58793-96-7; 2-fluoro-1-phenoxyethane, 405-97-0; 3-fluoro-1-phenoxypropane, 70659-93-7; 2-fluoro-1-phenoxypropane, 70659-94-8; 4-fluoro-1-phenoxybutane, 70659-95-9; 3-fluoro-1-phenoxybutane, 70659-96-0; 3-butenenitrile, 109-75-1; 4-pentenenitrile, 592-51-8; 2-butenenitrile, 4786-20-3; nitrosonium tetrafluoroborate, 14635-75-7; nitrosonium hexafluorophosphate, 16921-91-8; nitrosonium hexafluoroantimonate, 16941-06-3; BF_3, 7637-07-2; SbF_5, 7783-70-2; phenol, 108-95-2.

Steric Course of Halocyclopropyl Acetate Opening Reactions

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A number of acetoxydifluoro-, -dichloro-, -fluorochloro-, and monofluorocyclopropanes have been treated with base. The various products obtained seem to indicate that the course of the ring opening follows several pathways, resulting from the steric and electronic factors which are operative.

An efficient scheme for the expansion of cyclic ketones to the homologous compounds results from the addition of dichloro-[2-6] and dibromocarbene[6,7] to the enol ether or enol acetate derived from the parent ketone, followed by ring opening. In a previous study,[8] we have investigated the addition of difluorocarbene to various enol acetates, as well as the nature of the products obtained after base or acid treatment of the resulting acetoxydifluorocyclopropanes. This reaction sequence was shown to be a convenient homologation method, which can lead either to α-difluoro ketones or α-fluoro enones depending on the nature of the starting material. In addition, in all cases studied thus far the bond which is cleaved is the central bond of the cyclopropane ring, i.e., the bond opposite to the difluoromethylene group.

The mechanism of ring-opening reactions of cyclopropyl derivatives to carbonium ions is well documented, and the transformation of a cyclopropyl cation to an allylic cation has been treated as an electrocyclic ring opening. This reaction has been predicted[9,10] and found[11] to be stereospecific and disrotatory.

However, some observations made with difluorocyclopropyl acetates, yielding α-difluoro ketones,[8] suggested that their ring opening could follow a different pathway, without involving a carbonium ion intermediate, in contrast to simple dihalocyclopropanes. This is illustrated by the fact that no solvolysis was observed with the halocyclopropyl acetates **2b** and **2g**, **2h**, when treated with silver nitrate in pyridine solution in the presence of water, conditions known to open dihalocyclopropanes.[12] Thus, it appears that the presence of the acetoxy function on the three-membered ring is a determining factor, since the carbon–fluorine bonds present in both cases should not be dramatically different in nature and strength.[13,14]

It has been reported that base treatment of the 2α,-3α-difluorocarbene adduct **2a**, easily obtained from the steroidal enol acetate **1a**, provided exclusively the *A*-homodifluoro ketone **3a**, while the opening reaction under acidic conditions afforded the corresponding 17-acetate **3b**.

In contrast, addition of difluorocarbene[15] to the ring D cyclopentanone enol acetate **4** gave the *D*-homo α-fluoro enone **6a** as the main product, resulting from in situ ring opening of the strained pentacyclic intermediate **5a**, followed by elimination of fluoride. The adduct **5a** could be isolated in low yield and base treatment gave only one

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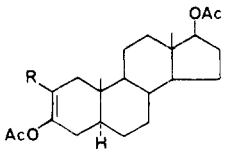
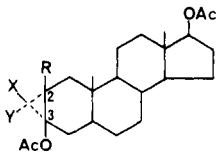
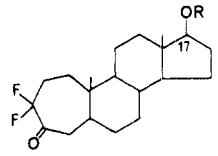


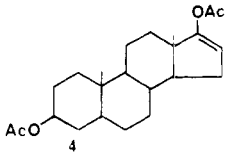
1 a, R = H
b, R = Me



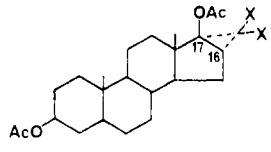
2 a, R = H, X = Y = F
b, R = Me, X = Y = F
c, R = H, X = Y = Cl
d, R = Me, X = Y = Cl
e, R = H, X = F, Y = Cl
f, R = H, X = Cl, Y = F
g, R = Me, X = F, Y = Cl
h, R = Me, X = Cl, Y = F



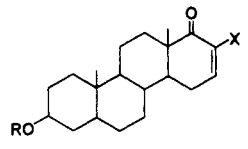
3 a, R = H
b, R = Ac



4



5 a, X = F
b, X = Cl



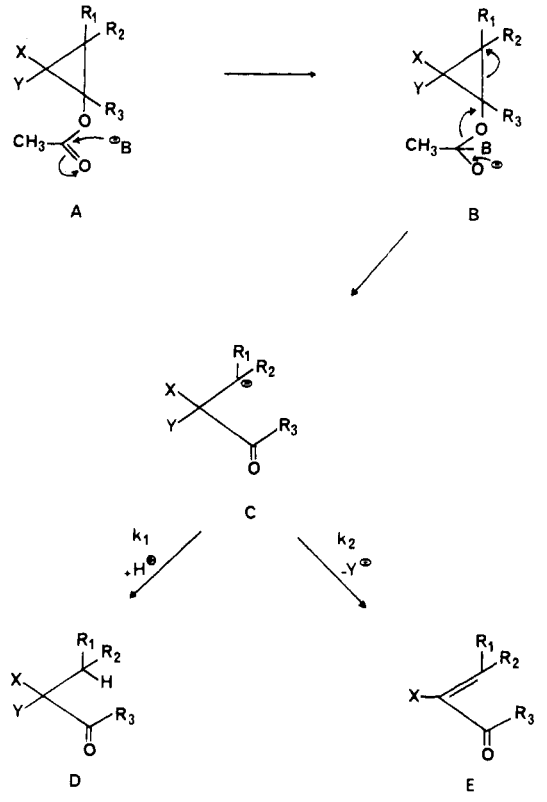
6 a, X = F, R = Ac
b, X = F, R = H
c, X = Cl, R = H

product, namely the fluoro enone **6b**, identical with a sample obtained by alkaline hydrolysis of the 3-acetoxy group in compound **6a**.[8]

An intermediary situation was encountered with the 2α,3α-difluorocyclopropyl acetate **2b**, obtained by addition of difluorocarbene[15] to the enol acetate (**1b**) of 2α-methyldihydrotestosterone. The α configuration of the dihalocyclopropane ring in **2b** is evidenced by the absence of long-range coupling between fluorine and 19-methyl protons[8,16] and confirmed by ^{19}F NMR studies (see Experimental Section). Treatment of the difluorocyclopropyl steroid **2b** with 2% methanolic sodium hydroxide provided a mixture of the *A*-homodifluoroketo steroid **7a** (72%) and the fluoro enone **8a** (28%), characterized by its typical ultraviolet absorption band at λ_{max} 248 nm, as well as by its vinylic methyl signal appearing at 1.85 ppm in the NMR spectrum.

Thus, as previously suggested[8] it is conceivable that in some cases a nonconcerted cleavage leads to an anion followed by either protonation or expulsion of halide. Earlier investigations[17] showing that there is no single factor allowing prediction of the mode of cleavage of substituted cyclopropanols would thus be confirmed.

It was then of interest to identify the factors responsible for the course of the reaction, which affords either the α-dihalo ketone or the α-enone, because it has been established that the latter is not formed by dehydrohalogenation of the former.[8] If it is likely that an intermediary anion of type C results from a base-catalyzed hydrolysis of the acetoxy group present in A, the factors favoring the rate of elimination of a halide ion (geometry, weakness of the C–X bond) should lead to the enone. Contrastingly,



A B C D E

factors which increase the accessibility of the anion, e.g. lack of steric hindrance, should result mainly in the formation of the dihalo ketone. This was tested by varying the nature of the halogens on the cyclopropane ring.

Addition of dichlorocarbene, generated by decomposition of phenyl(trichloromethyl)mercury in refluxing benzene,[18] to the enol acetate **1a** gave the 2α,3α-dichlorocyclopropyl derivative **2c**. The assignment of stereochemistry to the dichlorocyclopropyl group in steroid **2c** is based primarily on electronic factors and classical concepts of steric hindrance to reagent approach, as well as to ample precedents for such carbene additions from the α side.[8,19] Treatment of the acetoxydichloromethylene steroid **2c** with various types of bases (sodium hydroxide, ammonia) yielded the extremely reactive, hence unstable chloro enone **9a**, which could not be isolated in the pure form. Contrastingly, addition of dichlorocarbene to the enol acetate **1b** furnished the fully substituted cyclopropane derivative **2d**, which gave the conjugated ketone **8b**, in 90% yield, when treated with base.

The exclusive formation of the conjugated ketones **9a** and **8b** in particular is to be contrasted to the obtainment of the saturated *A*-homo steroids **3** by opening of the difluorocyclopropyl adduct **2a**. As anticipated (vide supra), addition of dichlorocarbene to the Δ^{16}-enol acetate **4**, followed by ring opening, provided exclusively the *D*-homo steroid **6c**, as a result of the ring strain previously observed in the pentacyclic intermediate.[8] Thus, it also appears that the α-enone becomes the major compound when the carbon–halogen bond becomes weaker.

It was then of interest to investigate the exact configuration of the halogen which is eliminated. We therefore turned our attention to the preparation of dihalo compounds bearing two different halogen atoms of known stereochemistry and to the course of their ring-opening

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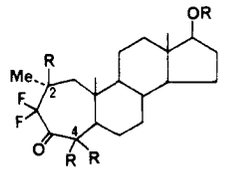
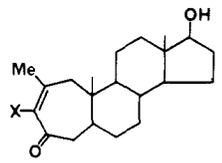
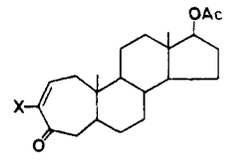


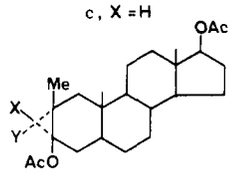
7 a, R = H
b, R = D



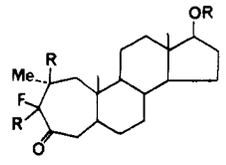
8 a, X = F
b, X = Cl
c, X = H



9 a, X = Cl
b, X = F



10 a, X = F, Y = H
b, X = H, Y = F



11 a, R = H
b, R = D

reaction. Chlorofluorocarbene, generated from phenyl(dichlorofluoromethyl)mercury,[20] was added to the enol acetate **1a** to provide a mixture of chlorofluoro adducts **2e** and **2f**. Similarly, addition of chlorofluorocarbene to the enol acetate **1b** yielded the isomeric adducts **2g** and **2h**, as an inseparable mixture.

^{19}F NMR spectroscopy was used to assign the configuration of the fluorine atoms in compounds **2e–h**. From previous studies[21] it is known that an exo fluorine atom resonates at a lower field than the corresponding endo epimer in fluorocyclopropyl compounds. Thus, it was observed that chlorofluorocarbene adds to the enol esters **1a** and **1b** to yield mixtures of steroids **2e** + **2f** and **2g** + **2h**, respectively, in which the isomer with the fluorine in the exo configuration predominates.

When treated with sodium hydroxide in aqueous methanol at room temperature, the mixture of isomeric steroids **2e** and **2f** gave the fluoro enone **9b** as the major product. Similarly, the isomeric mixture of **2g** and **2h** treated in refluxing methanolic sodium hydroxide led to the fluoro enone **8a**. In both cases, the chlorine atom was eliminated during the ring-opening process, which indicates the influence of the strength of the carbon–halogen bond on the course of the reaction. Since the endo chlorine atom is preferentially eliminated, it is also conceivable that during the ring-opening reaction an antiperiplanar relationship of the transient carbanion and the carbon–chlorine bond occurs, highly favoring the cleavage of the latter. This assumption was supported by the following experiments.

The difluorocyclopropyl steroid **2b** was treated with deuterated sodium hydroxide (5%) in deuteriomethanol. The mass spectrum of the tetradeuterated compound **7b**, which was isolated, confirmed the introduction of a deuterium atom at position 2, in addition to two deuterium atoms located at C-4 (due to enolization of the carbonyl group) and one deuterium atom on the 17β-hydroxyl group. Moreover, a comparative study of the ^{19}F NMR spectra of compounds **7a** and **7b** indicates that one single epimer at position 2 was obtained in each case. At low temperature (−93 °C), the spectrum of steroid **7a** showed significant modifications; i.e., while the quasiaxial (α) fluorine signals at higher field presented a coupling constant $J_{H_2-F_\alpha}$ = 17.5 Hz, coalescence was observed for the signals of the quasiequatorial (β) fluorine at lower field. These values agree[22] with a quasiaxial configuration of the C_2–H bond and hence of the intermediate anion of type C. The existence of such a species was also confirmed by solvent effects. Indeed, the opening of the cyclopropane ring in compound **2b** in a low polarity aprotic solvent, such as benzene, provided *exclusively* the fluoro enone **8a** (in 95% yield) by destabilization of the anion C.

The stereochemical requirements to afford either a saturated ketone or an α-enone, as shown by the ring opening of the mixed halogen compounds **2e-h**, were further confirmed by the following experiments.

The mixture of chlorofluorocyclopropanes **2g** and **2h**, obtained by addition of chlorofluorocarbene to the enol acetate **1b**, was reduced with tributyltin hydride. Under these conditions the chlorine was selectively removed, thus affording a mixture of epimeric fluorocyclopropanes **10a** and **10b**, which could be separated by preparative thin-layer chromatography. The assignment of configuration of the fluorine atom in these epimers was based on their ^{19}F NMR spectra. The fluorine coupled with the geminal hydrogen appeared as a doublet centered around 198 ppm for the exo fluorine and at ca. 202 ppm for the endo fluorine (with a coupling constant $J_{F,H}$ = 63 Hz). These values are significant and define the stereochemistry of the monofluorocyclopropanes.[21,23] They also confirm the exo configuration for the fluorine atom in the higher melting compound **10a** (224–225 °C) and the epimeric configuration in the low melting isomer **10b** (214–215 °C).

Treatment of the exo fluorinated cyclopropyl steroid **10a** gave exclusively the fluoro ketones **11a**, as a 2:1 mixture of α- and β-fluorinated compounds, resulting from the enolization of the carbonyl group, as shown by the deuterium-labeling experiment, which afforded the deuterated steroid **11b**. Similar treatment of the endo isomer **10b**, in which the carbon–fluorine bond is not as strong as in the difluoro compounds **2a** and **2b**,[13,14] provided *only* the cycloheptenone **8c** in yields higher than 95%.

These results indicate that the endo halogen atom is preferentially eliminated. When there is no endo halogen, as in compound **10a**, or when the carbon–halogen bond is relatively strong as in steroid **2a**, protonation of the carbanion C leads to the saturated ketone D.

In summary, the course of the opening reaction of halocyclopropyl acetates A in alkaline medium seems to involve an anion of type C. This anion can then follow two competitive pathways, i.e. either the elimination of a halide to provide E or protonation to afford D. It also appears that the factors responsible for the formation of ketones D and E affect the rate constant ratio k_1/k_2.

Some of these factors are the nature and the stereochemistry of the halogens, the stability of the carbanion C, and the steric hindrance to protonation. Adequate

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variations of the nature of the compounds as well as the reaction conditions have allowed obtainment of either the saturated ketones D or the enones E. The ring opening of dihalocyclopropyl and monohalocyclopropyl acetates can thus be considered as a useful homologation reaction. By using the appropriate halocyclopropyl acetates and reaction conditions, one can easily get access to either α-mono- and dihalogenated saturated ketones or α-halogenated, as well as nonhalogenated enones.

Experimental Section

Microanalyses are due to the Laboratoire Analytique, CNRS, Lyon. Melting points were determined with a Büchi Tottoli apparatus, and they are not corrected. Rotations were taken at 22 °C with a Perkin-Elmer 141 polarimeter, in chloroform solution, unless stated otherwise. IR spectra were taken in chloroform solution with a Beckman Acculab 4 instrument. UV absorption spectra were obtained with a Beckman DBT spectrophotometer. Unless stated otherwise the NMR spectra were recorded on a PMX 60 JEOL instrument, using 5–8% w/v solutions of substance in deuteriochloroform containing tetramethylsilane (Me_4Si) as an internal reference. Resonance frequencies, δ, are quoted as parts per million downfield from the Me_4Si reference (0.0 ppm). ^{19}F NMR spectra were recorded on a 60-MHz Bruker WP 60 instrument, in deuteriochloroform solution. Resonance frequencies are quoted in parts per million upfield from $CFCl_3$ as an internal standard. Coupling constants, J, are expressed in hertz (Hz) and are accurate to ±1 Hz: d = doublet, t = triplet; q = quartet; m = multiplet. The mass spectra were obtained with a MS-30 AEI spectrometer. Thin-layer chromatography (TLC) was on silica gel plates (Merck 240–400 mesh). We are indebted to Dr. C. Bosso for mass spectra determinations.

3,17β-Dihydroxy-2-methylandrost-2-ene Diacetate (1b). To a solution of 1.07 g of 2α-methyldihydrotestosterone in 5 mL of carbon tetrachloride and 600 mg of isopropenyl acetate, 5 drops of 70% perchloric acid was added at 0 °C. The reaction was followed by TLC and, when completed (10 min), 10% sodium bicarbonate–water was added and the organic fraction was extracted with CH_2Cl_2. The organic layer was washed with water until neutral, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. After chromatography of the crude product on a silica gel column, 800 mg of pure enol acetate **1b** was obtained after recrystallization in methylene chloride–methanol solution: mp 169–170 °C; $[\alpha]_D$ +45°; IR ν_{max} 1715, 1705 cm^{-1}; ^1H NMR 0.8 (s, 18-Me), 0.83 (s, 19-Me), 1.45 (s, 2-Me), 2.03 (s, 17-acetate), 2.10 (s, 3-acetate), 4.5 ppm (t, 17α-H); mass spectrum m/e 389 (M^+ + 1), 388 (M^+).

General Procedure for the Addition of Difluorocarbene to Enol Acetates. A solution of enol acetate in anhydrous diglyme is heated to reflux temperature with a Vigreux column so that the diglyme is allowed to distill slowly, while a solution of sodium chlorodifluoroacetate in the same solvent is progressively added.[15] Aliquots are taken periodically for TLC to monitor the progress of the reaction. When all the starting material is consumed, the resulting dark solution is cooled to room temperature and filtered on neutral alumina, and the solvent is evaporated under reduced pressure to give a brown syrup. Purification is achieved by column chromatography (Florisil or silica gel) or preparative TLC.

Preparation of 2α,3α-Difluoromethylene-3β,17β-dihydroxy-2β-methyl-5α-androstane Diacetate (2b). According to the above procedure, a solution of 388 mg of enol acetate **1b** in 10 mL of anhydrous diglyme was treated with 30 mL of a 0.7 M solution of sodium chlorodifluoroacetate.

After cooling, the solution was filtered over neutral alumina, the solvent was evaporated, and the residue was purified by column chromatography over silica gel to afford 300 mg of the difluorocyclopropyl steroid **2b**, recrystallized in methanol solution: mp 190 °C; $[\alpha]_D$ −7°; IR ν_{max} 1750, 1730 cm^{-1}; ^1H NMR 0.78 (s, 18-Me), 0.83 (s, 19-Me), 1.15 (t, 2-Me, J = 2 Hz), 2.03 (s, 17β-acetate), 2.05 ppm (s, 3β-acetate); ^{19}F AB spectrum δF_{exo} = 147.4, δF_{endo} = 151.7 ppm, J_{F-F} = 160 Hz; mass spectrum m/e 438 (M^+), 378.

Anal. Calcd for $C_{25}H_{36}O_4F_2$: C, 68.34; H, 8.27; F, 8.69. Found: C, 68.29; H, 8.08; F, 8.64.

Hydrolysis of 2b with Methanolic Sodium Hydroxide. To 70 mg of adduct **2b** in 1 mL of methanol, 0.1 mL of a 5% sodium hydroxide methanolic solution was added. The reaction mixture was heated under reflux for 30 min. After cooling to 0 °C, 10% HCl in H_2O was added until neutral. After extraction with ethyl acetate, the organic layer was washed with water, dried over anhydrous magnesium sulfate, filtered, and evaporated to dryness. The residue was chromatographed over silica gel (eluent hexane–ethyl acetate 9:1).

After recrystallization from ether–hexane, there was obtained 13 mg of fluoro enone **8a**: mp 159–161 °C; $[\alpha]_D$ +154°; UV λ_{max} 248 nm (ε 9900); IR ν_{max} 3450, 1685 cm^{-1}; ^1H NMR 0.75 (s, 18-Me), 0.86 (s, 19-Me), 1.85 (s, 2-Me); mass spectrum m/e 335 (M^+ + 1), 335 (M^+).

Anal. Calcd for $C_{21}H_{31}O_2F$: C, 76.04; H, 9.28; F, 5.68. Found: C, 76.15; H, 9.32; F, 5.53.

There was also obtained 35 mg of difluoro ketone **7a**, after recrystallization from ether–hexane: mp 115–116 °C; $[\alpha]_D$ +26°; UV λ_{max} 286 nm (ε 80); ^1H NMR 0.73 (s, 18-Me), 0.77 (s, 19-Me), 0.98 ppm (d, 2-Me, J = 2 Hz); ^{19}F NMR, AB part of an ABX spectrum (room temperature) δF = 108.7, δF = 121.1 ppm, J_{F-H} = 10 and 17.5 Hz, J_{F-F} = 256 Hz, (t = 253 K) J_{F-F} = 256 Hz, J_{F-H} = 10 and 17.5 Hz, (t = 188 K) J_{F-F} = 256 Hz, J_{F-H} = 0 and 17.5 Hz; mass spectrum m/e 355 (M^+ + 1), 354 (M^+).

Anal. Calcd for $C_{21}H_{32}O_2F_2$: C, 71.19; H, 9.04; F, 10.73. Found: C, 71.36; H, 9.20; F, 10.71.

Preparation of the Deuterated Ketone 7b. To 70 mg of compound **2b** in 1 mL of deuteriomethanol, 0.1 mL of NaOD in 5% CH_3OD was added. The mixture was heated under reflux for 30 min. After cooling and neutralization with DCl in D_2O, the product was extracted with ethyl acetate. The usual purification procedure afforded 10 mg of deuterated fluoro enone **8a** and 35 mg of difluoro ketone **7b** after recrystallization from ether–hexane: mp 117–119 °C; $[\alpha]_D$ +30.2°; IR ν_{max} 1700 cm^{-1}; ^1H NMR 0.73 (s, 18-Me), 0.77 (s, 19-Me), 0.98 ppm (d, 2-Me, J = 2 Hz); ^{19}F NMR AB spectrum δF_{eq} = 107.1, δF_{ax} = 120 ppm, J_{F-F} = 256 Hz; mass spectrum m/e 358 (M^+), 339 (M^+ − F).

Preparation of 2α,3α-Dichloromethylene-3β,17β-dihydroxy-5α-androstane Diacetate (2c). To a suspension of 632 mg (1.59×10^{-3} mol) of phenyl(trichloromethyl)mercury in 10 mL of anhydrous benzene, 500 mg (1.33×10^{-3} mol) of enol acetate **1a** was added. The mixture was heated at reflux temperature for 48 h under nitrogen. The mercuric salt was filtered off and the residue was filtered on a column of silica gel (eluent: n-hexane–ethyl acetate 8:2). There was isolated 534 mg of adduct **2c**: mp 208–209 °C (MeOH); $[\alpha]_D$ +15°; IR ν_{max} 1770, 1750 cm^{-1}; ^1H NMR 0.80 (s, 18-Me), 0.85 (s, 19-Me), 2.05 (s, 17-acetate), 2.10 ppm (s, 3-acetate).

Anal. Calcd for $C_{24}H_{34}O_4Cl_2$: C, 63.01; H, 7.49; Cl, 15.50. Found: C, 62.93; H, 7.54; Cl, 15.42.

Base Treatment of the Difluorocyclopropane (2b) in Benzene. To 43 mg of **2b** in 10 mL of benzene, there was added 0.1 mL of 5% sodium hydroxide–methanol solution. The mixture was heated at reflux temperature for 1 h and after a further addition of 0.2 mL of 5% sodium hydroxide solution, the mixture was allowed to reflux for an additional 10 min. The reaction mixture was concentrated in vacuo and chromatographed over silica gel. After the usual recrystallization, one obtained 30 mg of the enone **8a** (mp 157–159 °C) and 2 mg of the saturated ketone **7a** (mp 114–116 °C).

Preparation of 2α,3α-Dichloromethylene-3β,17β-dihydroxy-2β-methyl-5α-androstane Diacetate (2d). To a suspension of 240 mg of phenyl(trichloromethyl)mercury in 10 mL of anhydrous benzene, there was added 240 mg of enol acetate **1b**. The mixture was allowed to reflux for 48 h under a nitrogen atmosphere. The mercuric salt was filtered off and the residue was filtered on a column of silica gel. There was isolated 120 mg of adduct **2d** and 84 mg of recovered enol acetate **1b**.

The analytical sample of the dichloromethylene steroid **2d** obtained after recrystallization from methanol exhibited: mp 208–210 °C; $[\alpha]_D$ +16°; IR ν_{max} 1770, 1730 cm^{-1}; ^1H NMR 0.78 (s, 18-Me), 0.82 (s, 19-Me), 1.32 (s, 2-Me), 2.03 (s, 17-acetate), 2.08 ppm (s, 3-acetate); mass spectrum m/e 472 (M^+ + 1).

Anal. Calcd for $C_{25}H_{36}O_4Cl_2$: C, 63.69; H, 7.69; Cl, 15.04. Found: C, 63.67; H, 7.73; Cl, 15.34.

Base Treatment of the Dichlorocyclopropane (2d). A mixture of 80 mg of **2d** in 1 mL of methanol was treated with 0.2 mL of 5% sodium hydroxide–methanol solution at reflux for 10 min. After the usual workup 40 mg of enone **8b** was isolated, in addition to 20 mg of recovered starting material **2d**. Attempts to increase the yield by longer heating resulted in degradations. After recrystallization of the enone **8b** in ether–hexane, the analytical sample presented: mp 173–174 °C; $[\alpha]_D$ +250°; UV λ_{max} 264 nm (ϵ 10 400); IR ν_{max} 1730, 1680 cm^{-1}; ^{1}H NMR 0.77 (s, 18-Me), 0.86 (s, 19-Me), 2.0 (s, 2-Me), 2.16 ppm (s, 17-acetate); mass spectrum m/e 394–392 (M^+) corresponding to the isotope distribution of ^{35}Cl and ^{37}Cl.

Anal. Calcd for $C_{23}H_{33}O_3Cl$: C, 70.32; H, 8.40; Cl, 9.04. Found: C, 70.51; H, 8.50; Cl, 9.00.

Addition of Chlorofluorocarbene to the Enol Acetate 1b. To a solution of 880 mg of enol acetate **1b** in 10 mL of anhydrous dimethoxyethane (DME) there was added 1.4 g of phenyl(dichlorofluoromethyl)mercury and 1 g of sodium iodide (dried for 12 h at 150 °C in vacuo). The mixture was allowed to reflux for 15 h and concentrated and the precipitate was filtered. The residual solution was purified by chromatography over a silica gel column. One isolated 500 mg of the mixture of chlorofluoromethylene steroids **2g** and **2h**, along with 370 mg of recovered enol acetate **1b**.

The dihalocarbene adducts **2g** and **2h** could not be separated by usual techniques and the mixture was recrystallized from methanol: mp 166–171 °C; $[\alpha]_D$ +8°; IR ν_{max} 1770, 1750 cm^{-1}; ^{1}H NMR 0.77 (s, 18-Me), 0.82 (s, 19-Me), 1.1 (d, 2-Me, $J_{F\text{-}Me}$ = 2 Hz), 2.0 (3-acetate), 2.06 (17-acetate); ^{19}F NMR δF_{endo} = 151.2 (s, 61%), δF_{exo} = 150.3 ppm (s, 39%); mass spectrum m/e 376 (M^+ – CH_3COOF), 357, 316.

Anal. Calcd for $C_{25}H_{36}O_4ClF$: C, 66.00; H, 7.92; Cl, 7.81. Found: C, 65.86; H, 8.02; Cl, 7.68.

Addition of Chlorofluorocarbene to the Enol Acetate 1a. Following the procedure described above, 2 g of enol acetate **1a**[8] was transformed into 1.23 g of the mixture **2e** and **2f**, which was recrystallized from CH_2Cl_2–hexane: mp 171–173 °C; $[\alpha]_D$ –10°; IR ν_{max} 1750, 1720 cm^{-1}; ^{1}H NMR 0.76 (s, 19-Me), 0.82 (s, 18-Me), 2.03 (s, 6 H, 2 $COCH_3$), 4.52 ppm (t, 17 H); ^{19}F NMR δF_{exo} = 139 (d, J_{HF} = 22 Hz), δF_{endo} (minor isomer **2f** ~15%) = 154.7 ppm (br s, $W^{1/2}$ = 8 Hz).

Anal. Calcd for $C_{24}H_{34}O_4ClF$: C, 65.37; H, 7.77; Cl, 8.03. Found: C, 65.16; H, 7.44; Cl, 8.28.

Base Treatment of 2e and 2f. The above mixture (361 mg) dissolved in 8 mL of MeOH and 4 mL of THF was treated with 0.75 mL of 1.1 N methanolic sodium hydroxide. After 5 h at room temperature and the usual workup, the reaction mixture was chromatographed on silica gel plates (eluent benzene–dioxane, 97:3) to yield 149 mg of starting material and 90 mg of **9b**: mp 150–151 °C; $[\alpha]_D$ +114°; UV λ_{max} 240 nm (ϵ 4730); IR ν_{max} 1720, 1675 cm^{-1}; ^{1}H NMR 0.83 (s, 19-Me), 0.96 (s, 19-Me), 2.06 (s, $COCH_3$), 6.20 ppm (dt, J_{HF} = 23 Hz, $J_{H\text{-}H}$ = 6 Hz).

Attempts to improve the yield in **9b** resulted in the formation of many unidentified products.

Base Treatment of the Mixture 2g + 2h. To a solution containing 56 mg of **2g** and **2h** in 1 mL of methanol there was added 0.2 mL of a 5% sodium hydroxide methanolic solution. The mixture was allowed to reflux for 15 min. After the usual extraction procedure and purification, there was isolated 30 mg of fluoro enone **8a**.

Reduction of Chlorofluoromethylene Steroids 2g and 2h with Tributyltin Hydride. A solution of 47 mg of compounds **2g** and **2h** in 3 mL of tributlytin hydride was heated at 80 °C, in the presence of a trace of azodiisobutyronitrile as an initiator. After 45 min the reaction mixture was cooled and purified by column chromatography over silica gel.

Elution with methylene chloride afforded first the endo isomer **10b**, which after recrystallization from methanol gave 14 mg of the analytical sample: mp 214–215 °C; $[\alpha]_D$ –3°; IR ν_{max} 1770, 1730 cm^{-1}; ^{1}H NMR 0.77 (s, 18-Me), 0.82 (19-Me), 1.05 (d, 2-Me, $J_{H,F}$ = 3 Hz), 1.98 (17-acetate), 2.0 (3-acetate), 4.56 ppm (d, CHF, $J_{H,F}$ = 63 Hz); ^{19}F NMR δF_{endo} = 202 (d, $J_{H,F}$ = 63 Hz); mass spectrum m/e 360 (M^+ – CH_3COOF), 340, 300.

Anal. Calcd for $C_{25}H_{37}O_4F$ (420): C, 71.43; H, 8.80; F, 4.52. Found: C, 71.51; H, 8.84; F, 4.48.

Further elution with methylene chloride provided the exo isomer **10a**, which after recrystallization from methanol yielded 15 mg of the analytical sample: mp 224–225 °C; $[\alpha]_D$ –15°; IR ν_{max} 1770, 1730 cm^{-1}; ^{1}H NMR 0.77 (s, 18-Me), 0.82 (s, 19-Me), 1.1 (d, 2-Me, $J_{H,F}$ = 2 Hz), 2.0 (17-acetate), 2.05 (3-acetate), 4.56 ppm (d, CHF, $J_{H,F}$ = 63 Hz); ^{19}F NMR δF_{exo} = 198 (d, $J_{H,F}$ = 63 Hz); mass spectrum m/e 360 (M^+ – CH_3COOF), 300.

Anal. Calcd for $C_{25}H_{37}O_4F$ (420): C, 71.43; H, 8.80; F, 4.52. Found: C, 71.50; H, 8.83; F, 4.49.

Base Treatment of the Fluorocyclopropane (10a). A solution containing 35 mg of steroid **10a** in 1 mL of 5% methanolic sodium hyroxide was heated at reflux temperature for 15 min. After the usual extraction and isolation procedure, followed by purification by chromatography, one obtained the fluoro ketone **11a** (25 mg): mp 138–140 °C (hexane); $[\alpha]_D$ +27°; UV λ_{max} 298 nm (ϵ 40); IR ν_{max} 3400, 1700 cm^{-1}; ^{1}H NMR 0.77 (s, 18-Me), 0.85 (s, 19-Me), 1.1 (d, 2-Me, $J_{H,F}$ = 5 Hz), 2.1 (m, 4-CH_2), 4.2 (d,d, $J_{F,H}$ = 8.5 Hz, $J_{F,H}$ = 49 Hz), 5.4 (d,d, $J_{F,H}$ = 6.5 Hz, $J_{F,H}$ = 49 Hz); ^{19}F 3:2 ratio of axial F and equatorial F at C-3′: δF_{ax} = 193.5 (dd, $J_{F_{ax},H}$ = 14.7 Hz, $J_{F_{ax},H}$ = 49 Hz), δF_{eq} = 182 ppm (dd, $J_{F_{eq},H}$ = 14.7 Hz, $J_{F_{eq},H}$ = 49 Hz).

Anal. Calcd for $C_{21}H_{31}O_2F$ (334): C, 75.45; H, 9.28; F, 5.68. Found: C, 75.49; H, 9.30; F, 5.58.

Base Opening of Compound 10a by Sodium Deuterioxide. A solution containing 15 mg of steroid **10a** in 1 mL 5% deuteriomethanolic NaOD was heated at reflux temperature for 15 min. After the usual workup and purification, 8 mg of deuterated compound **11b** was obtained: mp 143–145 °C (n hexane); $[\alpha]_D$ +31.7°; IR ν_{max} 1700 cm^{-1}; ^{1}H NMR 0.78 (s, 18-Me), 0.82 (19-Me), 1.1 ppm (s, 2-Me); ^{19}F δF_{eq} = 185 ppm, δF_{ax} = 198 ppm; mass spectrum m/e 337 (M^+), 309 (M^+ – CO).

Registry No. **1a**, 981-64-6; **1b**, 1250-12-0; **2b**, 70659-51-7; **2c**, 70659-52-8; **2d**, 70659-53-9; **2e**, 70659-54-0; **2f**, 70659-55-1; **2g**, 70659-56-2; **2h**, 70659-57-3; **7a**, 70659-58-4; **7b**, 70659-59-5; **8a**, 70659-60-8; **8b**, 70659-61-9; **9b**, 70659-62-0; **10a**, 70659-63-1; **10b**, 70659-64-2; **11a** isomer 1, 70659-65-3; **11a** isomer 2, 70659-66-4; **11b** isomer 1, 70659-67-5; **11b** isomer 2, 70659-68-6; 2α-methyldihydrotestosterone, 58-19-5; sodium chlorodifluoroacetate, 1895-39-2; phenyl(trichloromethyl)mercury, 3294-57-3; phenyl(dichlorofluoromethyl)mercury, 19326-35-3.