyl groups at 3,7α (**28**), 3,17β (**30**), and 1,3,7α (**30**) gave active compounds but with diminished activity.

None of the gonadienes tested showed activity.

In summary, 7α-methyl- and 3,7α-dimethyl-17β-hydroxy-3,5-estradienes possess potent claudogenic activity with ED_{50}'s of 3 mg/kg, while the corresponding androstadienes are less active. The SAR shows a rather restricted substitution pattern for activity. A more detailed biological study of selected compounds in this series is being made to determine the mode of action and will be reported when completed.

Experimental Section

All melting points were determined in open capillary tubes on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 grating spectrophotometer using potassium bromide pellets. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrophotometer in ethanol. Proton magnetic resonance spectra were run on a Varian A-60A with tetramethylsilane as an internal standard and were run in $CDCl_3$ unless specified otherwise. The standard drying agent used was magnesium sulfate and the solvents were removed in vacuo on a rotary evaporator. The use of Kieselgel and silica gel was used for chromatography.

Biological Testing. Hamster Postcoital Antifertility Assay. Virgin female Golden Syrian hamsters (Engle Laboratory Animal, Inc., Farmersburg, Ind., 90–120 g) were mated with proven males. Animals with sperm present in their postestrus vaginal lavages (day 1 of pregnancy) were randomly assigned to treatment groups. Test compound was given on days 3–8 of pregnancy. At necropsy on day 15 of gestation, animals were classified as (i) pregnant with live fetuses, (ii) as nonpregnant, showing no evidence of prior pregnancy, or (iii) as resorbing with uteri containing degenerative embryos and/or implantation sites. The contragestative effects were evaluated by the number of total live fetuses (TLF) per group of eight impregnated hamsters. The ED_{100} as used is the test dose at which TLF is equal to 0, while ED_{50} is 21–40 TLF per treatment group.

General Procedure for Preparation of $\Delta^{3,5}$-Dienes. A solution of 7α-methyltestosterone (5.5 g, 18.2 mmol) in THF (150 ml) was added under N_2 to a stirred suspension of $LiAlH_4$ (1.1 g) in THF (150 ml). After 18 h, the excess hydride was decomposed by cautious addition of H_2O. $MgSO_4$ was added and the inorganic salts were removed by filtration. The ether was concentrated and the residue crystallized or used directly in the next step. The alcohol was dissolved in acetone (0.5 l.), diluted with 10% aqueous HCl (50 ml), and heated at reflux for 0.5 h. The solution was concentrated and the residue diluted with H_2O and filtered. The resulting solid was crystallized from aqueous acetone to give **24** (4.0 g, 77%).

General Procedure for Preparation of 3-Substituted $\Delta^{3,5}$-Dienes. A solution of 7α-methyltestosterone (6.04 g, 20 mmol) in THF (150 ml) and ether (200 ml) was treated with 1.6 M ethereal methyllithium[5] (70 ml). After 0.5 h, the mixture was poured into saturated aqueous NH_4Cl and the organic layer separated, dried, and concentrated. The residue was dissolved in acetone (0.5 l.), diluted with 10% aqueous HCl, and heated at reflux for 1 h. The solution was concentrated; the residue was diluted with H_2O and filtered. The resulting solid was dried and chromatographed on silica gel eluting with C_6H_6–5% acetone. The product was crystallized from aqueous acetone to give **28** (4.1 g, 68.4%).

General Preparation of 3-Halo-$\Delta^{3,5}$-dienes. 7α-Methyltestosterone acetate (4.4 g, 12.7 mmol) in acetic acid (25 ml) was treated with $POCl_3$ (2 ml). After 18 h, the solid was filtered off and crystallized from acetone to give **67** (1.0 g, 21.6%).

Saponification of the 17-acetoxy was done as follows. The above acetate (3 g, 8.29 mmol) in methanol (100 ml)–10% aqueous NaOH (10 ml) was heated at reflux for 4 h, then concentrated to ca. one-third its volume, and cooled and the solid filtered off and crystallized from aqueous acetone to give **66** (1.2 g, 45.2%).

General Preparation of 3-Alkoxy-$\Delta^{3,5}$-dienes. A suspension of 7β-methylandrost-4-ene-3,11,17-trione (6.5 g, 20.7 mmol), *p*-toluenesulfonic acid (0.4 g), and trimethyl orthoformate (7 ml) in dioxane (75 ml) was stirred at room temperature for 1 h. The solution was treated with pyridine (3 ml), followed by H_2O (100 ml). The solid was filtered off, washed with H_2O, dried, and crystallized from methanol to give **71**.

General Procedure for Oxidation of 17β-Hydroxyl. A solution of 3,7α-dimethylandrosta-3,5-dien-17β-ol (4.0 g, 13.3 mmol) in Me_2SO (20 ml)–C_6H_6 (20 ml) containing pyridine (1.0 ml), trifluoroacetic acid (0.5 ml), and dicyclohexylcarbodiimide (8.35 g) was stirred for 3 h. The mixture was diluted with ethyl acetate and treated with oxalic acid (4.5 g) in methanol (20 ml). After 20 min longer, the solid was filtered off. The filtrate was washed with H_2O and with aqueous $NaHCO_3$, dried, and concentrated. The residue was chromatographed on silica gel eluting with C_6H_6–5% acetone. The product was crystallized from aqueous acetone to give **49** (2.5 g, 62.8%).

7α-(Hydroxymethyl)androsta-3,5-dien-17β-ol (59). Methyl 17β-hydroxy-3-oxoandrost-4-ene-7α-carboxylate[6] (0.9 g, 2.6 mmol) was added to a stirred suspension of $LiAlH_4$ (1.0 g) in THF (200 ml). After 18 h, the reaction mixture was worked up in typical fashion and the resulting triol was dehydrated in the usual manner with acetone–10% aqueous HCl. The crude material was crystallized from acetone to give **59** (0.5 g, 63.7%).

7α-Acetyl-3-methylandrosta-3,5-dien-17β-ol (60) and 7α-Acetimidoyl-3-methylandrosta-3,5-dien-17β-ol (61). A mixture of 7α-cyanotestosterone (4.4 g, 14 mmol) in THF (150 ml) was treated with ethereal 1.85 M methyllithium[5] (100 ml). After 1 h, the reaction mixture was worked up in typical fashion and the resulting imino diol was dehydrated in the usual manner with acetone (500 ml)–10% aqueous HCl (50 ml). The crude material was purified by chromatography on Kieselgel (200 g), eluting with C_6H_6 (0.5 l.), C_6H_6–10% acetone (1 l.), C_6H_6–30% acetone, (0.1 l.), and C_6H_5–10% methanol. The first product off the column was crystallized from acetone to give **60** (0.8 g, 17.4%). The material coming off the column with the 10% methanol was crystallized from acetone to give **61** (0.2 g, 4.3%), mp 150–152 °C.

17β-Hydroxy-3-[(2-hydroxy)ethoxy]androsta-3,5-dien-7-one 17-Acetate (68). This compound was prepared inadvertently during an attempted Wittig-type reaction. Thus, sodium hydride (0.6 g, 25 mmol) was added under N_2 at ambient temperature with stirring to Me_2SO (50 ml). After 20 min, a solution of triethyl phosphonoacetate (5.6 g, 25 mmol) in THF (70 ml) was added dropwise. After 30 min, a solution of 17β-hydroxyandrost-6-ene-3,7-dione 17-acetate 3-cyclic ethylene ketal (4.0 g, 10.3 mmol) in THF (60 ml)–Me_2SO (60 ml) was added over 10 min. The mixture was stirred 20 h, then poured into cold H_2O, and extracted with CH_2Cl_2. The organic layer was separated, washed with H_2O, dried, and concentrated. The oily residue was chromatographed on Kieselgel to give **68** (0.9 g) after two recrystallizations from acetone–hexane.

Diethyl 17-Hydroxyandrosta-3,5-dien-3-yl Phosphorate (73). A solution of testosterone (5.78 g, 20 mmol) and sodium methylate (3.24 g, 60 mmol) in Me_2SO (50 ml) was stirred under N_2 for 1 h. This was poured into benzene (100 ml) and diethyl chlorophosphonate (5 ml) and stirred for 2 min before adding ice–H_2O. The organic layer was separated, washed with H_2O, dried, and concentrated. The solid residue was triturated with hexane and then crystallized from ether–hexane to give **73**.

References and Notes

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