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REGIOSELECTIVE SYNTHESIS OF RING A POLYMETHYLATED STEROIDS IN THE ANDROSTANE SERIES

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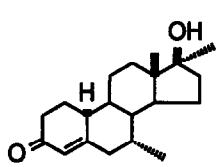
Summary. Properly protected derivatives **14** and **20** of the common precursor 17ß-hydroxy-1-methyl-5α-androst-1-en-3-one (**13**) have been transformed in a regioselective manner into highly methylated androsta-1,4-diene-3,17-dione derivatives **6-8.** Access to the manifold of 1,4-dimethylated derivatives was gained by methylation of the kinetic lithium dienolate derived from **20**, while thiomethylation of **14**, via the thermodynamic dienolate or an equivalent, followed by Raney nickel promoted desulfurization gave rise to **28.** A combination of these alkylation methods led successfully to the trimethylated androstane derivative **34**. Benzeneseleninic anhydride (BSA) mediated dehydrogenation of intermediates **23**, **28**, and **34** then furnished the 1,4-dienes **24**, **29**, and **35**, two conventional steps short of the target molecules **6-8.** A facile synthesis of the potent aromatase inhibitor **5** by subjecting **13** to a BSA-promoted oxidation is also described.

Introduction. Numerous synthetic steroid hormone analogues owe an essential part of their biological activity to the presence of methyl groups at key positions of the steroid nucleus. Advantageous properties of these types of molecules range from a higher affinity for the corresponding receptor protein to an improved metabolic stability. Well-known examples in this area include the orally active 7α,17α-dimethyl-19-nortestosterone (**1**)[1] and highly potent progestins like 17α-methyl-19-norprogesterone (**2**)[2] or 17α-acetyloxy-6α-methylprogesterone (**3**).[3]



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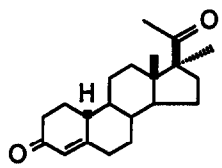

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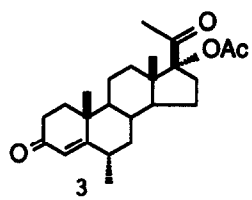

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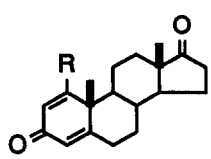


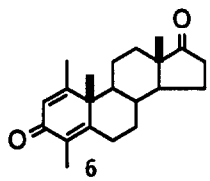
4 R = H

5 R = CH_3

A novel, promising approach for controlling estrogen biosynthesis and diseases mediated by these hormones has also capitalized on this principle.

The weak aromatase inhibitor androsta-1,4-diene-3,17-dione (**4**) becomes one of the most active steroidal inhibitors of this enzyme system, when a methyl substituent is attached to C-1, **5**.[4,5]

This striking effect of an additional methyl group on ring A promotes the hitherto unknown, highly substituted androsta-1,4-diene derivatives **6-8** to interesting targets for biological testing. In recording our successful elaboration of these compounds, together with a series of comparably congested intermediates, we anticipate that these compounds will also constitute valuable starting materials for advanced studies on the photochemistry of cross-conjugated cyclohexadienones,[6] the acid-promoted dienone-phenol rearrangement,[7] and structural phenomena.[8]



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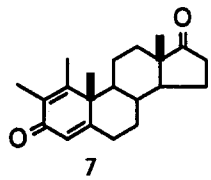

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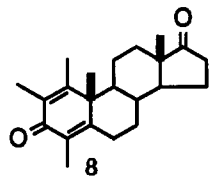

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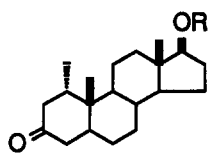
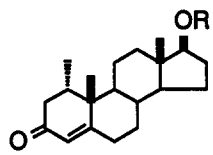
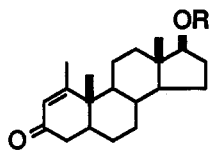


9 R = H
10 R = Ac



11 R = H
12 R = Ac



13 R = H
14 R = Ac

Discussion and Results. C-1 methylated steroids **9** - **14** qualify as attractive starting materials, since these compounds are available in bulk quantities.[9]

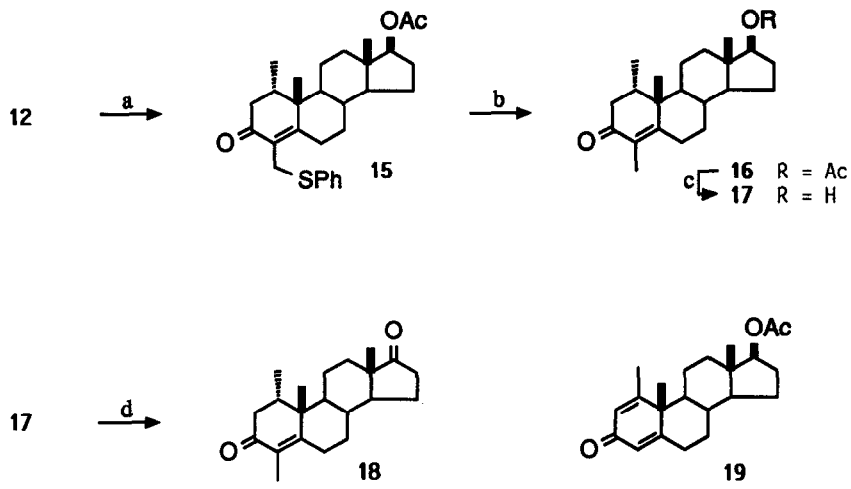
With this entry, the synthetic task was reduced to regioselective methylation[10] of positions adjacent to the 3-oxo functionality followed by proper dehydrogenation[11,12] of the polymethylated products.

Initial experiments on the direct alkylation of **9** or the reductive alkylation[13] of **11** or **13** followed by dehydrogenation of the resulting saturated derivatives were not very rewarding.

The strategy we consequently embarked on took advantage of the high flexibility inherent in the enolization behaviour of the cyclohexenone moiety and preserved unsaturation in ring A beyond the alkylation step.[14] Thus, employing a strong hindered base and nonequilibrating reaction conditions the kinetic, cross-conjugated dienolate is formed and subsequently alkylated with high regiocontrol to leave a product substituted at the saturated

α-carbon atom.[14] The opposite regioisomer, substituted at the olefinic α-carbon atom, is accessible by alkylation of the conjugated, thermodynamic dienolate which, in turn, is generated under equilibrating reaction conditions.[14] The latter process, however, is frequently marred by substantial polyalkylation, unless reaction conditions are controlled carefully.[15] Several elegant procedures, most notably those devised by Stork,[16] Kuehne,[17] Conia,[18] and Kirk and Petrow[19] circumvent this problem. For reasons of convenience we decided to rely on the two-step process introduced by the British group.[19] This thioalkylation-desulfurization protocol has also been successfully applied in natural product synthesis on several occasions.[20]

Gratifyingly, thiomethylation of **12** took place smoothly at 110 °C in triethanolamine in the presence of excess aqueous formaldehyde and thiophenol (Scheme I) to furnish **15** in 70 % yield after chromatography.



(a) $N(CH_2CH_2OH)_3$, PhSH, CH_2O, H_2O, 110 °C; (b) acetone, Raney nickel, 60-70 °C; (c) CH_3OH, KOH, 22 °C, 4 h; (d) Jones oxidation, 22 °C.

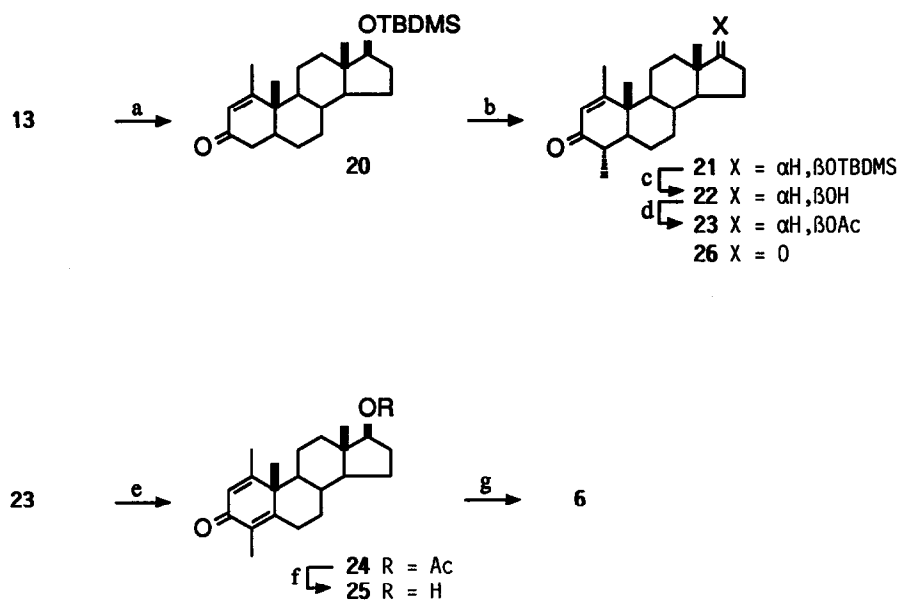
Scheme I

Desulfurization of this crystalline thioether over Raney nickel, which had been deactivated by prior refluxing in acetone for 1 h with vigorous stirring gave the dimethyl derivative **16** in 70 % yield following chromatography. Subsequent saponification of this acetate and Jones oxidation of the resulting alcohol **17** led to the diketone **18**.

Disappointingly however, all attempts to install a second double bond in ring A of both the acetate **16** and the diketone **18** employing 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[11] or a more recently developed oxidation procedure[12] based on benzeneseleninic anhydride (BSA) did not meet with success. Not unexpectedly, the monomethyl derivative **12** also failed to give a tractable reaction mixture under Barton's oxidation conditions.[12]

Given our inability to effect this crucial reaction on C-1α substituted Δ^4-3-oxo steroids, we investigated the behavior of the isomeric C-1 substituted Δ^1-3-oxo derivatives. In the simplest case, viz. **14**, Barton's procedure gave a clean dehydrogenation leading to the 1,4-diene **19** in 80 % yield, without affecting the allylic methyl group at C-1.[21]

When the unprotected steroid **13** was subjected to this oxidation reaction, **5** could be isolated in 51 % yield. This novel one-pot procedure constitutes an expeditious route to this biologically active compound,[4] starting from a commercially available bulk product.



(a) DMF, imidazole, TBDMSCl, 22 °C; (b) THF, LDA, -78/-30 °C; CH_3I, -78 °C; (c) HOAc, THF, H_2O, 60 °C; (d) pyridine, Ac_2O, DMAP, 22 °C; (e) toluene, $(PhSe)_2$, $PhIO_2$, 80-90 °C; (f) CH_3OH, KOH, 22 °C; (g) Jones oxidation, 22 °C.

Scheme II

With this model study satisfactorily completed, we focused on the preparation of **23** (Scheme **II**).

To this end, 1-methyl-5α-androst-1-en-3-one (**13**) was transformed into the corresponding silyl ether **20** in near quantitative yield under standard conditions.[22] The cross-conjugated dienolate, generated from the protected enone **20** at -78/-30 °C underwent clean alkylation[23] with methyl iodide at -78 °C in tetrahydrofuran (THF) to produce **21** in 79 % yield.

A vicinal coupling of 11.7 Hz between the remaining proton (δ 2.25 ppm, $CDCl_3$, 300 MHz) at C-4 in the alkylated product **21** and the proton at C-5 establishes their diaxial relationship and places the methyl group in the thermodynamically more favorable quasi-equatorial position as depicted.

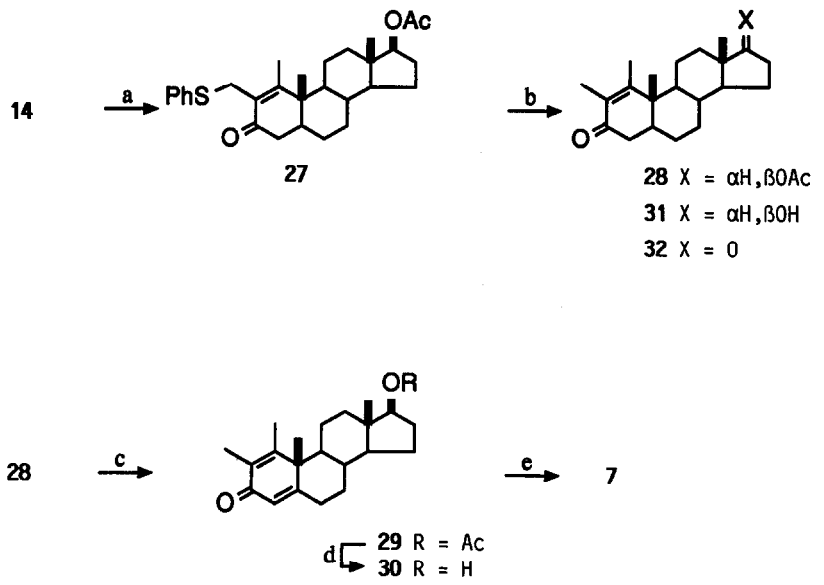
At this point, the protecting group at C-17 was exchanged by acid-promoted hydrolysis of the silyl ether and subsequent esterification of the resulting alcohol **22** in a mixture of pyridine and acetic anhydride in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) to afford the highly crystalline acetate **23** in 83 % overall yield. The stage was now set for the crucial dehydrogenation step. To our delight, Barton's reagent combination comprised of a catalytic amount of diphenyl diselenide and excess iodoxybenzene promoted the desired oxidation in toluene at 80 °C.[12] Chromatographic separation from several by-products furnished the pure acetate **24** in 31 % yield. Our first target compound was now accessible by two additional standard transformations. Thus, saponification and Jones oxidation of the resulting alcohol **25** led to 1,4-dimethylandrosta-1,4-diene-3,17-dione (**6**). Similarly, Jones oxidation of the intermediate alcohol **22** gave rise to the diketone **26**.

We next turned our attention to the synthesis of **7**. As outlined in Scheme **III**, the starting material again featured the approved functionality in ring A.

In this instance, thiomethylation, although somewhat less efficient than in the example described above, gave the crystalline thioether **27** in 61 % yield after chromatographic separation from unreacted starting material and polar by-products.

The ensuing desulfurization over deactivated Raney nickel proceeded uneventfully to the dimethyl derivative **28** in 73 % yield after chromatographic purification. Not suprisingly, **28** underwent BSA-mediated dehydrogenation according to Barton et al.[12] with similar ease as the monomethyl derivative **14** to give the dienone **29** in 78 % yield as an oil. Subsequent hydrolysis of the acetate afforded the crystalline dienol **30**, which was converted into our second target molecule **7** by Jones oxidation in 81 % yield. In like manner, the intermediate acetate **28** was transformed into the alcohol **31** and the diketone **32**.

By a combination of methods successfully applied for the preparation of **6** and **7**, the third target structure was made available as detailed in Scheme **IV**.

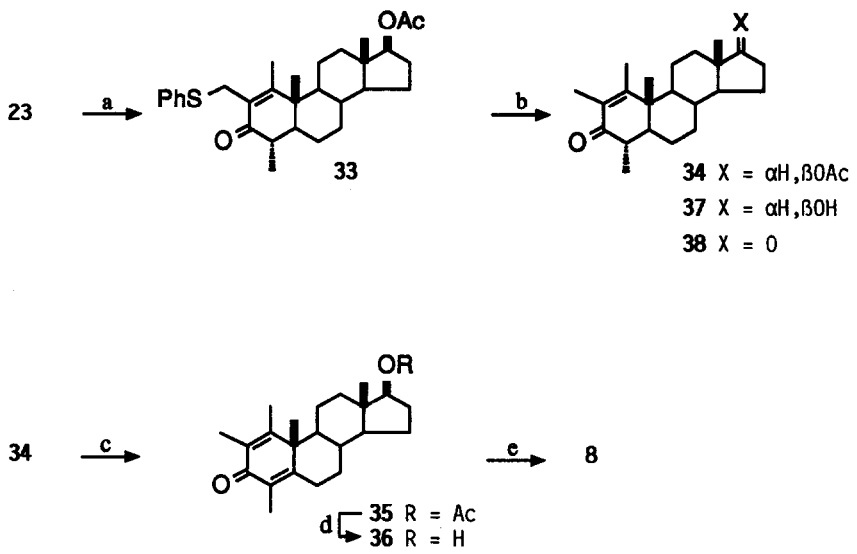


(a) $N(CH_2CH_2OH)_3$, PhSH, CH_2O, H_2O, 110 °C; (b) acetone, Raney nickel, 60-70 °C; (c) toluene, $(PhSe)_2$, $PhIO_2$, 80 °C; (d) CH_3OH, KOH, 22 °C; (e) Jones oxidation, 22 °C.

Scheme III

The synthesis commenced with 17ß-acetyloxy-1,4α-dimethyl-5α-androst-1-en-3-one (**23**), the key intermediate in the sequence leading to 1,4-dimethylandrosta-1,4-dien-3,17-dione (**6**). For reasons of solubility the thiomethylation was conducted in a mixture of ethanol and triethanolamine in the presence of excess thiophenol and aqueous formaldehyde at 100 - 110 °C. Under these reaction conditions the alkylation proceeded slowly and was accompanied by the formation of substantial amounts of side products. Since these by-products seemed to increase unproportionally at the expense of **33**, the reaction was interrupted at about 60-70 % conversion after 80 h. The thioether **33** was isolated by chromatography in 42 % yield along with 26 % of unreacted starting material.

In analogy to previous desulfurizations, thioether **33** was smoothly reduced to the trimethyl derivative **34** over partially deactivated Raney nickel. Upon treatment of this key intermediate with diphenyl diselenide and iodoxybenzene in toluene at 80 °C, dehydrogenation occurred slowly. Chromatography of the crude reaction mixture gave the desired diene **35** in 33 % yield as well as recovered starting material. Conventional saponification and Jones oxidation of the resulting alcohol **36** finally provided 1,2,4-trimethylandrosta-1,4-diene-3,17-dione (**8**).



(a) C_2H_5OH, $N(CH_2CH_2OH)_3$, PhSH, CH_2O, H_2O, 100 - 110 °C; (b) acetone, Raney nickel, 60-70 °C; (c) toluene, $(PhSe)_2$, $PhIO_2$, 80 - 90 °C; (d) CH_3OH, KOH, 22 °C; (e) Jones oxidation, 22 °C.

Scheme **IV**

Derivatives **37** and **38** were obtained from the acetate **34** on saponification and oxidation.

The spatial proximity of a methyl group at C-4 to the α-hydrogen atom at C-6 in derivatives like **24** or **35** was clearly evident from their ^1H NMR spectra.[24] In comparing these acetates with compounds **19** and **29**, which lack the substituent at C-4, a crossover in the chemical shifts of the α- and ß-protons at C-6 was noticed. In particular, the resonances of the α-protons at C-6 are shifted downfield by 0.46 ppm in derivatives **24** and **35** relative to those of **19** and **29**, while the ß-protons appear upfield by 0.21 ppm in the methylated series.

Experimental Section

Representative Thiomethylation Procedure. 17β-Acetyloxy-1α-methyl-4-[(phenylthio)methyl]-androst-4-en-3-one (15). A mixture of 17β-acetyloxy-1α-methylandrost-4-en-3-one (**12**) (17.22 g, 50 mmol), aqueous formaldehyde (4 ml), and thiophenol (4.40 g, 40 mmol) was stirred in triethanolamine (150 ml) for 10 h under an atmosphere of argon at 110 °C (bath temperature). After 4 h of reaction time additional aqueous formaldehyde (3 ml) and thiophenol (2.20 g, 20 mmol) were added to the reaction mixture. The yellow colored solution was allowed to cool to room temperature, poured into brine, and extracted with methylene chloride. Excess thiophenol was removed from the organic phase by two washings with dilute aqueous sodium hydroxide solution. After drying the extracts over anhydrous sodium sulfate, filtration and concentration in vacuo gave the reaction product as a yellow oil which was purified by chromatography. Elution with hexane/ethyl acetate (4:1) gave **15** (17.03 g, 70 %) as an oil which solidified on standing: mp 91-93 °C; $[\alpha]_D^{22}$ +95.2° (c 0.51, $CHCl_3$); IR (KBr) 2970, 2940, 2850, 1735, 1670, 1600, 1438, 1372, 1359, 1314, 1245, 1043, 740, 695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.15 (series of m, 5H), 4.60 (dd, J = 9.0, 7.8 Hz, 1H), 3.88 (s, 2H), 2.80-2.67 (series of m, 2H), 2.24 (dd, J = 16.2, 2.6 Hz, 1H), 2.04 (s, 3H), 1.25 (s, 3H), 0.86 (d, J = 6.9 Hz, 3H), 0.83 (s, 3H); HRMS, m/e (M^+) calcd 466.2542, obsd 466.2542.

17β-Acetyloxy-1-methyl-2-[(phenylthio)methyl]-5α-androst-1-en-3-one (27). The acetate **14** (17.22 g, 50 mmol) underwent thiomethylation with aqueous formaldehyde (7 ml) and thiophenol (6.60 g, 60 mmol) in triethanolamine (150 ml) during 24 h in analogy to the procedure described for the synthesis of **15**. The product (14.22 g, 61 %) was obtained by chromatography (hexane/ethyl acetate, 4:1) as an oil which solidified on standing: mp 112-114 °C; $[\alpha]_D^{22}$ +73.0° (c 0.53, $CHCl_3$); IR (KBr) 2970, 2920, 2870, 2850, 1732, 1665, 1583, 1480, 1438, 1372, 1320, 1247, 1075, 1025, 898, 737, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.17 (series of m, 5H), 4.63 (dd, J = 9.2, 7.6 Hz, 1H), 3.99 (1/2 ABq, J = 11.4 Hz, 1H), 3.71 (1/2 ABq, J = 11.4 Hz, 1H), 2.34 (dd, J = 18.5, 12.7 Hz, 1H), 2.23 (dd, J = 18.5, 5.3 Hz, 1H), 2.05 (s,3H), 0.99 (s, 3H), 0.84 (s, 3H); HRMS, m/e (M^+) calcd 466.2542, obsd 466.2529.

17β-Acetyloxy-1,4α-dimethyl-2-[(phenylthio)methyl]-5α-androst-1-en-3-one (33). A solution of the acetate **23** (14.34 g, 40 mmol), aqueous formaldehyde (6 ml), and thiophenol (5.50 g, 50 mmol) in triethanolamine/ethanol (4:1) gave **33** as an oil (8.08 g, 42 %) after 80 h of reaction time followed by chromatographic purification (hexane/ethyl acetate, 4:1): $[\alpha]_D^{22}$ +71.6° (c 0.52, $CHCl_3$); IR ($CHCl_3$) 2970, 2925, 2870, 2850, 1720, 1655, 1440, 1372, 1255,

1025 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.16 (series of m, 5H), 4.64 (dd, J = 9.1, 7.6 Hz, 1H), 4.02 (1/2 ABq, J = 11.5 Hz, 1H), 3.66 (1/2 ABq, J = 11.5 Hz, 1H), 2.05 (s, 3H), 2.01 (s, 3H), 1.07 (d, J = 7.0 Hz, 3H), 0.98 (s, 3H), 0.84 (s, 3H); HRMS, m/e (M^+) calcd 480.2698, obsd 480.2682.

Representative Desulfurization Procedure. 17β-Acetyloxy-1α,4-dimethylandrost-4-en-3-one (16). Raney nickel (50 g) was thoroughly rinsed with water (5 x) and subsequently with acetone (5 x). With vigorous stirring the metal was kept in 90 ml of acetone at reflux temperature for 1 h, whereupon the thioether **15** (4.67 g, 10 mmol) was added in acetone (15 ml) and refluxing was continued for 15 minutes. The hot organic phase was decanted and the metal was washed with hot 60 ml portions of solvent (5 x). The crude product obtained on concentration of the combined filtrates was chromatographed. Elution with hexane/ethyl acetate (4:1) furnished the dimethyl acetate **16** (2.50 g, 70 %) as a white crystalline material: mp 172-174 °C (cyclohexane); $[\alpha]_D^{22}$ +111.2° (c 0.50, $CHCl_3$); IR (KBr) 2970, 2948, 2920, 2890, 2850, 1735, 1670, 1605, 1450, 1374, 1310, 1245, 1230, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (dd, J = 9.1, 7.7 Hz, 1H), 2.85-2.71 (series of m, 2H), 2.22 (dd, J = 16.2, 2.6 Hz, 1H), 2.05 (s, 3H), 1.76 (d, J = 1.5 Hz, 3H), 1.27 (s, 3H), 0.90 (d, J = 6.9 Hz, 3H), 0.85 (s, 3H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.26; H, 9.62.

17β-Acetyloxy-1,2-dimethyl-5α-androst-1-en-3-one (28). Thioether **27** (2.33 g, 5 mmol) was reduced over Raney nickel (20 g) according to the general procedure to afford the dimethyl derivative **28** (1.31 g, 73 %) after chromatography (hexane/ethyl acetate, 4:1) as a crystalline solid: mp 126-128 °C (cyclohexane); $[\alpha]_D^{22}$ +44.2° (c 0.52, $CHCl_3$); IR (KBr) 2975, 2920, 2850, 1738, 1660, 1593, 1442, 1370, 1318, 1240, 1213, 1075, 1040, 1030, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (dd, J = 9.2, 7.6 Hz, 1H), 2.35 (dd, J = 18.2, 13.0 Hz, 1H), 2.22 (dd, J = 18.2, 5.0 Hz, 1H), 2.05 (s, 3H), 1.99 (d, J = 1.0 Hz, 3H), 1.75 (d, J = 0.9 Hz, 3H), 1.01 (s, 3H), 0.85 (s, 3H).

Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.23; H, 9.52.

17β-Acetyloxy-1,2,4α-trimethyl-5α-androst-1-en-3-one (34). On reduction of the thioether **33** (2.40 g, 5 mmol) over Raney nickel (25 g) the trimethyl derivative **34** (1.31 g, 70 %) was obtained after chromatography (hexane/ethyl acetate, 5:1) as white crystalline material: mp 140-141 °C (cyclohexane); $[\alpha]_D^{22}$ +40.4° (c 0.50, $CHCl_3$); IR (KBr) 2970, 2940, 2890, 2855, 1730, 1658, 1600, 1455, 1370, 1245, 1026 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.63 (dd, J = 9.2, 7.6 Hz, 1H), 2.05 (s, 3H), 1.97 (d, J = 1.0 Hz), 1.75 (d, J = 1.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.99 (s, 3H), 0.84 (s, 3H).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.38; H, 9.74. Found: C, 77.34; H, 9.70.

Representative Dehydrogenation Procedure. 17β-Acetyloxy-1-methylandrosta-1,4-dien-3-one (19). A suspension of iodoxybenzene (2.60 g, 11 mmol) and diphenyl diselenide (0.11g, 0.35 mmol) in dry toluene (50 ml) was stirred at 80 °C for 15 minutes. After this period the yellow color of the diselenide had disappeared and the acetate **14** (1.38 g, 4 mmol) was added to the reaction mixture. Stirring and heating was continued for 4 h. After cooling to room temperature the mixture was filtered and the residue was thoroughly washed with methylene chloride. The combined organic phases were washed with aqueous sodium bicarbonate solution, brine, and dried over anhydrous sodium sulfate. The crude product, obtained after filtration and evaporation of the solvent in vacuo, was chromatographed with hexane/ethyl acetate (3:2) to afford the diene **19** (1.10 g, 80 %): mp 139-140 °C (hexane/ethyl acetate); $[\alpha]_D^{22}$ -104.0° (c 0.52, $CHCl_3$); IR (KBr) 2940, 2870, 2850, 1730, 1665, 1620, 1600, 1445, 1330, 1245, 1045, 1025, 910, 900 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.17 (s, 1H), 6.08 (s, 1H), 4.54 (dd, J = 9.1, 7.7 Hz, 1H), 2.60 (td, J = 12.9, 5.3 Hz, 1H), 2.36 (ddd, J = 12.7, 5.0, 2.1 Hz, 1H), 2.11 (d, J = 1.1 Hz, 3H), 2.04 (s, 3H), 1.34 (s, 3H), 0.85 (s, 3H).
Anal. Calcd for $C_{22}H_{30}O_3$: C, 77.16; H, 8.83. Found: C, 77.21; H, 8.65.

1-Methylandrosta-1,4-diene-3,17-dione (5). **13** (1.21 g, 4 mmol) was oxidized employing iodoxybenzene (3.54 g, 15 mmol) and diphenyl diselenide (125 mg, 0.4 mmol) according to the procedure described above, except that 2.00 g of iodoxybenzene was initially present. The remainder was added in two portions (1.00 g; 0.54 g) after 4 h and 7 h, respectively. The total reaction time was 9 h. Purification of the crude product by chromatography (hexane/ethyl acetate gradient elution, 1:1) produced the dione **5** (610 mg, 51 %): mp 149-150 °C (ethyl acetate). Depending on the concentration and crystallization rate a second polymorph melting at 166-167 °C was also obtained; $[\alpha]_D^{22}$ -44.5° (c 0.51, $CHCl_3$); IR (KBr) 2975, 2945, 2930, 2845, 1735, 1663, 1620, 1600, 1390, 1375, 1300, 1050, 910, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.19 (t, J = 1.4 Hz, 1H), 6.10 (br s, 1H), 2.65 (td, J = 13.0, 5.4 Hz, 1H), 2.51-2.38 (m, 2H), 2.14 (d, J = 1.2 Hz, 3H), 1.37 (s, 3H), 0.93 (s, 3H).
Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.40; H, 8.95.

17β-Acetyloxy-1,4-dimethylandrosta-1,4-dien-3-one (24). Dehydrogenation of the acetate **23** (1.80 g, 5 mmol) was achieved with iodoxybenzene (3.80 g, 16 mmol) and diphenyl diselenide (156 mg, 0.5 mmol) during 7 h. The reaction product was purified by chromatography (hexane/ethyl acetate, 3:1) to afford **24** (553 mg, 31 %) as highly crystalline material: mp 182-184 °C (acetone); $[\alpha]_D^{22}$ -70.6° (c 0.51, $CHCl_3$); IR (KBr) 2935, 2900, 2845, 1729, 1651, 1620, 1600, 1453, 1444, 1388, 1375, 1364, 1240, 1040, 1022, 989, 878 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 6.21 (d, J = 1.1 Hz, 1H), 4.52 (dd, J = 9.1, 7.6 Hz, 1H), 2.81 (ddd, J = 13.1, 4.6, 2.6 Hz, 1H), 2.39 (td, J = 13.6, 4.7 Hz, 1H), 2.09 (d, J = 1.1 Hz, 3H), 2.04 (s, 3H), 1.91 (s, 3H), 1.34 (s, 3H), 0.85 (s, 3H).
Anal. Calcd for $C_{23}H_{32}O_2$: C, 77.49; H, 9.05. Found: C, 77.60; H, 8.88.

17β-Acetyloxy-1,2-dimethylandrosta-1,4-dien-3-one (29). Over a period of 4 h, dehydrogenation of **28** (1.08 g, 3 mmol) promoted by iodoxybenzene (2.36 g, 10 mmol) and diphenyl diselenide (128 mg, 0.4 mmol) gave the diene **29** (834 mg, 78 %) as a viscous oil after chromatography (hexane/ethyl acetate, gradient elution, 4:1): $[\alpha]_D^{22}$ -81.2° (c 0.50, $CHCl_3$); IR (KBr) 2940, 2855, 1735, 1660, 1623, 1445, 1380, 1348, 1042, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.12 (s, 1H), 4.53 (dd, J = 9.1, 7.6 Hz, 1H), 2.60 (td, J = 12.8, 5.6 Hz, 1H), 2.34 (ddd, J = 12.7, 5.1, 2.1 Hz, 1H), 2.04 (s, 3H), 2.01 (d, J= 1.0 Hz, 3H), 1.88 (d, J = 1.0 Hz, 3H), 1.33 (s, 3H), 0.85 (s, 3H); HRMS, m/e (M^+) calcd 356.2352, obsd 356.2353.

17β-Acetyloxy-1,2,4-trimethylandrosta-1,4-dien-3-one (35). **35** (490 mg, 33 %) was obtained from **34** (1.49 g, 4 mmol) employing iodoxybenzene (3.54 g, 15 mmol) and diphenyl diselenide (156 mg, 0.5 mmol). Chromatographic purification (hexane/ethyl acetate, 3:1) also gave recovered starting material **34** (370 mg).

Data for **35**: mp 162-164 °C (cyclohexane); $[\alpha]_D^{22}$ -41.5° (c 0.51, $CHCl_3$); IR (KBr) 2925, 2845, 1730, 1645, 1620, 1445, 1390, 1373, 1237, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, J = 9.0, 7.6 Hz, 1H), 2.80 (ddd, J = 13.2, 4.7, 2.5 Hz, 1H), 2.39 (td, J = 13.5, 4.9 Hz, 1H), 2.04 (s, 3H), 2.00 (d, J = 0.9 Hz, 3H), 1.93 (s, 3H), 1.90 (d, J = 0.8 Hz, 3H), 1.33 (s, 3H), 0.85 (s, 3H).
Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.72; H, 9.14.

17β-(tert.-Butyldimethylsilyloxy)-1-methylandrost-1-en-3-one (20). To 17β-hydroxy-1-methyl-5α-androst-1-en-3-one (**13**, 30.30 g, 100 mmol) in anhydrous dimethylformamide (400 ml) was added tert.-butyldimethylsilylchloride (15.80 g, 105 mmol) followed by imidazole (17.00 g, 250 mmol). The reagents dissolved under gentle swirling. The contents of the tightly stoppered reaction flask were kept at room temperature for one day and subsequently poured into ice water (2 l) under stirring. The steroid was extracted with ethyl acetate. The organic layer was washed thoroughly with water and brine and dried over anhydrous sodium sulfate. Filtration and concentration left the protected steroid as an oil which solidified on standing. Solvent residues were removed under vacuum to give **20** (40.00 g, 96 %). Recrystallization from hexane at dry-ice temperature furnished material with a mp 116-118 °C; $[\alpha]_D^{22}$ +47.5° (c 0.52, $CHCl_3$); IR (KBr) 2950, 2930, 2860, 1670, 1595, 1472, 1443, 1250, 1130, 1086, 910, 887, 835, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.71 (br s, 1H), 3.57 (m, 1H), 2.38 (dd, J = 18.3, 13.5 Hz, 1H), 2.19 (dd, J = 18.2, 4.2 Hz, 1H), 2.08 (d, J = 1.2 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H).
Anal. Calcd for $C_{26}H_{44}O_2Si$: C, 74.94; H, 10.64. Found: C, 74.87; H, 10.44.

17β-(tert.-Butyldimethylsilyloxy)-1,4α-dimethyl-5α-androst-1-en-3-one (21). A solution of lithium diisopropylamide in tetrahydrofuran was prepared in a dry reaction vessel under an atmosphere of argon by the careful addition of n-butyllithium/hexane (14 ml, 21 mmol) to diisopropylamine (2.53 g, 25 mmol) in dry tetrahydrofuran (60 ml) at 0 °C. The solution was stirred at this temperature for 15 minutes and then cooled to -78 °C, whereupon a solution of **20** (8.33 g, 20 mmol) in dry tetrahydrofuran (20 ml) was added dropwise via syringe. Stirring was continued for 3 hours during which time the reaction mixture gradually warmed to -30 °C (bath temperature).

The reaction mixture was then recooled again to -78 °C and methyl iodide (3.12 g, 22 mmol) in dry tetrahydrofuran (10 ml) was added by syringe. After an additional period of 15 minutes at -78 °C, the cooling bath was removed and the reaction mixture was stirred at ambient temperature for 30 minutes. The reaction mixture was carefully poured into 500 ml of ice water and extracted with methylene chloride. The organic phase was washed with dilute hydrochloric acid, saturated bicarbonate solution, brine, and dried over anhydrous sodium sulfate. Thin-layer chromatography (hexane/ethyl acetate, 9:1) revealed the presence of about 5-10 % of starting material. After filtration and concentration in vacuo the resultant crude product was purified by chromatography. Elution with hexane/ethyl acetate (9:1) furnished the product **21** (6.80 g) in 79 % yield as a colorless crystalline solid: mp 64-67 °C; $[\alpha]_D^{22}$ +28.2° (c 0.50, $CHCl_3$); IR (KBr) 2960, 2930, 2860, 1665, 1608, 1472, 1460, 1442, 1248, 1126, 1085, 890, 835, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.72 (d, J = 1.0 Hz, 1H), 3.57 (m, 1H), 2.25 (dq, J = 11.7, 6.7 Hz, 1H), 2.07 (d, J = 1.1 Hz, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.06 (s, 3H), 0.88 (s, 9H), 0.76 (s, 3H), 0.01 (s, 3H), 0.00 (s, 3H); HRMS, m/e (M^+ - C_4H_9) calcd 373.2563, obsd 373.2569.

17β-Hydroxy-1,4α-dimethylandrost-1-en-3-one (22). A solution of the silyl ether **21** (18.10 g, 42 mmol) in tetrahydrofuran (150 ml) containing water (30 ml) and acetic acid (60 ml) was stirred for three days at 50-60 °C. The reaction mixture was concentrated in vacuo, diluted with methylene chloride (500 ml) and thoroughly washed with water. Residual acetic acid was removed from the organic phase by two washings with aqueous sodium carbonate solution. The organic phase was dried over anhydrous sodium sulfate. After filtration and concentration in vacuo the crude product was obtained as a white solid. Purification by chromatography (hexane/ethyl acetate, 1:1) gave **22** (11.60 g) in 87 % yield: mp 173-174 °C (acetone/cyclohexane); $[\alpha]_D^{22}$ +22.8° (c 0.52, $CHCl_3$); IR (KBr) 3460, 2970, 2950, 2900, 2868, 1648, 1596, 1450, 1370, 1320, 1123, 1072, 1055, 855 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, J = 1.2 Hz, 1H), 3.71 (m, 1H), 2.26 (dq, J = 11.8, 6.9 Hz, 1H), 2.08 (d, J = 1.3 Hz, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.07 (s, 3H), 0.81 (s, 3H).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.45; H, 10.04.

17β-Acetyloxy-1,4α-dimethylandrost-1-en-3-one (23). Under the exclusion of moisture, 17β-hydroxy-1,4α-dimethylandrost-1-en-3-one (**22**, 9.50 g, 30 mmol) was allowed to react in a mixture of pyridine (150 ml) and acetic anhydride (8 ml) containing a catalytic amount of dimethylaminopyridine (30 mg) at room temperature for 4 h. The reaction mixture was poured into ice water under stirring and the steroid was extracted into methylene chloride. The organic phase was washed with aqueous bicarbonate solution followed by brine and then dried over anhydrous sodium sulfate. Evaporation of the solvent at reduced pressure left the crude product as a white crystalline mass. Further purification by chromatography (hexane/ethyl acetate, 7:1) afforded the acetate **23** (10.22 g, 95 %): mp 120-122 °C (ethyl acetate/cyclohexane); $[\alpha]_D^{22}$ +17.4° (c 0.51, $CHCl_3$); IR (KBr) 2980, 2950, 2920, 2880, 2850, 1733, 1668, 1605, 1444, 1378, 1248, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.73 (d, J = 1.2 Hz, 1H), 4.63 (dd, J = 9.2, 7.6 Hz, 1H), 2.25 (dq, J = 11.7, 6.8 Hz, 1H), 2.07 (d, J = 1.3 Hz, 3H), 2.05 (s, 3H), 1.14 (d, J = 6.9 Hz, 3H), 1.07 (s, 3H), 0.85 (s, 3H).
Anal. Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.09; H, 9.59.

Representative Saponification Procedure. 17β-Hydroxy-1α,4-dimethylandrost-4-en-3-one (17). The acetate **16** (2.15 g, 6 mmol) was dissolved in methanolic potassium hydroxide solution (60 ml, 3 %) and kept at room temperature for 4 h under an atmosphere of argon. The saponification mixture was concentrated in vacuo, partioned between methylene chloride and water, the organic layer was washed with brine, and dried over anhydrous sodium sulfate. Filtration, concentration, and chromatography of the resultant residue (hexane/ethyl acetate, gradient elution, 3:2) furnished the product (1.75 g) as a white crystalline material in 92 % yield: mp 179-180 °C (acetone/hexane); $[\alpha]_D^{22}$ +131.3° (c 0.51, $CHCl_3$); IR (KBr) 3490, 2970, 2950, 2900, 2880, 2860, 2850, 1645, 1595, 1370, 1310, 1060, 1025, 993 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.66 (t, J = 8.2 Hz, 1H), 2.83-2.72 (m, 2H), 2.23 (dd, J = 16.2, 2.6 Hz, 1H), 1.76 (d, J = 1.5 Hz, 3H), 1.28 (s, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.81 (s, 3H).
Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.94; H, 10.17.

17β-Hydroxy-1,4-dimethylandrosta-1,4-dien-3-one (25). Saponification of the acetate **24** (1.07 g, 3 mmol) gave the crystalline alcohol **25** (868 mg, 92 %) after chromatography (hexane/ethyl acetate, gradient elution, 1:1): mp 217-218 °C (acetone/ethyl acetate); $[\alpha]_D^{22}$ -99.4° (c 0.52, $CHCl_3$); IR (KBr) 3500, 2970, 2910, 2855, 1653, 1613, 1596, 1445, 1385, 1140, 1076, 880, 874 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.21 (d, J = 1.1 Hz, 1H), 3.63-3.56 (m, 1H), 2.80 (ddd, J = 13.0, 4.6, 2.6 Hz, 1H), 2.39 (td, J = 13.4, 4.9 Hz, 1H), 2.10 (d, J = 1.2 Hz, 3H), 1.90 (s, 3H), 1.34 (s, 3H), 0.80 (s, 3H).
Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 80.18; H, 9.45.

17β-Hydroxy-1,2-dimethylandrosta-1,4-dien-3-one (30). Saponification of the acetate **29** (713 mg, 2 mmol) provided the alcohol **30** (590 mg, 94 %) after chromatography (methylene chloride/acetone, 9:1) as colorless crystals: mp 173-174 °C (ether/pentane); $[\alpha]_D^{22}$ -107.6° (c 0.50, $CHCl_3$); IR (KBr) 3450, 2948, 2870, 2850, 1657, 1610, 1461, 1443, 1385, 1082, 1070, 1050, 910, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.11 (s, 1H), 3.64-3.56 (m, 1H), 2.59 (td, J = 13.2, 5.6 Hz, 1H), 2.33 (ddd, J = 12.7, 5.1, 2.1 Hz, 1H), 2.02 (d, J = 1.0 Hz, 3H), 1.88 (d, J = 1.0 Hz, 3H), 1.34 (s, 3H), 0.81 (s, 3H); HRMS, m/e (M^+) calcd 314.2246, obsd 314.2250.

17β-Hydroxy-1,2-dimethyl-5α-androst-1-en-3-one (31). The alcohol **31** (590 mg, 93 %) was obtained on saponification of the acetate **28** (717 mg, 2 mmol) after chromatography (hexane/ethyl acetate, gradient elution, 1:1) as a colorless oil: $[\alpha]_D^{22}$ +51.8° (c 0.51, $CHCl_3$); IR (KBr) 3440, 2920, 2870, 2850, 1660, 1586, 1443, 1372, 1315, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.67 (t, J = 8.4 Hz, 1H), 2.35 (dd, J = 18.1, 13.2 Hz, 1H), 2.21 (dd, J = 18.1, 4.9 Hz, 1H), 2.00 (d, J = 1.0 Hz, 3H), 1.75 (d, J = 1.0 Hz, 3H), 1.02 (s, 3H), 0.81 (s, 3H); HRMS, m/e (M^+) calcd 316.2402, obsd 316.2383.

17β-Hydroxy-1,2,4-trimethylandrosta-1,4-dien-3-one (36). The acetate **35** (1.11 g, 3 mmol) furnished the product **36** (887 mg, 90 %) on saponification followed by chromatography (hexane/ethyl acetate, 1:1) in crystalline state: mp 248-250 °C (acetone/ethyl acetate); $[\alpha]_D^{22}$ -69.6° (c 0.51, $CHCl_3$); IR (KBr) 3475, 2960, 2933, 2880, 2845, 1645, 1614, 1412, 1385, 1124, 1070, 985 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.58 (t, J = 8.9 Hz, 1H), 2.80 (ddd, J = 13.1, 4.7, 2.6 Hz, 1H), 2.39 (td, J = 13.6, 5.0 Hz, 1H), 2.01 (d, J = 1.0 Hz, 3H), 1.93 (s, 3H), 1.90 (d, J = 1.0 Hz, 3H), 1.34 (s, 3H), 0.80 (s, 3H); HRMS, m/e (M^+) calcd 328.2402, obsd 328.2402.

17β-Hydroxy-1,2,4α-trimethyl-5α-androst-1-en-3-one (37). Saponification of the acetate **34** (745 mg, 2 mmol) afforded **37** (608 mg, 92 %) after chromatography (hexane/ethyl acetate, 3:2) as a white crystalline mass: mp 185-187 °C (cyclohexane); $[\alpha]_D^{22}$ +46.0° (c 0.50, $CHCl_3$); IR (KBr) 3508, 2960, 2925, 2875, 1646, 1595, 1450, 1377, 1315, 1125, 1065 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.71-3.63 (m, 1H), 2.20 (dq, J = 11.3, 7.0 Hz, 1H), 1.98 (d, J = 1.0 Hz, 1H), 1.75 (d, J = 1.0 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 0.80 (s, 3H).

Anal. Calcd for $C_{22}H_{34}O_2$: C, 79.95; H, 10.37. Found: C, 79.93; H, 10.29.

Representative Oxidation Procedure. 1α,4-Dimethylandrost-4-ene-3,17-dione (18). Chromium trioxide (6.67 g, 66.7 mmol) was dissolved in a mixture of water (60 ml) and concentrated sulfuric acid (6 ml) under ice cooling and stirring. The resulting solution was transferred to a volumetric flask and diluted with water to a total volume of 100 ml. Slightly more than one equivalent (4.2 ml) of this standard solution was added dropwise to a solution of

the alcohol **17** (1.27 g, 4 mmol) in acetone (30 ml) at room temperature with stirring. Excess oxidant was destroyed after 15 minutes by the addition of 1 ml of isopropanol. The oxidation mixture was concentrated in vacuo, diluted with 250 ml of ethyl acetate and the resulting organic solution was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The crude diketone **18** was obtained as a slightly yellow colored mass which was chromatographed using hexane/ethyl acetate (3:1) to give pure **18** (1.07 g) in 85 % yield as colorless crystals: mp 189-191 °C (cyclohexane); $[\alpha]_D^{22}$ +212.6° (c 0.51, $CHCl_3$); IR (KBr) 2970, 2940, 2920, 2880, 2860, 1735, 1660, 1600, 1455, 1378, 1310, 1260, 1210, 1108, 1057, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (ddd, J = 15.6, 4.0, 2.7 Hz, 1H), 2.76 (dd, J = 16.2, 5.0 Hz, 1H), 2.53-2.44 (m, 1H), 2.24 (dd, J = 16.2, 2.6 Hz, 1H), 1.78 (d, J = 1.5 Hz, 3H), 1.30 (s, 3H), 0.93 (s, 3H), 0.91 (d, J = 7.0 Hz, 3H).

Anal. Calcd for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 80.21; H, 9.46.

1,4-Dimethylandrosta-1,4-diene-3,17-dione (6). The alcohol **25** (630 mg, 2 mmol) underwent smooth oxidation to give the diketone **6** (520 mg, 83 %) as colorless crystalline material after chromatography (hexane/ethyl acetate, 1:1): mp 190-192 °C (acetone); $[\alpha]_D^{22}$ -9.0° (c 0.50, $CHCl_3$); IR (KBr) 2950, 2915, 2900, 2855, 2835, 1735, 1655, 1618, 1600, 1453, 1445, 1388, 1362, 1047, 1000, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.22 (d, J = 1.1 Hz, 1H), 2.86 (ddd, J = 13.1, 4.7, 2.6 Hz, 1H), 2.50-2.37 (m, 2H), 2.11 (d, J = 1.2 Hz, 3H), 1.92 (s, 3H), 1.36 (s, 3H), 0.93 (s, 3H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.75; H, 9.13.

1,4α-Dimethyl-5α-androst-1-ene-3,17-dione (26). Oxidation of the alcohol **22** (950 mg, 3 mmol) afforded the diketone **26** (793 mg, 84 %) after chromatography (hexane/ethyl acetate, 3:1) as colorless crystals: mp 119-121 °C (cyclohexane); $[\alpha]_D^{22}$ +111.9° (c 0.51, $CHCl_3$); IR (KBr) 2970, 2940, 2880, 2860, 1735, 1665, 1605, 1450, 1373, 1280, 1255, 1203, 1056, 1047, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (d, J = 1.2 Hz, 1H), 2.47 (dd, J = 19.2, 8.5 Hz, 1H), 2.27 (dq, J = 11.7, 6.9 Hz, 1H), 2.08 (d, J = 1.3 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.09 (s, 3H), 0.94 (s, 3H); HRMS, m/e (M^+) calcd 314.2246, obsd 314.2245.

1,2-Dimethylandrosta-1,4-diene-3,17-dione (7). On Jones oxidation of the alcohol **30** (630 mg, 2 mmol), the crystalline diketone **7** (506 mg, 81 %) was obtained following chromatographic purification (hexane/ethyl acetate, 1:1): mp 211-212 °C (acetone/hexane); $[\alpha]_D^{22}$ -25.1° (c 0.51, $CHCl_3$); IR (KBr) 2940, 2920, 2890, 2855, 1735, 1658, 1620, 1440, 1377, 1320, 1178, 1045, 886 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.14 (s, 1H), 2.64 (td, J = 13.1, 5.5 Hz, 1H), 2.51-2.36 (m, 2H), 2.03 (d, J = 1.0 Hz, 3H), 1.89 (d, J = 1.0 Hz, 3H), 1.36 (s, 3H), 0.93 (s, 3H).

Anal. Calcd for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.74; H, 9.24.

1,2-Dimethyl-5α-androst-1-ene-3,17-dione (32). The alcohol **31** (316 mg, 1 mmol) was oxidized to furnish the diketone **32** (270 mg, 86 %) after chromatographic purification (hexane/ethyl acetate, 3:1) as colorless crystalline material: mp 93-95 °C (cyclohexane); $[\alpha]_D^{22}$ +141.6° (c 0.50, $CHCl_3$); IR (KBr) 2972, 2930, 2875, 2860, 1742, 1665, 1655, 1600, 1380, 1315, 1077, 1048, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (dd, J = 19.2, 8.6 Hz, 1H), 2.37 (dd, J = 18.2, 13.1 Hz, 1H), 2.24 (dd, J = 18.2, 5.0 Hz, 1H), 2.01 (d, J = 1.0 Hz, 3H), 1.76 (d, J = 0.9 Hz, 3H), 1.04 (s, 3H), 0.93 (s, 3H); HRMS, m/e (M^+) calcd 314.2246, obsd 314.2247.

1,2,4-Trimethylandrosta-1,4-diene-3,17-dione (8). Jones oxidation of the alcohol **36** (330 mg, 1 mmol) provided the diketone **8** (268 mg, 82 %) as a crystalline solid following chromatography (hexane/ethyl acetate, 2:1): mp 183-185 °C (acetone/hexane); $[\alpha]_D^{22}$ +10.2° (c 0.50, $CHCl_3$); IR (KBr) 2920, 2850, 1738, 1646, 1612, 1460, 1370, 1125, 1048, 1035, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.86 (ddd, J = 13.2, 4.7, 2.5 Hz, 1H), 2.50-2.38 (m, 2H), 2.02 (d, J = 1.0 Hz, 3H), 1.94 (d, J = 0.7 Hz, 3H), 1.91 (d, J = 1.0 Hz, 3H), 1.36 (s, 3H), 0.93 (s, 3H); HRMS, m/e (M^+) calcd 326.2246, obsd 326.2228.

1,2,4α-Trimethyl-5α-androst-1-ene-3,17-dione (38). The alcohol **37** (330 mg, 1 mmol) was transformed to the diketone **38** by Jones oxidation. The product **38** (273 mg, 83 %) was purified by chromatography (hexane/ethyl acetate, gradient elution, 1:1), colorless crystals: mp 165-167 °C (cyclohexane); $[\alpha]_D^{22}$ +130.4° (c 0.50, $CHCl_3$); IR (KBr) 2968, 2930, 2860, 1740, 1660, 1600, 1440, 1373, 1310, 1050, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.47 (dd, J = 19.2, 8.6 Hz, 1H); 2.22 (dq, J = 11.2, 7.0 Hz, 1H), 1.98 (d, J = 1.0 Hz, 3H), 1.76 (d, J = 1.0 Hz, 3H), 1.11 (d, J = 7.0 Hz, 3H), 1.02 (s, 3H), 0.93 (s, 3H); HRMS, m/e (M^+) calcd 328.2402, obsd 328.2400.

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