70.2 (d), 70.9 (t), 60.9 (q), 60.3 (q), 59.2 (q), 55.3 (q).

12: ^{1}H NMR ($CDCl_3$) δ 4.89 (1 H, d, H-1), 4.30 (1 H, d, 8.5, H-1′), 3.62 (6 H, s, 2 OMe), 3.53 (1 H, dd, 3, 9, H-2), 3.54 (3 H, s, OMe), 3.51 (3 H, s, OMe), 3.41 (3 H, s, OMe), 3.38 (3 H, s, OMe), 3.34 (3 H, s, OMe), 3.12 (1 H, dd, 8.5, 8.5, H-2′); ^{13}C NMR ($CDCl_3$) δ 104.8 (d), 99.6 (d), 86.7 (d), 83.3 (d), 82.5 (d), 80.5 (d), 79.9 (d), 79.4 (d), 74.4 (d), 71.5 (t), 71.0 (t), 69.6 (d), 60.8 (q), 69.6 (q), 60.5 (q), 60.4 (q), 60.3 (q), 59.2 (q), 59.1 (q), 55.1 (q).

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Synthesis of 10β-Oxiranyl and 10β-Thiiranyl Steroids†

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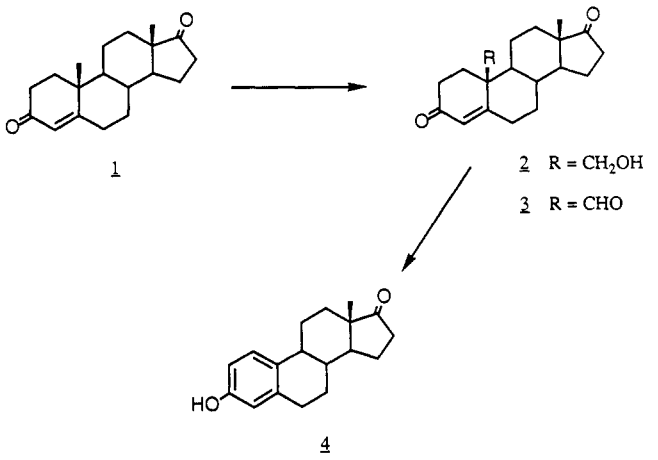
The 10β-oxiranylestr-4-ene-3,17-diones (**7a** and **7b**) have been prepared from 19-oxo intermediate **5** by ylide reactions. Compounds **7a** and **7b** were converted to the thiiranes **8b** and **8a**, respectively, with stereochemical inversion at C-19 by a modified triphenylphosphine sulfide (TPS) reaction using TPS–picric acid. Reaction of **7a** and **7b** with TPS–trifluoroacetic acid gave, respectively, (19*R*)- and (19*S*)-5,19-(thiomethylene)-19-(trifluoroacetoxy)-5β-androstane-3,17-dione (**9a** and **9b**) through internal trapping of a reaction intermediate. Hydrolysis of **9a** and **9b** gave, respectively, the corresponding 19-hydroxy heterocycles, **10a** and **10b**, which could also be obtained by reaction of oxiranes **7a** and **7b** with TPS–methanesulfonic acid. The reactions involving formation or hydrolysis of **9a**, **9b**, **10a**, and **10b** proceeded stereospecifically.

Human placental aromatase[1] is a cytochrome P-450 enzyme complex that is responsible for the conversion of androgens (**1**) to estrogens (**4**) (Scheme I). This biologically important process is of great mechanistic interest. Furthermore, inhibitors of this enzyme may be useful in the treatment of breast cancer.[2] As part of continuing studies on the mechanism and inhibition of this enzyme, we describe below the synthesis of the 10β-oxiranyl and 10β-thiiranylestr-4-ene-3,17-diones **7a**, **7b** and **8a**, **8b**, respectively. The oxiranes **7a**, **7b** were synthesized as analogues of intermediate **2** in the enzymatic reaction sequence, and their powerful inhibitory effects[3] on aromatase induced us to prepare the corresponding thiiranes **8a**, **8b**, which proved[4] to be even more potent inhibitors.

The two most obvious approaches to the desired epoxides **7a** and **7b** would involve either peracid epoxidation of a 10β-vinyl steroid or reaction of a 10β-formyl steroid with the sulfur-based ylides described[5] by Corey and Chaykovsky. Attempts to epoxidize selectively the 10β-vinyl group in the presence of a 5,6-olefin or a 4-ene-3-one grouping proved unsuccessful. Therefore we studied the reaction of the 10β-formyl steroid[6] (**5**) with dimethylsulfonium and dimethylsulfoxonium methylide (Scheme II). The 3- and 17-hydroxyl groupings were protected as tetrahydropyranyl ethers (THP) in order to avoid destruction of the basic ylides or methylation of the hydroxyl groups. Treatment of **5** with dimethylsulfonium methylide and dimethylsulfoxonium methylide in dimethyl sulfoxide/tetrahydrofuran gave comparable overall yields of total epoxidized products. The ratios of C-19 diastereomeric epoxides **6a** and **6b** resulting from each reagent were determined by high-pressure liquid chromatography (HPLC) analysis after removal of the THP protecting groups with pyridinium *p*-toluenesulfonate–methanol. Reaction with dimethylsulfonium methylide gave a **6a**:**6b** ratio of 9:1 while the corresponding ratio for dimethyl-

Scheme I



† Dedicated to Sir Derek Barton on the occasion of his 70th birthday.

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(6) Marcotte, P. A.; Robinson, C. H. *Steroids* **1982**, *39*, 325–344.

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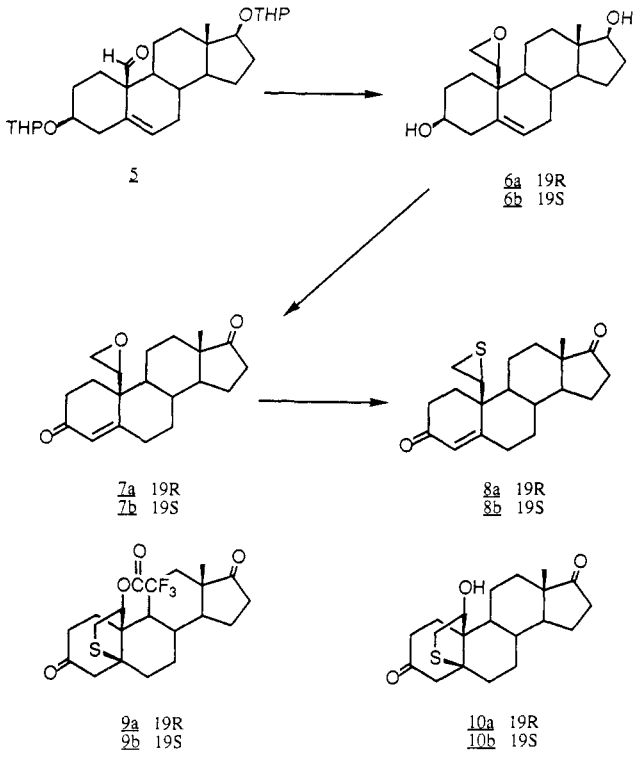
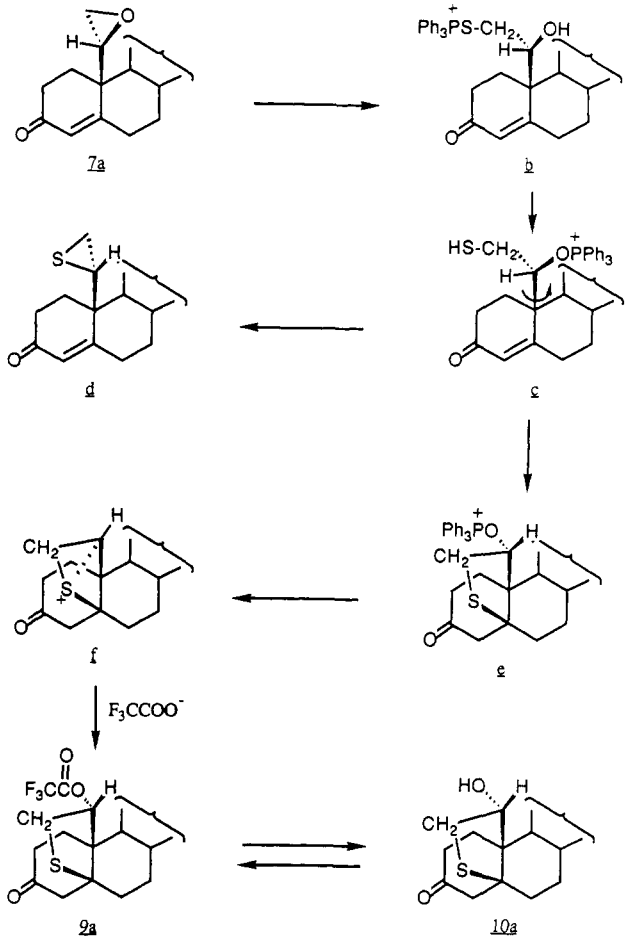
Scheme II



Scheme III



sulfoxonium methylide was 1:3. Reagent-dependent differences in stereochemical outcome have been described[7] for other steroids by use of these reagents, but the reasons for the stereoselectivity patterns in our case are not easy to discern. These ylide processes are characterized by reversible attack on the carbonyl group, and the resulting dipolar adduct then cyclizes to give epoxide with ejection of dimethyl sulfide or dimethyl sulfoxide. Consequently, the outcome of a given epoxidation depends on such factors as the relative stabilities of the charged intermediates and their relative rates of formation and decomposition.[8]

The diastereomers **6a** and **6b** were then separated by flash chromatography on silica gel and were converted separately to the corresponding 4-ene-3,17-diones **7a** and **7b** by Oppenauer oxidation. X-ray crystallographic analysis of each compound (reported previously[3]) established the C-19 stereochemistry as 19*R* for **7a** and 19*S* for **7b**.

Spectroscopic studies[9] with purified aromatase suggested that the epoxide oxygen of **7a** coordinates with the heme iron at the active site of the enzyme. Because sulfur is a better coordinating ligand for iron than is oxygen, we undertook the synthesis of the thiiranes **8a**, **8b** corresponding to **7a**, **7b**. The classical conversion of oxiranes to thiiranes, employing thiocyanate ion,[10] failed in the case of the 19-oxiranyl system, and treatment of the oxiranes with thiourea under acid catalysis[11] gave no reaction. Consequently we turned to the reaction of 3,3-dimethyl-1-(methylthio)oxazoline[12] with the 10β-formyl system. This also failed to yield the desired thiiranes.

We then explored the method of Chan and Finkenbine,[13] which involves the use of triphenylphosphine sulfide (TPS) and trifluoroacetic acid (TFA) to convert oxiranes to thiiranes. This reaction is postulated to involve nucleophilic attack by triphenylphosphine sulfide on the protonated epoxide followed by rearrangement to a triphenylphosphinoxy thiol intermediate. The latter then closes to give a thiirane, with expulsion of triphenylphosphine oxide (cf. Scheme III, **a**–**d**). Treatment of (19*R*)-oxirane **7a** with these reagents gave no thiirane, but instead gave a single sulfur-containing product. This product showed no high-intensity UV absorption, while the infrared spectrum showed, in addition to the C-17 carbonyl, a new saturated carbonyl absorption as well as an absorption at 1785 cm^{-1} attributable to a trifluoroacetate grouping. This latter assignment was further supported by the ^{19}F NMR spectrum, which showed a singlet at −75.8 ppm (from Freon 11). The mass spectrum and high-field proton NMR (including spin-decoupling studies) were consistent with the formulation of this product as **9a**. Compound **9a** presumably results from trapping of a thiol intermediate by internal Michael-type addition to the conjugated 4-ene-3-one system (Scheme III). The possibility that **9a** might arise from decomposition of the thiirane system was excluded because authentic thiirane (vide infra) was shown to be stable.

An isomeric but chromatographically different adduct **9b** was obtained when the (19*S*)-oxirane **7b** was treated with TPS/TFA. The NMR spectrum of **9b** was very similar to that of **9a**. The proton NMR spectra of **9a** and **9b**

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showed, respectively, resonances at 6.05 and 6.02 ppm assigned to the methine hydrogen at C-19 in each case. These signals were shifted, respectively, to 5.03 and 5.04 ppm in the hydrolysis products **10a** and **10b** (vide infra). The structure assignments made tentatively on spectroscopic grounds were established firmly by X-ray crystallographic analysis of **10a**.[14] Analogy for the formation of such propellane-like adducts can be found in the intramolecular Michael-type addition of a 19-hydroperoxy group[15] or a 10β-(2-hydroxyethyl) group[16] to the steroidal 4-ene-3-one system.

Chan and Finkenbine had demonstrated the need for strong acid catalysis in the TPS/TFA reaction, and so we explored alternatives to trifluoroacetic acid. The use of acidic Nafion resin proved ineffective, while mineral acid catalysis resulted in polar products that presumably result from epoxide ring opening. We therefore tried TPS–methanesulfonic acid, which gave no thiirane with the (19*S*)-oxirane **7b** but instead furnished a new sulfur-containing adduct. The same reagents converted the (19*R*)-oxirane **7a** to an isomeric but chromatographically distinguishable adduct, along with the desired thiirane **8b**. These adducts, derived respectively from oxiranes **7a** and **7b**, are formulated as the 19-hydroxy adducts **10a**, **10b** on the basis of their spectra and their formation from the trifluoroacetates **9a**, **9b** by hydrolysis with sodium methoxide in tetrahydrofuran as mentioned above.

The isolation of the 19-ols **10a**, **10b** from the methanesulfonic acid catalyzed process is attributed to lability of the expected 19-methanesulfonates corresponding to the trifluoroacetates **9a**, **9b**. Our belief that the postulated methanesulfonates were hydrolyzed during workup is supported by studies with the trifluoroacetates **9a**, **9b**. Thus, the 19-trifluoroacetate group in **9a**, for example, was lost during prolonged chromatography on Florisil, or simply on stirring in methylene chloride with Florisil. The quantitatively formed 19-ol **10a** was identical with the product obtained by hydrolysis of **9a** with sodium methoxide in tetrahydrofuran and could be reconverted to **9a** in quantitative yield by using trifluoroacetic anhydride in methylene chloride. These experiments confirm that the stereochemistry at C-19 remains intact during hydrolysis of **9a** or acylation of **10a**. The constitution and stereochemistry of **10a** (and consequently of **9a**, **9b**, and **10b**) were established by X-ray crystallography.[14]

The stereochemical aspects of the formation of these heterocyclic adducts from oxiranes **7a** and **7b** are of interest. In each case, the 19-oxirane yields only one adduct, and the stereochemistry of the C-19 carbon–oxygen bond is the same as that of the C-19 carbon–oxygen bond in the precursor epoxide. Since the postulated reaction intermediate (**c**, Scheme III) would have a triphenylphosphinoxy group attached to C-19 with the same C-19 carbon–oxygen configuration as the starting oxirane, then the trifluoroacetate group in products **9a** and **9b** must in each case have replaced the triphenylphosphinoxy group with retention of configuration (Scheme III). The thiiranes, as noted earlier, are stable to the reaction conditions, thus excluding opening of the thiirane ring by trifluoroacetate.

A plausible explanation for these results is that expulsion of the triphenylphosphinoxy grouping in **e** (Scheme III) involves participation by sulfur with inversion at C-19, followed by opening of the resulting episulfonium intermediate **f**, also with inversion,[17a] upon attack by trifluoroacetate. The overall outcome would then be retention of configuration at C-19.[17b] Similar arguments can be made for the (19*S*)-oxirane derived sequence.

We therefore sought a strong but sterically bulky acid that would be unlikely to be incorporated at the hindered 19-position of the steroid. Picric acid met these requirements, and, when oxirane **7a** was treated with TPS–picric acid in refluxing benzene, smooth conversion to the desired thiirane **8b** resulted in 75% yield. Analogously, oxirane **7b** generated thiirane **8a** in 65% yield with the same reagents. The conversion is stereospecific, as each oxirane gave only one thiirane based on HPLC analysis. Each of the thiiranes was smoothly desulfurized to the known[6] 10β-vinylestr-4-ene-3,17-dione by treatment with triphenylphosphine in refluxing toluene.

An X-ray crystallographic study of thiirane **8b** established[14] the *S* configuration at C-19 and therefore also established **8a** as 19*R*. Thus each epoxide gave thiirane with clean inversion at C-19. This observation is consistent with the mechanism originally proposed[13] by Chan and Finkenbine and with reactions described[18] in studies with carbohydrates in which configurations were established by ^{13}C NMR spectroscopy.

In summary, we have synthesized and established the stereochemistry of novel 10β-oxiranyl and 10β-thiiranyl steroids. Attempts to prepare the thiiranes by the TPS/TFA reaction of Chan and Finkenbine led to unusual adducts formed by internal trapping of a reaction intermediate. This problem was circumvented by the use of TPS–picric acid, which converted the 10β-oxiranes **7a**, **7b** stereospecifically with inversion at C-19 to the 10β-thiiranes **8b**, **8a**. The 19*R* isomers **7a** and **8a** have proved of considerable interest as inhibitors of human placental aromatase.

Experimental Section

General Methods. Melting points were determined on a Kofler micro hot stage and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 462 or 710B spectrometers, in $CHCl_3$ solution or KBr disks. Ultraviolet spectra were obtained in methanol on a Perkin-Elmer Lambda 3 instrument. Proton NMR spectra were recorded in $CDCl_3$ with IBM-80 MHz, Bruker-300 MHz, or Varian XL-400 MHz spectrometers. Fluorine NMR spectra were obtained at 75.4 MHz on an IBM-80 instrument in $CDCl_3$ solutions. Mass spectra were obtained at 70 eV on LKB 9000 or VG70S spectrometers. HPLC separations were performed on a Waters Associates Model 6000 instrument using a Whatman Magnum 10 Partisil semipreparative column. Column chromatography was performed on silica gel (Baker) according to Still's method[19] or on Florisil (Fisher Scientific). Elemental analyses were determined by Galbraith Laboratories, Inc., Knoxville, TN, and by Spang Microanalytical Laboratory, Eagle Harbor, MI.

10β-Oxiranylestr-4-ene-3,17-diones (7a, 7b) from 19-Oxoandrost-5-ene-3β,17β-diol Bis(tetrahydropyranyl ether) (5). (a) Action of Dimethylsulfoxonium Methylide on 19-Oxo Compound 5. In a 500-mL three-necked round-bottom flask equipped with a nitrogen inlet was placed 2.44 g (50 mmol) of

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(15) Cole, P. A.; Robinson, C. H. *J. Chem. Soc., Chem. Commun.* **1986**, 1651–1653.
(16) Beusen, D. H.; Carrell, H. L.; Covey, D. F. *Biochemistry* **1987**, *26*, 7833–7841.
(17) (a) Cf. Peterson, L. A.; Harris, T. M.; Guengerich, F. P. *J. Am. Chem. Soc.* **1988**, *110*, 3284–3291. (b) One of the referees suggested an alternative pathway. This process invokes the attack of trifluoroacetate or methanesulfonate on the phosphorus atom of systems **c** or **e** (Scheme III), with loss of the PPh_3 group and protonation of the resulting 19-alkoxide to give the corresponding 19-alcohol with retention of configuration at C-19. This sequence could generate the product **10a** or, as a result of trifluoroacetylation in situ, the product **9a**. We thank the referee for this suggestion.
(18) Adlgasser, K.; Hönig, H.; Zenk, R. *Justus Liebigs Ann. Chem.* **1987**, 283–288.
(19) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

50% oil-dispersed sodium hydride. This dispersion was washed with two portions of dry THF (60 mL), and the solvent was pipetted out under a stream of nitrogen gas. A mixture of 11 g (50 mmol) of trimethylsulfoxonium iodide and dry THF (60 mL) was then charged into the flask, and the reaction mixture was heated to reflux and stirred for 2 h. The reaction temperature was then held at 55–60 °C and a solution of 19-oxoandrost-5-ene-3β,17β-diol bis(tetrahydropyranyl ether)[6] (**5**, 2.36 g, 5 mmol) in dry THF (60 mL) was added dropwise. The reaction mixture was stirred at 55–60 °C for 24 h and then at room temperature for 48 h, when TLC (silica gel) indicated completion of the reaction. The reaction mixture was evaporated in vacuo, and the residue was dissolved in $CHCl_3$ and washed successively with 10% aqueous $NaHCO_3$ and brine. The combined organic layers were dried (K_2CO_3) and concentrated to a yellow-brown residue, which was then subjected to the following hydrolysis process to remove the THP groups.

The above crude product was dissolved in MeOH (60 mL), pyridinium tosylate (590 mg) was added, and the mixture was stirred overnight at room temperature under nitrogen. When TLC (silica gel, 1:2 acetone–$CHCl_3$) indicated completion, the reaction mixture was evaporated in vacuo. The residue was dissolved in $CHCl_3$ and washed successively with 10% aqueous $NaHCO_3$ and brine. The organic layers were combined, dried (K_2CO_3), and concentrated to give a yellow oil (3.0 g). This oil was then purified by flash chromatography (silica gel, 1:2 acetone–ethylene dichloride). The major component was a white solid (1.49 g, 4.69 mmol, 94%), which contained two diastereomeric epoxides as indicated by the ^1H NMR (300 MHz) spectrum and TLC (4:1 ethyl acetate–hexane; plate run three times) as well as HPLC (ethyl acetate, silica gel). Crystallization from methylene chloride–hexane gave pure (19*S*)-10β-oxiranylestr-5-ene-3β,17β-diol (**6b**, 720 mg, 2.26 mmol, 45%), mp 170–173 °C: IR ($CHCl_3$) 3585, 2935 cm^{-1}; ^1H NMR (300 MHz) δ 5.59 (m, 1, vinyl H), 3.62 (m, 1, 17α-H), 3.51 (m, 1, 3α-H), 2.91 (m, 1, epoxide CH), 2.75 (m, 1, epoxide CH), 2.57 (m, 1, epoxide CH), 0.85 (s, 3, 18-CH_3), MS (M^+), *m/z* 318, 300, 282. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.63; H, 9.54.

The above oxiranyl diol (**6b**, 710 mg, 2.23 mmol) was dissolved in a mixture of cyclohexanone (15 mL) and toluene (125 mL) in a three-necked round-bottom flask fitted with reflux condenser and Dean–Stark trap. The stirred mixture was heated under reflux until about 12 mL of toluene was collected via the Dean–Stark trap and was then cooled to room temperature. Dry aluminum isopropoxide (1.62 g, 8.1 mmol) was added, and the stirred reaction mixture was heated under reflux for 3.5 h and was then cooled, diluted with ethyl acetate, and washed successively with 5% aqueous $NHCO_3$ and brine. The organic phase was evaporated in vacuo and chromatographed on silica gel (acetone–ethylene dichloride, 3:47). The resulting solid (406 mg, 1.29 mmol, 58%) was recrystallized from methylene chloride–hexane to give (19*S*)-10β-oxiranylestr-4-ene-3,17-dione (**7b**), mp 202–203 °C: IR ($CHCl_3$) 1732, 1665, 1620 cm^{-1}; λ_{max} (MeOH) 242 nm (ε 12 600); ^1H NMR (400 MHz) δ 5.90 (s, 1, vinyl H), 3.26 (dd, *J* = 2.8, 4.0 Hz, 1, epoxide CH), 2.74 (dd, *J* = 4.0, 5.0 Hz, 1, epoxide CH), 2.53 (dd, *J* = 2.8, 5.0 Hz, 1, epoxide CH), 0.96 (s, 3, 18-CH_3); MS (M^+) *m/z* 314, 296, 270. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.17; H, 8.35.

Although (19*R*)-10β-oxiranylestr-4-ene-3,17-dione (**7a**) could also be obtained in moderate yield by HPLC separation (ethyl acetate, silica gel) after Oppenauer oxidation of the crude mixture of epoxy diols (**6a** and **6b**) obtained in the ylide reaction described above, it was more convenient to obtain the 19*R* series of oxiranes by the following procedure:

(b) Action of Dimethylsulfonium Methylide on 19-Oxo Compound 5. In a 250-mL three-necked round-bottom flask fitted with a nitrogen inlet was placed 0.96 g (20 mmol) of 50% oil-dispersed sodium hydride. The dispersion was washed twice with dry THF (20 mL portions), which was removed by syringe under nitrogen. Dry dimethyl sulfoxide (15 mL) was added, and the mixture was heated at 70–75 °C under nitrogen with stirring for 30 min. The solution was cooled to 25 °C, dry THF (15 mL) was added, and the mixture was cooled to −5 °C with an ice–ammonium chloride bath. A solution of trimethylsulfonium iodide (4.1 g, 26 mmol) in dry dimethyl sulfoxide (17.5 mL) was added dropwise with stirring at such a rate as to maintain the reaction mixture temperature between 0 and 5 °C. When the addition was complete, stirring was continued for 3 min, and a solution of 19-oxoandrost-5-ene-3β,17β-diol bis(tetrahydropyranyl ether) (**5**, 2.11 g, 4.5 mmol) in dry THF (82.5 mL) was added dropwise. The resulting mixture was then stirred at 0–5 °C under nitrogen for 1 h, followed by 19 h of stirring under nitrogen at 25 °C. The reaction mixture was concentrated in vacuo, and methylene chloride was added, followed by washing with 5% aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in methanol (55 mL) containing pyridinium *p*-toluenesulfonate (550 mg) for 3.5 h at 25 °C to remove the THP protecting groups. The mixture was evaporated in vacuo, and the residue was taken up in methylene chloride, washed with 5% aqueous $NaHCO_3$ and brine, dried (Na_2SO_4), and evaporated in vacuo. The resulting oil was purified by flash chromatography on silica gel (hexane–ethyl acetate, 1:4) and HPLC (silica gel, ethyl acetate) giving, after crystallization from methylene chloride–hexane, pure (19*R*)-10β-oxiranylestr-5-ene-3β,17β-diol (**6a**, 477 mg, 1.5 mmol, 30%), mp 177–180 °C: IR ($CHCl_3$) 3600, 2940 cm^{-1}; ^1H NMR (300 MHz) δ 5.55 (m, 1, vinyl H), 3.64 (m, 1, 17α-H), 3.50 (m, 1, 3α-H), 3.02 (m, 1, epoxide CH), 2.66 (m, 1, epoxide CH), 2.57 (m, 1, epoxide CH), 0.76 (s, 3, 18-CH_3); MS (M^+), *m/z* 318, 320, 282. Anal. Calcd for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.51; H, 9.35.

A portion of the above oxiranyl diol (**6a**, 315 mg, 1 mmol) was subjected to Oppenauer oxidation exactly as for the oxidation of **6b**, with toluene (40 mL), cyclohexanone (7.6 mL), and aluminum isopropoxide (800 mg, 4 mmol) for 3.5 h. The crude product was purified by flash chromatography (silica gel, ethyl acetate–ethylene dichloride, 1:4) and HPLC (silica gel, ethyl acetate) to give (19*R*)-10β-oxiranylestr-4-ene-3,17-dione (**7a**, 170 mg, 0.54 mmol, 54%), mp 211–214 °C: IR ($CHCl_3$) 1735, 1665, 1620 cm^{-1}; λ_{max} (MeOH) 239 nm (ε 12 400); ^1H NMR (400 MHz) δ 5.85 (s, 1, vinyl H), 3.28 (dd, *J* = 3.1, 4.1 Hz, 1, epoxide CH), 2.74 (dd, *J* = 4.6, 4.1 Hz, 1, epoxide CH), 2.57 (dd, *J* = 3.1, 4.6 Hz, 1, epoxide CH), 0.93 (s, 3, 18-CH_3); MS (M^+), *m/z* 314 and 296. Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.38; H, 8.46.

Estimation of 19*R*:19*S* Ratios Produced during the Formation of the 10β-Oxiranylestr-5-ene-3β,17β-diols. The reactions of 19-oxoandrost-5-ene-3β,17β-diol bis(tetrahydropyranyl ether) **5** with either dimethylsulfoxonium methylide or dimethylsulfonium methylide were carried out as described above, and the total crude reaction product was hydrolyzed to give the 19-oxiranyl 3β,17β-diol mixture. The amounts of 19*R* and 19*S* isomers (**6a**, **6b**) in each mixture were determined by HPLC (silica gel, ethyl acetate), by using standard curves obtained by HPLC analysis of the pure individual (19*R*)- and (19*S*)-oxiranes.

(19*R*)-10β-Thiiranylestr-4-ene-3,17-dione (8a). Into a three-necked 100-mL round-bottom flask equipped with nitrogen inlet was placed a solution of (19*S*)-10β-oxiranylestr-4-ene-3,17-dione (**7b**, 80 mg, 0.25 mmol) and triphenylphosphine sulfide (1.50 g, 5 mmol) in anhydrous benzene (30 mL, distilled from CaH_2 and stored over 4-Å molecular sieves under nitrogen). To this stirred solution, under nitrogen, was added dry recrystallized picric acid (1.168 g, 5 mmol), and the mixture was heated under reflux in a nitrogen atmosphere for 18 h. The reaction mixture was cooled, diluted with ether (40 mL), and washed four times with 10% aqueous $NaHCO_3$ (100 mL) to remove picric acid. The organic phase was then dried (Na_2SO_4) and evaporated in vacuo, and the yellow residue was chromatographed on Florisil (15 g) and eluted with methylene chloride (50 mL) to remove triphenylphosphine sulfide. Elution with ethyl acetate (100 mL) then gave steroidal products, and the desired thiirane (**8a**) was obtained by HPLC on silica gel with ethyl acetate–hexane (2:1). The pure (19*R*)-thiirane (**8a**, 50 mg, 0.15 mmol, 61%) had mp 162–163 °C (methylene chloride–hexane): IR (KBr) 1740, 1670, 1620 cm^{-1}; λ_{max} (MeOH) 234 nm (ε 11 500); ^1H NMR (400 MHz) δ 5.81 (s, 1 vinyl H), 3.27 (t, *J* = 6.4 Hz, 1, thiirane CH), 2.52 (m, 1, thiirane CH), 2.44 (dd, *J* = 6.4, 2.0 Hz, 1, thiirane CH), 0.96 (s, 3, 18-CH_3); MS (M^+), *m/z* 330. Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.68; H, 7.93; S, 9.70. Found: C, 72.89; H, 8.06; S, 9.79.

(19*S*)-10β-Thiiranylestr-4-ene-3,17-dione (8b). Into a three-necked 100-mL round-bottom flask equipped with nitrogen inlet was placed a solution of (19*R*)-10β-oxiranylestr-4-ene-3,17-dione (**7a**, 50 mg, 0.16 mmol) and triphenylphosphine sulfide (940 mg, 3.2 mmol) in anhydrous benzene (50 mL, distilled from CaH_2

and stored over 4-Å molecular sieves under nitrogen). To this stirred solution under nitrogen was added dry recrystallized picric acid (730 mg, 3.2 mmol), and the mixture was heated under reflux in a nitrogen atmosphere for 18 h. Workup and chromatography as described above for the preparation of compound **8a** gave pure (19*S*)-thiirane (**8b**, 37 mg, 0.11 mmol, 70%) as needles, mp 155–156 °C (methylene chloride-hexane): IR (KBr) 1740, 1665, 1615 cm^{-1}; λ_{max} (MeOH) 232 nm (ϵ 12 500); ^1H NMR (400 MHz) δ 5.89 (s, 1, vinyl H), 3.22 (t, J = 6.8 Hz, 1, thiirane CH), 2.77 (m, 1, thiirane CH), 2.56 (dd, J = 6.8, 2.0 Hz, 1, thiirane CH), 0.98 (s, 3, 18-CH_3); MS (M^+), m/z 330. Anal. Calcd for $C_{20}H_{26}O_2S$: C, 72.68; H, 7.93; S, 9.70. Found: C, 72.67; H, 7.89; S, 9.99.

Desulfurization of the (19*R*)- and (19*S*)-10β-Thiiranylestr-4-ene-3,17-diones (8a and 8b). (a) A solution of the (19*R*)-thiiranyl compound (**8a**, 10 mg) and triphenylphosphine (14.6 mg) in toluene (5.0 mL) was heated under reflux for 6 h. The solution was evaporated in vacuo, and the residue was chromatographed on silica (0.2 g). Elution with hexane–ethyl acetate (1:1) gave 10β-vinylestr-4-ene-3,17-dione, identified by melting point, IR, UV, ^1H NMR, and TLC comparison with authentic material.

(b) A solution of the (19*S*)-thiirane (**8b**, 10 mg) in toluene (5.0 mL) containing triphenylphosphine (14.6 mg) was heated under reflux for 12 h. Workup and purification as for (a) above gave 10β-vinylestr-4-ene-3,17-dione, identical in all respects with authentic material.

(19*S*)-5,19-(Thiomethylene)-19-(trifluoroacetoxy)-5β-androstane-3,17-dione (9b). To a stirred solution of the (19*S*)-oxirane (**7b**, 40 mg, 0.13 mmol) in dry benzene (15 mL) at 25 °C under nitrogen were added triphenylphosphine sulfide (376 mg, 1.3 mmol) and trifluoroacetic acid (0.13 mL, 1.3 mmol). The mixture was stirred at 25 °C for 18 h and was then concentrated in vacuo to about 2 mL and applied to a Florisil column (12 × 1 cm). Elution with methylene chloride removed triphenylphosphine sulfide, and the column was then eluted with ethyl acetate, which removed steroidal material. The latter was chromatographed on silica gel (ethyl acetate–hexane, 1:1) to give product, which was crystallized from methylene chloride–hexane, yielding **9b** (39 mg, 0.09 mmol, 68%), mp 121–122 °C: IR ($CHCl_3$) 1785, 1740, 1720, 1220 cm^{-1}; ^1H NMR (400 MHz) δ 6.02 (dd, J = 6.8, 8.8 Hz, 1, C-19H), 3.55 (dd, J = 8.8, 11.9 Hz, 1, S-CH_2), 2.85 (d, J = 16.6 Hz, 1, C-4H), 2.78 (dd, J = 8.8, 11.9 Hz, 1, S-CH_2), 2.26 (d, J = 16.6 Hz, 1, C-4H), 0.83 (s, 3, C-18); ^{19}F NMR (75.4 MHz) δ −77.1 (from Freon 11); high-resolution mass spectrum (HRMS) calcd 444.1582 ($C_{22}H_{27}O_4SF_3$), found 444.1600.

(19*S*)-5,19-(Thiomethylene)-19-hydroxy-5β-androstane-3,17-dione (10b). A stirred solution of the (19*S*)-oxirane (**7b**, 50 mg, 0.16 mmol), triphenylphosphine sulfide (470 mg, 1.6 mmol), and methanesulfonic acid (0.11 mL, 1.6 mmol) in dry benzene (15 mL) was stirred at 25 °C under nitrogen for 18 h. The reaction mixture was then concentrated, in vacuo, to 2 mL and applied to a Florisil column (12 × 1 cm). Elution with methylene chloride removed triphenylphosphine sulfide, and the column was then eluted with ethyl acetate to remove steroidal material. The latter was chromatographed on silica gel (ethyl acetate–hexane, 2:1) to give product (**10b**, 33 mg, 0.10 mmol, 59%), mp 168–169 °C: IR ($CHCl_3$) 3320, 1735, 1715 cm^{-1}; ^1H NMR (400 MHz) δ 5.04 (dd, J = 7.3, 8.4 Hz, 1, C-19H), 3.28 (dd, J = 8.4, 11.3 Hz, 1, S-CH_2), 2.80 (d, J = 15.8 Hz, 1, C-4H), 2.68 (dd, J = 7.3, 11.3 Hz, 1, S-CH_2), 2.13 (d, J = 15.8 Hz, 1, C-4H), 0.93 (s, 3, 18-CH_3); HRMS calcd 348.1759 ($C_{20}H_{28}O_3S$), found 348.1754.

(19*R*)-5,19-(Thiomethylene)-19-(trifluoroacetoxy)-5β-androstane-3,17-dione (9a). A solution of (19*R*)-oxirane (**7a**, 40 mg, 0.13 mmol), triphenylphosphine sulfide (376 mg, 1.3 mmol), and trifluoroacetic acid (0.13 mL, 1.3 mmol) in dry benzene (15 mL) was stirred at 25 °C under nitrogen for 18 h. The mixture was worked up as described above for the preparation of compound **9b**, and the product was purified by HPLC (ethyl acetate–hexane, 1:1) to give pure **9a** (44 mg, 0.10 mmol, 76%), mp 126–127 °C (from methylene chloride–hexane): IR ($CHCl_3$) 1780, 1735, 1715, 1220 cm^{-1}; ^1H NMR (400 MHz) δ 6.05 (dd, J = 6.8, 9.2 Hz, 1, C-19H), 3.62 (dd, J = 9.2, 12.4 Hz, 1, S-CH_2), 2.90 (d, J = 16 Hz, 1, C-4H), 2.79 (dd, J = 6.8, 12.4 Hz, 1, S-CH_2), 2.25 d, J = 16 Hz, 1, C-4H), 0.86 (s, 3, 18-CH_3); ^{19}F NMR (75.4 MHz) δ −75.8 ppm (from Freon 11); HRMS calcd 444.1582 ($C_{22}H_{27}O_4SF_3$), found 444.1614.

(19*R*)-5,19-(Thiomethylene)-19-hydroxy-5β-androstane-3,17-dione (10a). (a) Sodium methoxide (13.6 mg, 0.25 mmol) was added to a stirred solution of the foregoing trifluoroacetate derivative (**9a**, 22 mg, 0.05 mmol) in dry tetrahydrofuran (10 mL) at 0 °C. The reaction mixture was allowed to warm to 25 °C and was stirred for 1 h further and poured into saturated aqueous NH_4Cl solution. The aqueous mixture was extracted with ethyl acetate, and the organic extract was washed with water, dried (Na_2SO_4), and evaporated in vacuo to give an oily product. This material was chromatographed on silica (ethyl acetate–hexane, 1:1), and the resulting solid was crystallized from methylene chloride–hexane to give product (**10a**, 15 mg, 0.04 mmol, 86%), mp 171–172 °C: IR ($CHCl_3$) 3330, 1735, 1710 cm^{-1}; ^1H NMR (400 MHz) δ 5.03 (dd, J = 7.2, 9.6 Hz, 1, C-19H), 3.35 (dd, J = 9.6, 11.2 Hz, 1, S-CH_2), 2.86 (d, J = 16.4 Hz, 1, C-4H), 2.68 (dd, J = 7.2, 11.2 Hz, 1, S-CH_2), 2.10 (d, J = 16.4 Hz, 1, C-4H), 0.92 (s, 3, 18-CH_3); HRMS calcd 348.1759 ($C_{20}H_{28}O_3S$), found 348.1751.

(b) To a stirred suspension of Florisil (50 mg) in methylene chloride (1 mL) was added the trifluoroacetate (**9a**, 1.5 mg), and stirring was continued for 18 h at 25 °C. The suspension was filtered, and the residue was washed with ethyl acetate. The combined filtrate and washings were evaporated in vacuo, and the residue was shown to be identical with authentic **10a** by TLC, MS, and high-field NMR comparisons.

(c) A solution of (19*R*)-oxirane (**7a**, 30 mg, 0.10 mmol), triphenylphosphine sulfide (282 mg, 1.0 mmol), and methanesulfonic acid (0.068 mL, 1.0 mmol) in dry benzene (5 mL) was stirred under nitrogen at 25 °C for 18 h. The reaction mixture was poured into water, washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by HPLC (ethyl acetate–hexane, 1:1) to give pure (19*S*)-thiirane (**8b**, 19 mg, 0.06 mmol, 58%), identified by chromatographic and spectroscopic comparison with an authentic sample. Also isolated was compound **10a** (5 mg, 0.01 mmol, 14%), described in part (a) above, identified by chromatographic and spectroscopic comparison with authentic material. Samples of the above 19-ol (**10a**) derived from the methoxide hydrolysis or from the TPS–methanesulfonic acid reaction were converted quantitatively to the (19*R*)-trifluoroacetoxy compound (**9a**) using trifluoroacetic anhydride (10 equiv) in methylene chloride at 25 °C for 16 h.

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