Registry No.—1, 23726-93-4; **3a**, 10063-97-5; **4**, 69795-74-0; **5a**, 69795-75-1; **5b**, 69795-76-2; **6b**, 69795-77-3; **7**, 15874-80-3; **8**, 19041-17-9; allyllithium, 3052-45-7; allyl phenyl ether, 1746-13-0.

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Solvolytic Rearrangement Route to *D*-Homosteroids

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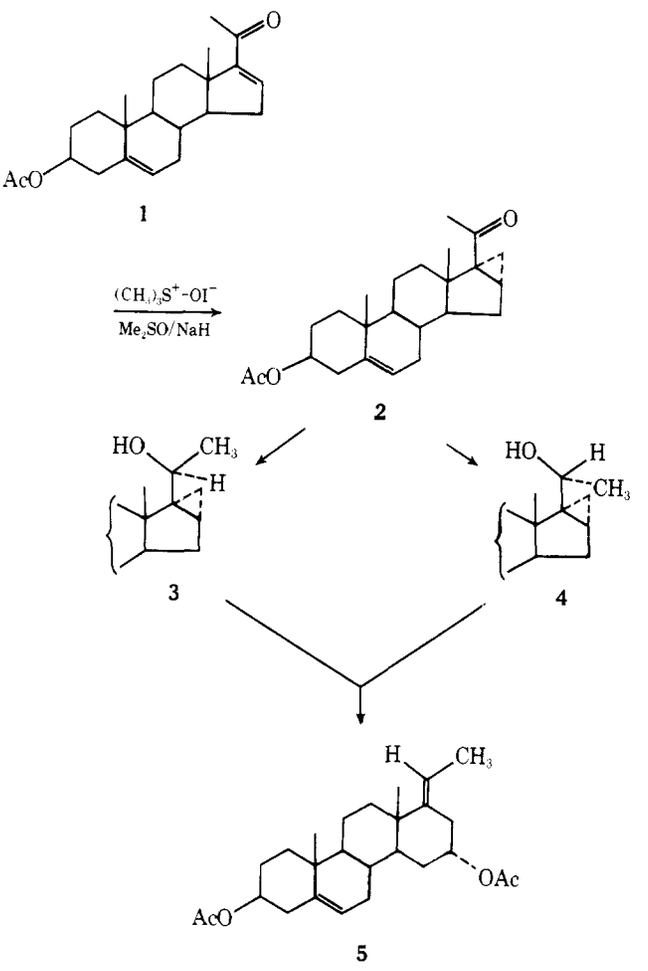
In connection with previous studies aimed at modifying the ring system of steroids,[2,3] we have carried out an acid-promoted ring expansion on the *D* ring of 16α,17α-cyclopropano steroids **3** and **4.** This rearrangement has been previously observed in the simple 1-bicyclo[3.1.0]hexylethan-1-ol systems.[4]

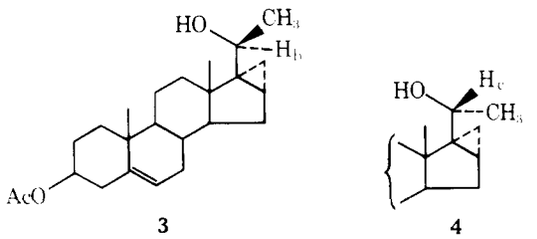
Scheme I



The synthesis of key intermediates **3** and **4** was accomplished by reaction of dimethylsulfoxonium methylide with **1** to form the cyclopropyl ketone **2** which was then reduced to a mixture of epimeric alcohols with sodium borohydride (Scheme I).

The stereochemistry of the introduced methylene group in **2** was assumed to be that which would result from the preferred α attack of the ylide on the least hindered side of the molecule. The orientation of addition to steroid cyclohexenones and cyclopentenones with dimethylsulfoxonium methylide generally corresponds to that of the Michael reaction and of the conjugate addition of organometallic reagents.[5-7]

Unambiguous evidence of the presence of a cyclopropyl methylene group in **2** was obtained from spectroscopic data. The chemical ionization mass spectrum (methane as carrier gas) shows *m/e* 371 $(M + H)^+$. The NMR spectrum clearly shows the cyclopropyl protons at δ 0.76–0.80 as well as the loss of the Δ^{16}-hydrogen. The IR spectrum exhibits a higher frequency absorption at 1677 cm^{-1} for the C-20 carbonyl as compared to that observed in the spectrum of the unsaturated ketone **1** (1663 cm^{-1}). The reduction of **2** afforded, after chromatographic separation, the two diastereoisomers **3** and **4** in a ratio of 1:1. The two isomers were readily distinguished



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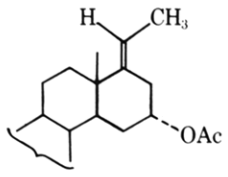
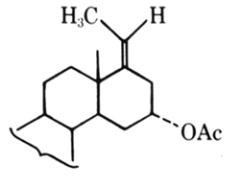
by differences in the chemical shift of the C-20 methine protons at δ 4.25 (q) and 4.37 (q). Because of the unique environment of these hydroxyl groups, the stereochemistry of the newly created asymmetric center could not be unambiguously assigned by analogy with reported methods of determining stereochemistry at the C-20 position.[8]

Treatment of either **3** or **4** with glacial acetic acid at 110–112 °C for 2 h resulted in the formation of the major product **5**.[9,10]

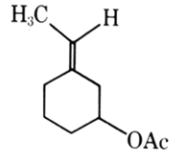


5

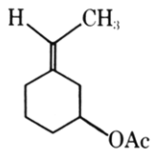


6

The acetoxy group at C-16 has been assigned to axial orientation. This is apparent in the ^{1}H NMR of **5** where the 16-hydrogen appears as a quintet at 5.13 ppm with only small coupling values ($\leq$3 Hz) indicating an equatorial orientation of the hydrogen in the six-membered ring. The assignment of the *E* configuration to **5** is based on ^{13}C NMR chemical shift data which was correlated with the predicted values based on the flexible models **7** and **8**.[4]



7



8

However, before this correlation could be made, assignments in the ^{13}C spectrum of **5** were essential. Single-frequency off-resonance decoupling (SFORD)[11] and noise off-resonance decoupling (NORD)[12] experiments were used to establish the multiplicities associated with the signals seen in the fully proton decoupled carbon spectrum. Assignments of the carbons in the *A* and *B* rings in **5** were made by comparison with the cholest-5-en-3β-yl acetate[13] which differs only in the *D* ring. All of the remaining signals could be assigned based on their multiplicities in the SFORD spectrum and ^{13}C chemical shifts with the exception of two methylene carbons corresponding to C-15 and C-17. However, the two carbons in question appear at 27.7 and 29.3 ppm, and unequivocal assignment is not necessary for comparison with the predicted values.[14]

Since models **7** and **8** most likely have equatorially oriented acetoxy groups, and **5** has an axial acetoxy group, parameters from Schneider and V. Hoppen's[15] work were used to predict chemical shifts in **7** and **8** resulting from axial orientation of the acetoxy group. Using androstane[13] and cyclopentane,[16] shielding parameters were obtained for the effect of the rest of the steroid skeleton on the *D* ring. These parameters were then used on models **7** and **8** to give predicted values for C-15 at 29.4 ppm in both isomers and for C-17 at 34.6 in the *Z* (**6**) and 28.4 in the *E* isomer (**5**). The prediction of 29.4 and 28.4 for C-15 and C-17, respectively, correlates quite well with the experimental values if **5** is assigned as having the *E* configuration.

We suggest that the severe steric repulsion between the C-21 methyl group and the C-12 methylene group prevents the formation of **6**. Space filling models corresponding to structures **5** and **6** clearly demonstrate the nature of this interaction in the latter structure (Figures 1 and 2).

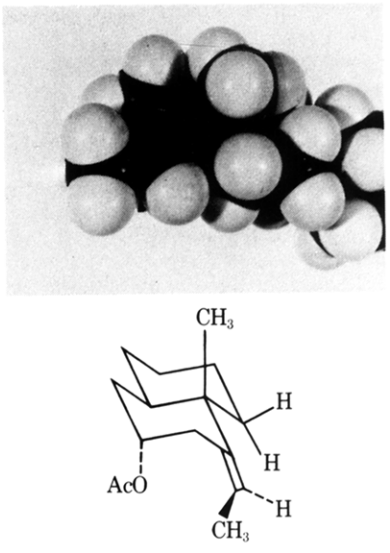


Figure 1.

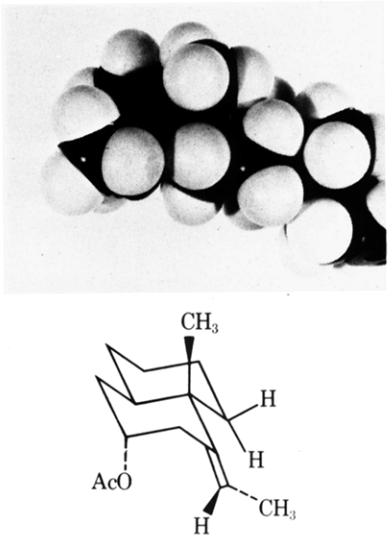


Figure 2.

Experimental Section

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. Infrared (IR) spectra were recorded on a Perkin-Elmer 137B spectrophotometer and are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra (MS) were determined on an LKB-9000 spectrometer. Chemical ionization mass spectra (CI–MS) were determined on a Biospect mass spectrometer manufactured by Scientific Research Instrument Corp., Baltimore, Md. (using methane and isobutane as carrier gases). Nuclear magnetic resonance spectra were measured on a Varian SC-300 or an EM-390 Varian instrument for proton (^{1}H NMR) and on a Varian CFT-20 for carbon-13 (^{13}C NMR). The resonances are reported in parts per million (δ) downfield from tetramethylsilane; the abbreviations b, d, s, t, q, and m refer to broad, doublet, singlet, triplet, quartet, and multiplet.

3β-Acetoxy-16α,17α-methylene-5-pregnen-20-one (2). A solution of the ylide was prepared at room temperature under nitrogen from 120 mg of sodium hydride (99%), 880 mg of trimethylsulfoxonium iodide, and 6.0 mL of dimethyl sulfoxide (Me_2SO). The mixture was stirred at room temperature under nitrogen until evolution of hydrogen ceased. A solution of 1.43 g of **1** in 6.0 mL of Me_2SO and 6.0 mL of ether was added dropwise with stirring under nitrogen. After being stirred at room temperature overnight, the mixture was poured into 100 mL of cold 5% hydrochloric acid and extracted with ether; the extracts were washed twice with water and once with saturated salt solution and dried over magnesium sulfate. After the solvent was evaporated under reduced pressure, the residue was crystallized from methanol to give white needles (575 mg, 38.6% yield): mp 202–203 °C; IR (Nujol mull) 1692, 1669, 1176, 1027 cm^{-1}; MS *m/e* 310, (M – CH_3COOH)$^+$ CI–MS (methane as carrier gas) *m/e* 371 (M + H)$^+$; ^{1}H NMR ($CDCl_3$) 0.75–0.81 (m, cyclopropyl methylene), 0.97 (s, 18-CH_3), 1.0 (s, 19-CH_3), 1.97 (s, $CH_3C(O)$–), 2.01 (s, $CH_3C(O)OC_3$

equatorial), 4.6 (m, 3-CH, axial), 5.18 (broad d, 6-olefinic C-H).

3β-Acetoxy-16α,17α-methylene-5-pregnen-20-ols (3 and 4). To a solution of 557.0 mg of **2** in 10 mL of dry tetrahydrofuran and 30 mL of 2-propanol was added 557.0 mg of sodium borohydride. The rapidly stirred suspension was reacted at room temperature for 3 h. After being cooled to 0 °C, the reaction mixture was diluted with 10 mL of methanol and allowed to proceed for an additional 2 h at 25–27 °C. The reaction mixture was cautiously treated with saturated aqueous potassium dihydrogen phosphate and extracted with ether. The combined extracts were washed with water and saturated salt solution and dried over magnesium sulfate; the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on eight 20 × 20 silica plates (1000 μm) using 95:5 benzene/ether as eluent to give the fast moving alcohol **3** which crystallized from chloroform as white needles (173 mg, 30.89% yield): mp 149–151 °C; IR (Nujol mull) 3448, 1727, 1266, 1089, 1044 cm^{-1}; CI-MS (CH_4) *m/e* 373 $(M + H)^+$; ^1H NMR (EM-390) ($CDCl_3$) δ 0.3–0.73 (m, cyclopropyl methylene), 0.92 (s, 18-CH_3), 1.03 (s, 19-CH_3), 1.2 (d, J = 6 Hz, 21-CH_3), 2.03 (s, $CH_3C(O)OC_3$, equatorial), 4.25 (q, J = 6 Hz, 20-CH), 4.6 (m, 3-CH, axial), 5.4 (broad d, 6-olefinic CH).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.42; H, 9.15. Found: C, 77.52; H, 9.20.

The slow moving alcohol **4** crystallized from chloroform as white needles (139.0 mg, 24.8%): mp 140–144 °C; IR (Nujol mull) 3571, 1709, 1259, 1036 cm^{-1}; CI-MS (CH_4) *m/e* 373 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 0.3–0.8 (m, cyclopropyl methylene), 0.92 (d, 21-CH_3, half of the doublet obscured), 0.97 (s, 18-CH_3), 1.03 (s, 19-CH_3), 2.02 (s, $CH_3C(O)OC_3$, equatorial), 4.37 (q, J = 6 Hz, 20-CH), 4.5 (m, 3-CH, axial), 5.3 (broad doublet, 6-olefinic CH).

Anal. Calcd for $C_{24}H_{36}O_3$: C, 77.42; H, 9.15. Found: C, 77.40; H, 9.11.

(17a*E*)-*D*-Homo-5,17a(20)-pregnadien-3β,16α-diyl Diacetate (5). (a) From the Fast Moving Alcohol. A solution of 40 mg of the fast moving alcohol derivative in 2.0 mL of glacial acetic acid was heated at 110–112 °C (oil-bath temperature) under nitrogen for about 2 h. After being cooled to room temperature, the reaction mixture was diluted with cold water and brought to pH 8 with sodium bicarbonate. The aqueous mixture was extracted with ether. The ethereal solution was washed with water and saturated salt solution, dried over magnesium sulfate, and filtered; the filtrate was evaporated under reduced pressure. The residue was chromatographed on a 20 × 20 silica plate (1000 μm) using 95:5 benzene/ether as eluent to give **5** as a white foam (39 mg, 88%) homogeneous on a TLC analysis: R_f = 0.54 (95:5 benzene/ether); IR (Nujol mull) 1739, 1242, 1136, 1030 cm^{-1}; MS *m/e* 354 $(M - CH_3COOH)^+$; CI-MS (isobutane as gas carrier) *m/e* 415, $(M + H)^+$; ^1H NMR (SC-300) ($CDCl_3$) δ 0.92 (s, 18-CH_3), 1.01 (s, 19-CH_3), 1.55 (d, J = 6 Hz, 21-CH_3), 1.99 (s, $CH_3C(O)OC_{16}$), 2.03 (s, $CH_3C(O)OC_3$), 4.6 (m, 3-CH, axial), 5.13 (quintet, 16-CH, equatorial), 5.28–5.4 (m, 2 H, vinyl H at C-6 and C-20).

(b) From the Slow Moving Alcohol. A solution of 40 mg of slow moving alcohol in 2.0 mL of glacial acetic acid was heated at 110–112 °C (oil bath temperature) under nitrogen for about 2 h. Workup as described above (39.3 mg, 88.3%) gave material homogeneous on TLC analysis, R_f = 0.54 (95:5 benzene/ether), whose spectral data are identical in all respects with those of the above described product **5**.

The combined products from (a) and (b) experiments were analyzed by ^{13}C NMR ($CDCl_3$) and showed δ_c 13.04 (C-19), 17.74 and 19.19 (C-21 and C-18), 20.54 (C-11), 21.93 (2 CH_3CO_2), 27.73, 28.12, and 29.26 (C-2, C-15, and C-17), 31.87 (C-7 and C-8), 35.93 (C-12), 36.63 (C-1), 36.82 (C-10), 37.85 (C-4), 38.67 (C-13), 45.85 (C-14), 49.50 (C-9), 70.89 (C-16), 73.83 (C-3), 115.48 (C-20), 122.31 (C-6), 139.35 (C-5), 143.06 (C-17a), 170.46 and 170.75 (2 CH_3CO_2).

Subsequently, the compound **5** was crystallized from methanol, mp 158–159 °C (effervesces), and analyzed as a dimethanol solvate.

Anal. Calcd for $C_{26}H_{34}O_4 \cdot (2CH_3OH)$: C, 70.26; H, 9.60. Found: C, 70.38; H, 9.87.

Acknowledgment. N.G.S. sincerely thanks Drs. L. Z. Pollara and A. K. Bose for their encouragement and for very helpful discussions during his stay at Stevens Institute of Technology and Dr. Alan Douglas for his helpful collaboration with the ^{13}C NMR studies. We are also indebted to Mr. B. Pramanik of the Stevens Institute of Technology for the chemical ionization mass spectrum measurements. The mass spectrum was measured by Mr. Jack Smith at Merck Sharp and Dohme Research Laboratories. The authors wish to thank Dr. B. Arison for determination and interpretation of ^1H NMR spectra (Varian SC-300).

Registry No.—**1**, 979-02-2; **2**, 6173-60-0; **3**, 69867-42-1; **4**, 69867-43-2; **5**, 69867-44-3; dimethylsulfoxonium methylide, 5367-24-8; trimethylsulfoxonium iodide, 1774-47-6; dimethyl sulfoxide, 67-68-5.

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A-Ring Iodination of Estradiol

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Contrary to the earlier reports, A-ring monoiodination of estradiol was found not to be a selective process in the present work. Unambiguous syntheses of 2-iodo- and 4-iodoestradiols are described here for the first time.

Iodination of estradiol was explored to extend our synthesis and to investigate the biological activity of A-ring substituted estrogen derivatives.[1] Thirty years ago it was reported that 2 equiv of *N*-iodoacetamide or molecular iodine under alkaline conditions reacts with estradiol to give 2,4-diiodoestradiol, a mixture of monoiodinated steroids, and unreacted starting material.[2] Four years later Hillmann-Elias and co-workers reported that mercuric acetate catalyzed iodination of estradiol gave a 90% yield of 2-iodoestradiol.[3] The remarkably selective monoiodination reaction remained a standard for the preparation of 2-iodoestradiol for over two decades.[4-7] Although selective monobromination of estradiol has also been reported,[8] this reaction was unequivocally shown to give an isomeric mixture of 2- and 4-bromoestradiols.[9] Thus, it seemed that the earlier reported selective monoiodination of estradiol was questionable.

We repeated the mercuric acetate catalyzed iodination of estradiol[3] and consistently obtained mixtures of four or five components. Therefore, we attempted to obtain direct monoiodination of estradiol by employing different reaction conditions. Iodination of estradiol in the presence of sodium

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