Chemistry of Difluorocyclopropyl Acetates. Application of Difluorocarbene Chemistry to Homologation Reactions

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Abstract: The chemical behavior of difluorocyclopropyl acetates, generated by addition of difluorocarbene to the enol acetate of aliphatic, alicyclic, and aromatic ketones, has been investigated. Treatment of these difluoromethylene adducts under either basic or acidic conditions provides a convenient homologation sequence which can lead to α-difluoro ketones, α-fluoro enones, and substituted tropones, depending on the reaction conditions and steric as well as electronic factors. The diverse products formed in these reactions can be explained in terms of two possible competitive mechanisms, *in extenso* a concerted solvolysis of a difluorocyclopropyl system, and a cleavage resulting from nucleophilic attack of the ester carbonyl, followed by protonation or elimination processes. Solvent effects appear to play a major role on the course of these reactions.

The solvolysis of cyclopropyl derivatives tends to proceed with concerted disrotatory ring opening, in agreement with the orbital symmetry rules.[2-6] Usually, ring opening is simultaneous with departure of a leaving group, leading to a transition state in which the positive charge is delocalized over all three-ring carbon atoms. However, the effect of fluorine as a leaving group on the reactivity of substituted cyclopropanol derivatives has received little attention.[7] Apparent discrepancies in the hydrolysis results for acetoxydifluorocyclopropanes led to the present investigation.

One of the most efficient schemes for the expansion of a cyclic ketone to the homologous conjugated ketone involves the addition of dichloro-[8-12] and dibromocarbene[12,13] to the enol ether or enol acetate derived from the parent ketone, followed by ring opening. Our general interest in fluorocarbene chemistry[14] led us to investigate the addition of difluorocarbene to various enol acetates and to study the nature of the products formed after base or acid treatment of the resulting acetoxydifluorocyclopropanes.

Results

Difluorocarbene, generated by pyrolysis of the sodium salt of chlorodifluoroacetic acid,[15] adds readily to the enol acetate **1** obtained from diisobutyl ketone, to afford 1-isobutyl-3-isopropyl-2,2-difluorocyclopropan-1-ol acetate (**2**). Treatment of **2** with 1% ethanolic sodium hydroxide provides a 2:7 mixture of *cis*-**3** and *trans*-**4** fluoro enones. Both compounds exhibit the molecular ion peak at *m/e* 172 by mass spectral analysis, but they differ in their other physical properties (see Experimental Section). In particular, whereas the vinylic proton in the cis compound **3** appears in the nmr spectrum as a pair of doublets centered at 5.45 ppm (J_{HF} = 23 Hz, J_{HH} = 10 Hz), in the trans isomer **4** this pair is centered at 5.85 ppm with a distinctly different J_{HF} coupling constant (J_{HF} = 35 Hz). While this result is in accord with the cleavage of similar dichloro- and dibromocarbene adducts[8-13] obtained from the corresponding cyclanones, it is interesting to note that the opening reaction is not stereospecific and leads to a mixture of geometric isomers **3** and **4**.

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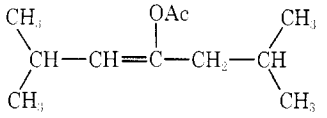
Although *a priori* this might be attributed to the fact that neither the enol acetate **1** nor the adduct **2** is stereochemically pure, as evidenced by nmr analysis, such a simple explanation had to be discarded (*vide infra*).



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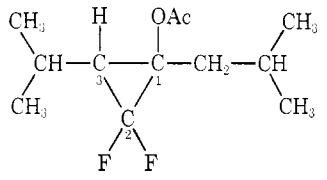

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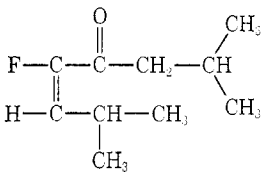

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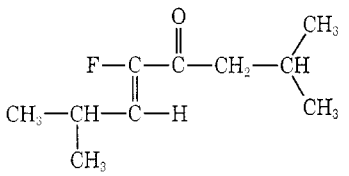


4

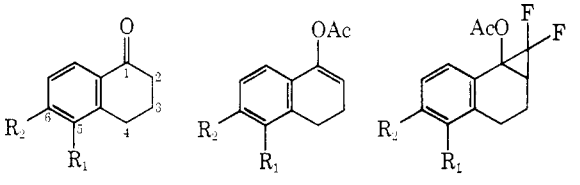
This homologation reaction was then applied to various difluorocyclopropane adducts of substituted tetralones, formed by addition of difluorocarbene to the enol acetates **6a** and **6b**, obtained from the tetralones **5a** and **5b**. The difluorocyclopropanes **7a** and **7b** were isolated in moderate yield (*ca.* 60%), along with a small amount of the difluoromethyl ethers **8a** and **8b**. The latter are characterized by a pair of doublets in their nmr spectrum with a large coupling constant (J_{HF} = 72 Hz), typical of the $OCHF_2$ grouping. The formation of such ethers under these conditions has some precedent in the steroid literature.[16] Reaction of the acetoxydifluorocyclopropanes **7a** and **7b** with 2% sodium hydroxide in methanol does not provide any of the expected fluoro enones.[8-10] It yields exclusively a 2:3 mixture of difluorobenzosuberones **9a** and **9b** and benztropones **10a** and **10b**, respectively, thus making this sequence a new and efficient synthetic approach to the benztropone system.

Similarly, the enol acetate **12** of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (**11**) when submitted to the same sequence of reactions affords the difluoro ketone **14** and the novel heterocyclic system, thiophentropone **15**, through the crystalline intermediate **13a**.

These results induced us to believe that in the strongly basic reaction medium the highly reactive fluoro enones are converted into the corresponding tropones. This hypothesis was verified by treatment of the difluoromethylene adduct **7b** with ammonium hydroxide in dioxane solution at room temperature, thus affording the fluoro enone **16**, along with starting material. The enone **16** is then converted quantitatively into tropone **10b** when exposed to a 2% methanolic sodium hydroxide solution.

In this respect, it is worth noting that although the formation of the tropone system has been observed in the case of cleavage of methoxydibromocyclopropanes with silver ion,[12,13] we have not found a reference to the formation of *gem*-dihalo ketones under such conditions. However, on occasion dihalo ketones have been postulated as possible reaction intermediates in monocyclic systems.[3]

Various attempts (sodium hydroxide, lithium chloride, etc.) to convert the difluoro ketone **9b** into the benztropone **10b** were unsuccessful, thus showing the former not to be an intermediate in the conversion of **7b** into **10b** under these reaction conditions. In contrast, treatment of **9b** with zinc in acetic acid in the presence of a trace of cupric acetate for 90 min affords a mixture of monofluoro derivative **9c** (41%) and 10-methoxybenzosuberone **9d** (56%). The mass spectra of **9c** and **9d** exhibit the correct molecular ions of 208 and 190 mass units, respectively. The yield of **9d** reaches 95% when the reaction is performed for 24 hr, thus showing **9c** to be easily converted into **9d** under these conditions.



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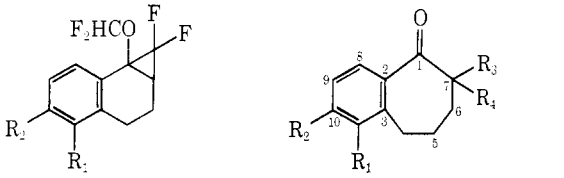
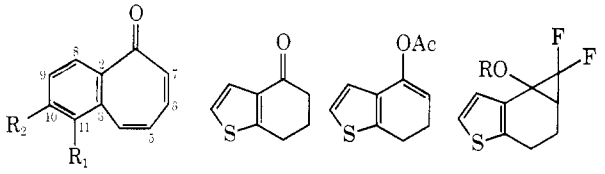


8a, R_1 = OMe; R_2 = H
b, R_1 = H; R_2 = OMe

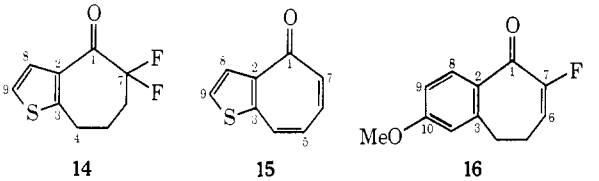
9a, R_1 = OMe; R_2 = H; R_3 = R_4 = F
b, R_1 = H; R_2 = OMe; R_3 = R_4 = F
c, R_2 = OMe; R_1 = R_3 = H; R_4 = F
d, R_2 = OMe; R_1 = R_3 = R_4 = H



10a, R_1 = OMe; R_2 = H
b, R_1 = H; R_2 = OMe

11 12

13a, R = Ac
b, R = CHF_2



14 15 16

Subsequently, we turned our attention to the application of this homologation reaction to various alicyclic systems with different degrees of rigidity.

The 2,3-difluorocarbene adduct **18** is easily obtained from the steroidal enol acetate **17** by the usual technique.[15] The α configuration of the difluorocyclopropane ring is evidenced by the absence of long-range coupling between fluorine and 19-methyl protons.[17]

(16) (a) T. L. Popper, F. E. Carlon, H. M. Marigliano, and M. D. Yudis, *Chem. Commun.*, 277 (1968); (b) C. Beard, B. Berkoz, N. H. Dyson, I. T. Harrison, P. Hodge, L. H. Kirkham, G. S. Lewis, D. Giannini, B. Lewis, J. A. Edwards, and J. H. Fried, *Tetrahedron*, **25**, 1219 (1969).

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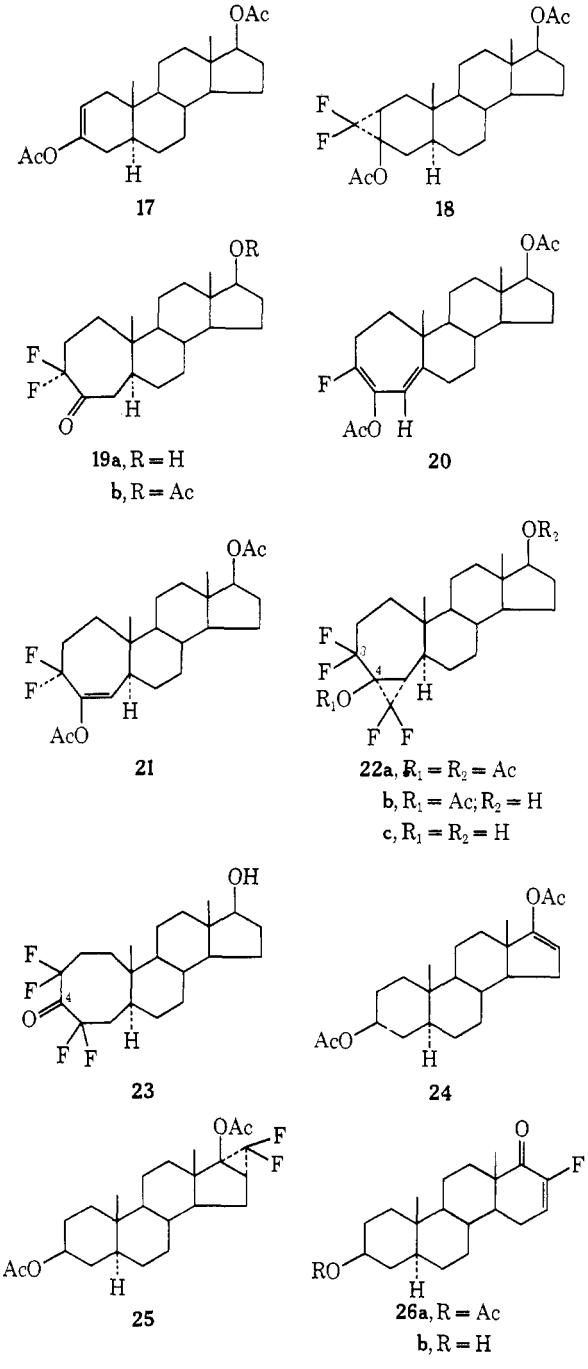
Treatment of the adduct **18** with 2% methanolic potassium hydroxide gives exclusively the saturated *A*-homodifluoro ketosteroid **19a**. Similarly, reaction of **18** with an ethanolic solution of perchloric acid affords only the *A*-homodifluoro ketone **19b**, identical with the compound obtained after acetylation of **19a**, thus showing the course of the opening reaction of the difluorocyclopropane ring in **18** to be substantially different from that of corresponding dichloro- and dibromocyclopropanes.[8-13,18] No trace of the conjugated ketone is detected in these reactions. However, the corresponding enol acetate **20** can be obtained, along with the enol acetate **21**, by treatment of the difluoro ketone **19a** with acetic anhydride at reflux temperature in the presence of *p*-toluenesulfonic acid. The structure of **20** is supported by its physical properties (see Experimental Section), including its correct molecular ion peak at *m/e* 404, and the appearance of one vinylic proton at *ca.* 5.2 ppm in the nmr spectrum, as well as by alkaline hydrolysis affording a conjugated ketone. In turn, addition of difluorocarbene to the enol acetate **21** yields the *A*-homodifluorocyclopropane steroid **22a**. The mass spectrum of this tetrafluoro steroid **22a** presents the correct molecular ion of 474 mass units. The difluoromethylene group in **22a** probably presents the α stereochemistry, since the signal corresponding to the 19-methyl group is not split.

Whereas reaction of the difluoro adduct **22a** with base affords a complex mixture of products, treatment with a methanolic solution of hydrochloric acid gives first the 17-alcohol **22b**, then the corresponding diol **22c**. When **22c** is heated in a 5% hydrochloric acid–tetrahydrofuran solution for 3 hr, one isolates the bis-*A*-homotetrafluoro ketosteroid **23**, characterized by its typical ir absorption at 1765 cm^{-1}, and a very weak molecular ion peak of 366 mass units. Thus, the above sequence of reactions constitutes a useful method for the preparation of tetrafluoro ketones.

In contrast to the carbene addition to the enol acetates **17** and **21**, and the opening of the difluoromethylene adducts **18** and **22**, addition of difluorocarbene to the ring D cyclopentanone enol acetate **24** gives a low yield of the strained difluorocyclopropane **25**, along with *ca.* 50% of the *D*-homofluoro enone **26a**, resulting from the elimination of fluoride. Base treatment of **25** gives the fluoro enone **26b**, also obtained by alkaline hydrolysis of **26a**, in quantitative yield.[19]

Difluorocarbene adds exclusively to the Δ^6 double bond of the enol acetate **27** to provide the adduct **28**. Reaction of the difluorocyclopropyl acetate **28** with methanolic potassium carbonate affords only the *B*-homo steroidal bisenone **29**, in agreement with the classical opening reaction of dichlorocarbene adducts,[9] and with the previously discussed opening of the difluoro adduct **25**. The structural assignment of the *B*-homopregnane **29** is based on its nmr spectrum showing the C-4 olefinic proton at 6.35 ppm and the C-7a vinylic proton which appears as a pair of doublets at 6.25 ppm. Furthermore, the bisenone **29** exhibits a typical uv absorption band at 262 nm.



A further example, germane to the cases reported above, is the addition of difluorocarbene to the Δ^5 double bond of the *B*-nor steroid **30** to provide the 5α,6α-difluorocyclopropane **31a**. The stereochemistry of **31a** is supported by the absence of long-range coupling between fluorine and the 19-methyl protons,[17] which appear as a sharp singlet at 1.1 ppm. Base hydrolysis of the 3-acetoxy group gives the corresponding alcohol **31b**, readily oxidized with chromic acid[20] into the diketone **32**. Alkaline treatment of the pentacyclic steroid **32** affords the 6-fluoro steroid **33** in high

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yield. The structural assignment of the dienone **33** is based on physical and spectroscopic properties, including the expected uv maximum at 284 nm. This substance presumably results from the formation of an anion at position 4, followed by cleavage of the carbon–carbon bond between C-5 and C-7 and expulsion of fluoride ion, as represented schematically in A, making this ring expansion[21] reminiscent of the reactions reported above.

In order to study the possible influence of the stereochemistry of the enol acetate on the nature of the substances formed by cleavage of the difluorocyclopropyl acetate, difluorocarbene was also added separately to the exocyclic cis enol acetate **34a** and its trans isomer **34b**.[22] The pentacyclic steroids **35a** and **36a** obtained from **34a** and **34b**, respectively, possess a fully substituted cyclopropane ring. The α stereochemistry is assigned to the difluoromethylene bridge in **35a** and **36a**, since no long-range coupling was observed in their nmr spectra. They are treated separately with 2% methanolic sodium hydroxide. The cleavage of the cis adduct **35a**, obtained from the cis enol acetate **34a**, provides in addition to some difluoro ketone **38** a mixture of the geometrically isomeric fluoro enones **37a** and **37b**. When the trans adduct **36a**, formed from the trans enol acetate **34b**, is submitted to an identical base treatment, a mixture of trans enone **37a** and cis enone **37b** was isolated, with no evidence for the presence of the difluoro ketone **38**.

The assignment of the isomeric structures **37a** and **37b** is based on the higher extinction coefficient of the uv maximum of the trans enone **37a** which has less distortion from planarity of the enone chromophore, lacking the 12-methylene–22-methyl interaction.[23] Additionally, the configurations of these *cis*- and *trans*-α-fluoro enones are unequivocally established by their nmr spectra. The chemical shifts and relative peak areas are as expected. One observes a slight downfield shift (*ca.* 0.5 Hz) of the 18-methyl protons[24] and a 1 Hz downfield shift of the 22-methyl protons in the cis isomer **37b**. Steric repulsions between the 12β hydrogen and the 22-methyl protons in the cis derivative **37b** could lead to such a shift. Examination of the geometry of the cis isomer **37b** with molecular models indicates that the 12β hydrogen should also suffer a downfield shift, and indeed the integration confirms that there are three protons in the 2.40–2.65-ppm region, two of them corresponding to the chemical shift of the protons at C-16. These protons appear at 2.50 in **37b** *vs.* 2.68 ppm in the trans isomer **37a**.

The nmr spectra of the fluoro enones **37a** and **37b**, and of the difluoro ketone **38**, were also measured in benzene-d_6 in an attempt to confirm their structure. In the saturated ketone **38** and the cis isomer **37b** there is essentially no shift of the 18-methyl protons, while in the trans compound **37a**, one observes a 15 Hz downfield shift, attributed to the fact that the angular methyl at C-13 falls into the shielding cone of the aromatic ring. Molecular models indicate that this shielding effect would be smaller in **37b** and **38**. Moreover, the $^5J_{HF}$ in the difluoro ketone **38** follows the rules for these long-range couplings,[25] with the observation that the $^5J_{HF}$ is larger than $^4J_{HF}$ through the carbonyl (2.2 Hz *vs.* 1.7 Hz). Finally, the large long-range couplings (J_{HF} = 5.6 Hz) in the unsaturated ketones **37a** and **37b** are quite remarkable. Conversely, in these unsaturated compounds $^5J_{HF}$ is much smaller due to the absence of vector crossing of the saturated difluoro ketone **38**.

It is worthwhile to mention that whereas the ring A difluoro ketone **19a** exhibits a rather intense positive Cotton effect[26] and the difluoro ketosteroid **38** a weak positive Cotton effect around 300 nm, the tetrafluoro keto derivative **23** does not allow one to detect any Cotton effect in the same region. This may be due to the conformational mobility existing in the eight-membered ring A of compound **23** and/or more probably to the remoteness of an asymmetric center from the carbonyl group.

The isolation of both the *cis*-**37b** and *trans*-**37a** fluoro enones during the hydrolysis of either the difluorocyclopropyl acetate **35a** or **36a** is surprising. Furthermore, it appears from recent experiments that the course of the ring opening is quite sensitive to the nature of the solvent.

The relative importance of the various solvent–solute interactions in determining the solvent effects is clearly illustrated in the case of the hydrolysis of the difluorocyclopropyl acetate **2**. Table I lists different reaction conditions used for the hydrolysis of the difluorocyclopropyl acetate **2**. These results emphasize the dramatic role played by the nature of the medium, *i.e.*, the importance of the dielectric constant of the solution on the course of the reaction.[27] In fact, it has been shown[7b]

Table I. Hydrolysis of the Difluorocyclopropyl Acetate **2** under Different Reaction Conditions

Reaction conditions	Percentage of cis isomer **3**	Percentage of trans isomer **4**	Recovered starting material **2**, %
(A) 2% NaOH in MeOH–H_2O (9:1), 1 hr at reflux (63°)[a]	5	40	*ca.* 20
(B) 1% NaOH in EtOH–H_2O (9:1), 1 hr at reflux (71°)[a]	12	43	*ca.* 20
(C) 2% NaOH in dioxane–H_2O (1:1), 1 hr at reflux (80°)[a]	11	33	*ca.* 20
(D) 1% Na in *t*-BuOH, 1 hr at reflux (76°)[a]	36	46	*ca.* 15
(E) 5% Na_2CO_3 in MeOH–H_2O (3:2), 1 hr at reflux (69°)[a]		25	*ca.* 20
(F) 4% $HClO_4$ (70%) in MeOH, 1 hr at reflux (63°)[a]		28	*ca.* 30

[a] The atmospheric pressure in Mexico City (7000 ft) is 565 mm.

(21) *Inter alia:* (a) P. S. Skell and S. R. Sandler, *J. Amer. Chem. Soc.*, **80**, 2024 (1958); (b) J. Sonnenberg and S. Winstein, *J. Org. Chem.*, 27, 748 (1962); see also ref 8 and 18.

(22) C. W. Marshall, T. H. Kirtchevsky, S. Lieberman, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **70**, 1837 (1948).

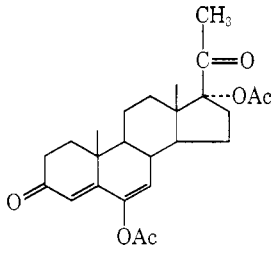
(23) For a preliminary communication, see P. Crabbé, H. Carpio, A. Cervantes, J. Iriarte, and L. Tökés, *Chem. Commun.*, 79 (1968).

(24) *Cf.* F. A. Mackellar and G. Slomp, *Steroids*, **11**, 787 (1968).

(25) (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959; (b) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969; (c) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964; (d) see also ref 17.

(26) P. Crabbé, "ORD and CD in Chemistry and Biochemistry: An Introduction," Academic Press, New York, N. Y., 1972.

(27) *Inter alia:* (a) P. S. Wharton and A. R. Fritzberg, *J. Org. Chem.*, **37**, 1899 (1972); (b) J. Lhomme, A. Díaz, and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 1548 (1969); (c) G. E. Maciel and G. C. Ruben, *ibid.*, **85**, 3903 (1963).



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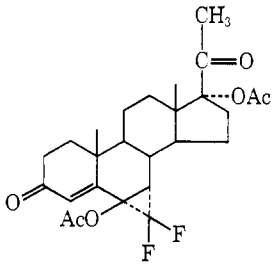

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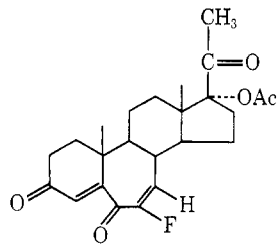

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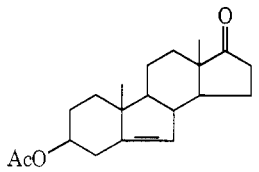

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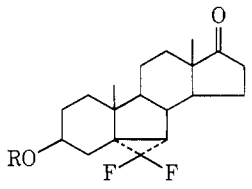
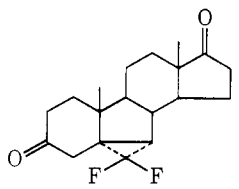


31a, R = Ac
b, R = H



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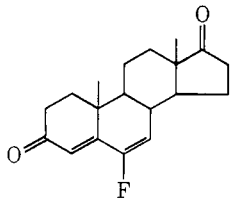

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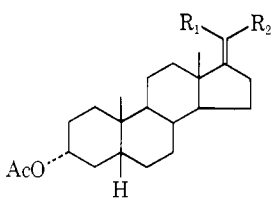
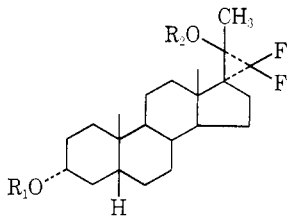
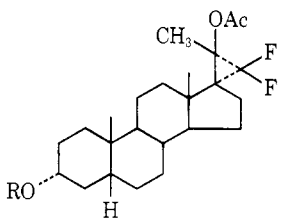


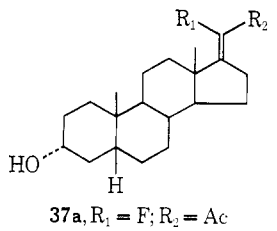
34a, R_1 = OAc; R_2 = Me
b, R_1 = Me; R_2 = OAc



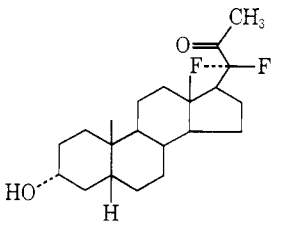
35a, $R_1 = R_2$ = Ac
b, R_1 = H; R_2 = Ac
c, $R_1 = R_2$ = H



36a, R = Ac
b, R = H



37a, R_1 = F; R_2 = Ac
b, R_1 = Ac; R_2 = F



38

that fluorine as a leaving group is subject to remarkable and specific proton catalysis. Additionally, the operation of such catalysis in cyclopropyl fluoride openings has recently been demonstrated with chlorofluorocarbene adducts of norbornene.[28] These results emphasize the contrary behavior observed earlier with isomeric chlorofluorocarbene adducts.[29]

Table II reports the quantitative experiments run with the pure *cis*-**35a** and the pure *trans*-**36a** difluoro adducts under various alkaline conditions. It is immediately apparent that, besides the absence of difluoro ketone, after the cleavage of the trans adduct **36a**, the presence of water in the medium, the time of the reaction, as well as the higher reaction temperature are factors increasing the yield of trans enone **37a**, with concurrent decrease of the proportion of cis enone **37b**. These factors, however, do not affect the yield of difluoro ketone **38** isolated from **35a**. In no case was there any starting material recovered after the reaction. Moreover, various attempts to convert the difluoro ketone **38** into either **37a** or **37b** under basic conditions failed.

Table II. Quantitative Hydrolysis Experiments of the Cis Adduct **35a** and Trans Adduct **36a**

	Cis enone **37b**, %	Trans enone **37a**, %	Difluoro ketone **38**, %
Cis Adduct **35a**			
(A) 0.22 mmol in 10 ml of a solution of 70 ml of MeOH, 30 ml of H_2O, and 2 g of NaOH, 0.5 hr at room temperature	26	65	2
(B) 0.22 mmol in 10 ml of a solution of 98 ml of MeOH (96%), 2 ml of H_2O, and 2 g of NaOH, 0.5 hr at room temperature	39	52	6
(C) 0.22 mmol in 10 ml of a solution of 100 ml of MeOH (96%) and 2 g of NaOH, 1.5 hr at room temperature	27	49	10
(D) 0.22 mmol in 10 ml of anhydrous MeOH and 0.2 g of MeONa, 1 hr at room temperature	32	39	6
(E) 0.22 mmol in 10 ml of anhydrous MeOH and 0.2 g of MeONa, 1.5 hr at reflux	5	84	6
Trans Adduct **36a**			
(F) 0.23 mmol in 10 ml of a solution of 100 ml of MeOH (96%) and 2 g of NaOH, 1 hr at reflux	1	88	0
(G) 0.12 mmol in 10 ml of a solution of 98 ml of MeOH (96%), 2 ml of H_2O, and 2 g of KaOH, 1 hr at room temperature	1	90	0

In addition, the *trans*-difluoro adduct **36a** gives essentially the trans enone **37a**, accompanied by a low yield of the cis isomer **37b** under rather severe conditions (higher temperature; see Table II).

These results suggest that the alkaline hydrolysis of the cis adduct **35a** initially gives the cis enone **37b** and some difluoro ketone **38**. The former then isomerizes into the trans isomer **37a** under the experimental conditions. This conclusion results from a kinetic study of the alkaline hydrolysis of the cis adduct **35a**, as shown in Table III. After 5 min, tlc indicates that there is no starting material left, but 80% of the product is the cis derivative **37b**, with 20% of the trans isomer

(28) C. W. Jefford, A. N. Kabengele, and U. Burger, *Tetrahedron Lett.*, 4799 (1972).

(29) (a) L. Ghosez, G. Slinckx, M. Glineur, P. Hoet, and P. Laroche *Tetrahedron Lett.*, 2773 (1967); (b) C. W. Jefford and D. T. Hill, *ibid.*, 1957 (1969).

Table III. Kinetic Study of the Alkaline Hydrolysis of the Cis Adduct **35a**

Cis adduct **35a**	Time	Cis enone **37b**, %	Trans enone **37a**, %
(A) 98 ml of MeOH (96%), 2 ml of H_2O, and 2 g of NaOH, at room temperature	5 min	80	20
	15 min	70	30
	20 min	50	50
	30 min	20	80
	60 min	20	80
	24 hr	2–3	90
(B) Same solution as above, at reflux	5 min	2–3	90
	15 min		
	30 min		
	1 hr		
(C) 100 ml of MeOH (96%) and 2 g of NaOH, at room temperature	5 min	90	10
	10 min	80	20
	15 min	75	25
	30 min	50	50
	60 min	25	75
	90 min	5	95
(D) 100 ml of MeOH (96%) and 2 g of NaOH, at reflux	5 min	10	90
	10 min	5	95
	30 min	3	97
	60 min		
	90 min		

37a. With time the cis compound **37b** is converted into the trans isomer **37a**, to reach a ±90 to 2% ratio of **37a** and **37b**, after 24 hr. When the same reaction is performed at reflux temperature, an identical equilibrium is reached after 5 min, and is not affected with time. Furthermore, Table III clearly shows the effect of water[27–29] on the rate of conversion of **37b** into **37a**. It is worth noting that when the adduct **35a** is treated with base, there is always some cis enone **37b** present in the reaction mixture. This tends to indicate that in alkaline medium the trans enone **37a** is in *equilibrium* with the cis isomer **37b**, the equilibrium being considerably displaced toward the trans isomer **37a**. This is confirmed by treatment of a sample of the pure cis enone **37b** with 2% sodium hydroxide in a 98:2 methanol–water solution which affords 87% of the trans enone **37a** as well as 3% of unchanged cis isomer **37b**. Moreover, when a pure sample of the trans isomer **37a** is submitted to an identical treatment, 5% of the cis enone **37b** is isolated, in addition to 85% of recovered starting material **37a**. This shows unequivocally that the cis compound **37b** is the kinetic product of the hydrolysis of **35a**, which is then isomerized to the thermodynamically more stable trans isomer **37a**, and also that there is an equilibrium between the cis and the trans forms under the reaction conditions.

Thus, base treatment of the cis adduct **35a** gives initially and rapidly a mixture of some difluoro ketone **38** and mainly the cis enone **37b**, rapidly converted into an equilibrium mixture with its trans isomer **37a**, in which the latter predominates.

Although various attempts to cleave the acetoxydifluorocyclopropane ring of **35a** in hexamethylphosphoric triamide were unsuccessful, the hydrolysis experiments under acidic conditions confirm the observations made in basic medium. In addition, treatment of the diacetate **35a** with 5% hydrochloric acid in methanol gives the corresponding difluorocyclopropanol **35c**. Recrystallization of **35c** in hexane–ether provides mainly the cis enone **37b**, along with some of its trans isomer **37a**. However, by further crystallization compound **37b** is readily converted into **37a**.

Conversely, alkaline hydrolysis of the trans adduct **36a** gives predominantly the trans enone **37a**, which slowly forms an equilibrium with its cis isomer **37b** (see Table II).

It is interesting to note that during recent studies of the cleavage of cyclopropanols with mercury(II) acetate[30a] and solvolysis of 2,3-diphenylcyclopropyl chlorides,[30b] both inversion and retention stereochemical pathways have been observed.

Discussion

The above results indicate that the adduct formed by addition of difluorocarbene to an enol acetate can be cleaved to afford either a *gem*-difluoro ketone, or an α-fluoro conjugated ketone, or a mixture thereof. Hence, hydrolysis of these acetoxydifluoro adducts always leads to homologation reactions. Moreover, in all the cases studied so far the bond which is cleaved is the central bond of the cyclopropane ring, *i.e.*, the bond not adjacent to the difluoromethylene.

The mechanism of ring opening in carbonium ion reactions of cyclopropyl derivatives is well documented, and the transformation of a cyclopropyl cation to an allyl cation has been elegantly treated as an electrocyclic ring opening.[2,3] It has been predicted[2,3] and found[4] to be stereospecific and disrotatory.

In the solvolytic ring opening of the difluorocyclopropyl cation, such as in the generation of the intermediate C,[31] substituents would move inward in a disrotatory manner, because one of the fluorines is always cis to the two ring member. On this basis, it could have been anticipated that alkaline treatment of **25** would give **26**, since the solvolytic process is known to be especially favorable in bicyclo[3.1.0] system, where the geometry of the substituents is correct,[5,18] as in the case of the steroid **25**.

Additionally, it has been shown that the rate of solvolysis of cyclopropanols, cyclopropylamines, dichlorocyclopropyl ethers,[8–10] and cyclopropyl esters is enhanced, by the lone-pair electrons, and that ionization and ring opening are concerted.[2,6] It appears to be the case of the cleavage of several difluorocyclopropyl acetates discussed above, in which the presence of the acetate lone-pair electrons has the ability to increase the electron density of the cyclopropane ring. This may polarize the carbon–fluorine bond and, in the case of the formation of fluoro enones, the reaction may be depicted as concerted solvolysis of the trans anti periplanar type,[2] with loss of fluoride ion.

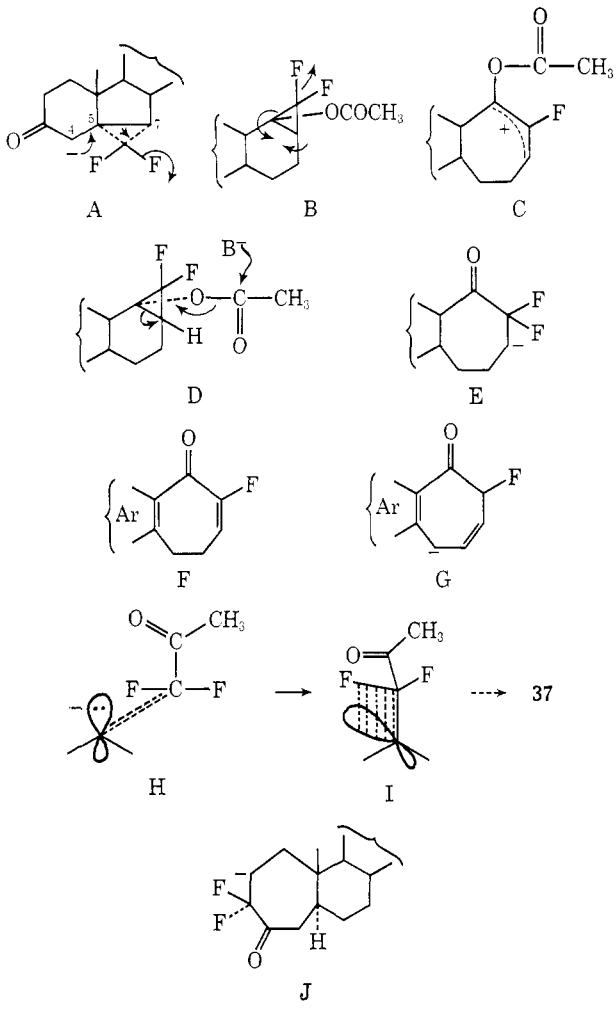
However, the observations made with the adducts **7**, **13a**, **18**, **22a**, and **35a** tend to support the hypothesis that the electrocyclic ring opening of difluorocyclopropyl acetates is not the exclusive process. Because of the intrinsic nature of the carbon–fluorine bond,[7,32] making the fluorine a rather poor leaving group, it seems likely that in these instances, a nonconcerted

(30) (a) A. DeBoer and C. H. DePuy, *J. Amer. Chem. Soc.*, **92**, 4008 (1970); (b) J. W. Hausser and J. T. Uchic, *J. Org. Chem.*, 37, 4087 (1972).

(31) Such a type of enhanced stabilized intermediate has been postulated during the pyrolysis of 1-ethoxy-7,7-dichloronorcarane; see ref 8a, also: (a) D. G. Lindsay and C. B. Reese, *Tetrahedron*, **21**, 1673 (1965); (b) G. A. Olah and G. Ligand, *J. Amer. Chem. Soc.*, **94**, 6434 (1972).

(32) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 260.

base-induced cleavage of type D, leading to an anion E, is followed by protonation and/or expulsion of fluoride.



In the case of the formation of the substituted tropones **10** and **15**, it is conceivable that in the strongly basic reaction medium, the nonisolated highly reactive enone species F is converted into an anion of type G, which readily loses a fluoride ion leading to the tropone ring.

If a nonconcerted cleavage is indeed responsible for the main formation of the enones **37a** and **37b** by acid or base treatment of **36** and **35**, respectively, one could perhaps invoke the operation of a memory effect.[33] This effect could be due to stabilizing hyperconjugation between the developing two-electron orbital with the C–F bond (H) situated on the same side of the developing orbital (I).[34] It appears that either the reduced steric strain associated with the bicyclo[4.1.0] system in **18** and/or the stability[34] of the α-difluoro anion of type J contributes to the retention of both fluorines during the fragmentation of the difluorocyclopropane ring. Finally, the isolation of the difluoro ketone **38** from **35a** and not from its isomer **36a** may be due to an hyperconjugative property of the intermediary anion[34] whose conformation is not necessarily identical in both cases.

(33) (a) J. A. Berson, *Angew. Chem., Int. Ed. Engl.*, 7, 779 (1968); (b) J. A. Berson, J. M. McKenna, and H. Junge, *J. Amer. Chem. Soc.*, **93**, 1296 (1971).

(34) R. Hoffmann, L. Radom, J. A. Pople, P. v. R. Schleyer, W. J. Hehre, and L. Salem, *J. Amer. Chem. Soc.*, **94**, 6221 (1972).

Conclusion

Although cyclopropanes are simple systems which lend themselves to an easy examination of the fission of a carbon–carbon single bond, the present study confirms earlier investigations[35] which showed that in some cases there is as yet no single factor allowing one to predict the mode of cleavage of substituted cyclopropanols.

Indeed, a tentative explanation which would account for the above results could imply that the difluorocyclopropane ring opening is occurring by two different mechanisms. On the one hand, a nonconcerted cleavage of the difluorocyclopropane ring, followed by either proton capture gives the *gem*-difluoro ketones, or fluoride ion loss, thus affording the fluoro enones. On the other hand, a concerted disrotatory solvolysis gives the enones directly.

The nonconcerted base or acid induced cleavage of difluorocyclopropyl acetate seems to be the exclusive process operating in the case of the formation of the *A*-homodifluoro ketosteroids **19**.

Finally, a comparison of alkyl substituent effects with those found in other secondary systems provides an estimate of the anchimeric assistance in difluorocyclopropyl acetate solvolysis. In the absence of steric strain, it is conceivable that the strong positive inductive effect of the alkyl groups in the cyclo adduct **2** favors the elimination process, thus preventing the formation of *gem*-difluoro ketone. Conversely, the ring size may favor a conformation of the anion (J) in which the elimination of fluoride ion is not being favored; protonation becomes the exclusive process.

Experimental Section

Microanalyses are due to Dr. A. Bernhardt, Mühlheim (Germany), and Midwest Microlab, Inc., Indianapolis, Ind. Melting points were determined with a Mel-Temp apparatus; they are corrected. Rotations were taken between 16 and 22° with a 1-dm tube at the sodium D line in chloroform solution. CD curves were recorded on a Roussel-Jouan Dichrograph-185, at concentrations of about 1 mg ml^{-1} and with a path length of 1 mm. Ir spectra were taken with a Perkin-Elmer Model 21 NaCl prism. Uv absorption spectra were obtained with a Beckman spectrophotometer, Model DU. Unless otherwise stated, the nmr spectra were recorded at 60 and 100 MHz using 5–8% w/v solutions of substance in deuteriochloroform containing tetramethylsilane (TMS) as an internal reference. Resonance frequencies, δ, are quoted as ppm downfield from the TMS reference (0.0 ppm). 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 an Atlas CH-4 spectrometer. Tlc were performed with silica gel GF-254 (Merck A.G., Germany). We are indebted to Mr. E. Avila, Analytical Dept., Syntex, S. A., for most physical data, to Dr. L. Throop, Dr. L. Tökés, and Dr. M. Maddox, Syntex Research, Palo Alto, Calif., for several nmr and mass spectra, and to Professor W. Klyne and Dr. P. M. Scopes, Westfield College, London, for several CD curves.

General Procedure for the Addition of Difluorocarbene to the Enol Acetates. A solution of the 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. Aliquots are taken periodically for thin layer chromatography (tlc) to monitor the progress of the reaction. When all starting material is consumed, the resulting dark solution is cooled to room temperature (RT) and filtered on neutral alumina and the solvent evaporated under reduced pressure to yield a brown syrup. Purification

(35) *Inter alia:* (a) R. T. LaLonde, J. Ding, and M. A. Tobias, *J. Amer. Chem. Soc.*, **89**, 6651 (1967); (b) R. J. Ouellette, R. D. Robins, and A. South, *ibid.*, **90**, 1619 (1968); (c) K. B. Wiberg and G. Szeimies, *ibid.*, **90**, 4195 (1968), and references cited.

is achieved be column chromatography (Florisil or silica gel) or preparative tlc or by combination of these techniques.

Diisobutyl Ketone Enol Acetate (1). A solution of 20 g of diisobutyl ketone in 400 ml of acetic anhydride and 5 g of *p*-toluenesulfonic acid (TsOH) was heated at reflux temperature for 5 hr, with slow distillation of the solvent. The cooled solution was carefully poured into 500 ml of 5% sodium bicarbonate–water solution. The product was extracted with methylene chloride and washed with water. After drying and distillation of the solvent, the crude material was purified by distillation. The product, obtained in 56% yield, is a mixture of cis and trans enol acetates **1** as indicated by its nmr spectrum: liquid, bp 171°; ν_{max} 1760 and 1715 cm^{-1}; nmr 0.90 (4 Me), 2.10 (OAc), 4.83 ppm (d, J = 10 Hz, vinylic H).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.63; H, 10.67.

1-Isobutyl-3-isopropyl-2,2-difluorocyclopropan-1-ol Acetate (2). A solution of 115 g (0.75 mol) of sodium chlorodifluoroacetate in 200 ml of anhydrous diglyme was added dropwise over the lapse of 4 hr to a solution of 14 g (0.075 mol) of diisobutyl ketone enol acetate (**1**) in 60 ml of dry diglyme. The cooled reaction mixture was filtered to remove the insoluble salts and the liquid was concentrated *in vacuo* to give 1-isobutyl-3-isopropyl-2,2-difluorocyclopropan-1-ol acetate (**2**) (40% yield), which appeared by nmr to be a 2:1 mixture of stereochemical isomers: liquid; ν_{max} 1760 cm^{-1}; nmr 0.96 (4 Me), 2.03 (OAc), ~3.26 and 3.76 ppm (mixture of cyclopropyl H); mass spectrum *m/e* 219 ($M^+ - CH_3$), 177 ($M^+ - C_4H_9$).

Anal. Calcd for $C_{12}H_{20}O_2F_2$: C, 61.51; H, 8.60; F, 16.21. Found: C, 61.89; H, 8.27; F, 15.37.

Treatment of Adduct (2) with Sodium Hydroxide. A solution of 5 g of adduct **2** in 100 ml of 1% ethanolic sodium hydroxide solution was gently refluxed for 1 hr. Dilution with water, extraction with methylene chloride, drying, and evaporation of the solvents afforded a mixture of two compounds, which were separated by preparative tlc. The less polar product, isolated in 12% yield, corresponded to the cis conjugated ketone **3**: colorless oil; λ_{max} 234 nm (ϵ 4070); ν_{max} 1740, 1710, and 1640 cm^{-1}; nmr 0.97 (4 Me), 5.45 ppm (pair of d, J_{HF} = 23 Hz, J_{HH} = 10 Hz, vinylic H); mass spectrum *m/e* 172 (M^+), 129 ($M^+ - C_3H_7$), 85 (C_4H_9CO), 57 (C_4H_9).

Anal. Calcd for $C_{10}H_{17}OF$: C, 69.76; H, 9.88; F, 11.04. Found: C, 69.58; H, 9.94; F, 10.97.

The second product, isolated in 43% yield, corresponded to the trans enone **4**: amorphous; λ_{max} 232 nm (ϵ 9950); ν_{max} 1740, 1695, and 1650 cm^{-1}; nmr 0.93, 1.05 (superimposed d, J_{HH} = 7 Hz, 4 Me), 5.85 ppm (pair of d, J_{HF} = 35 Hz, J_{HH} = 10 Hz, vinylic H); mass spectrum *m/e* 172 (M^+), 157 ($M^+ - CH_3$), 129 ($M^+ - C_3H_7$), 115 ($M^+ - C_4H_9$), 85 (C_4H_9CO).

Anal. Calcd for $C_{10}H_{17}OF$: C, 69.76; H, 9.88; F, 11.04. Found: C, 69.61; H, 9.96; F, 11.26.

5-Methoxy-1-tetralone Enol Acetate (6a). A solution of 25 g of 5-methoxy-1-tetralone (**5a**) in isopropenyl acetate containing 4 g of PTS was distilled slowly through a Vigreux column for 18 hr. The reaction mixture was cooled to room temperature, and then poured into a saturated sodium bicarbonate–water solution. Extraction with benzene followed by usual work-up gave an amorphous residue which was chromatographed on Florisil. Elution with methylene chloride–hexane (1:1) furnished 29 g of 5-methoxy-1-tetralone enol acetate (**6a**): amorphous; λ_{max} 264 nm (ϵ 8800); ν_{max} 1770, 1580, 1520, and 1240 cm^{-1}; nmr 2.26 (OAc), 3.80 (OMe), 5.73 (t, J = 4 Hz, 2-H), 6.60–7.33 ppm (aromatic H). This unstable material was directly allowed to react with difluorocarbene.

6-Methoxy-1-tetralone enol acetate (6b) was prepared as described for **6a**. Compound **6b** showed: amorphous; λ_{max} 272 nm (ϵ 14,130); ν_{max} 1750, 1650, 1600 and 1240 cm^{-1}; nmr 2.28 (OAc), 3.80 (OMe), 5.53 (t, J = 4 Hz, 5-H), 6.60–7.10 ppm (aromatic H). This unstable compound was immediately reacted with difluorocarbene.

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene enol acetate (12) was prepared from ketone **11**[36] by the above described procedure. Compound **12** exhibited the following properties: amorphous; λ_{max} 224, 274 nm (ϵ 19,320, 3500); ν_{max} 1760, 1650, and 1220 cm^{-1}; nmr 2.23 (OAc), 5.40 (t, J = 4 Hz, 5-H), 6.73 (d, J = 5 Hz, 3-H), 6.98 ppm (d, J = 5 Hz, 2-H). This unstable substance was immediately used for the next step.

Difluorocarbene Addition to 5-Methoxy-1-tetralone Enol Acetate (6a). A solution of 522 g (3.9 mol) of sodium chlorodifluoroacetate in 1200 ml of diglyme was added dropwise, in a period of 5 hr, to a solution of 40 g (180 mmol) of **6a** in 300 ml of diglyme at reflux. After usual work-up, the methylene chloride extract was evaporated and chromatographed on Florisil. Elution with ether–hexane (19:1) gave 300 g of an oil, purified by preparative tlc (ether–hexane, 1:24), affording the ether **8a**: amorphous; λ_{max} 246, 276, 283, 304, 348, 364 nm (ϵ 6610, 2510, 2675, 870, 760, 710); ν_{max} 1670, 1635, and 1590 cm^{-1}; nmr 3.79 (OMe), 6.17 (pair of d, J_{HF} = 72 Hz, $OCHF_2$), 7.70–7.26 ppm (aromatic H); mass spectrum *m/e* 276 (M^+), 226 ($M^+ - CF_2$), 248 ($M^+ - C_2H_4$), 51 (CHF_2^+).

Anal. Calcd for $C_{13}H_{12}OF_4$: C, 56.53; H, 4.38; F, 27.50. Found: C, 56.44; H, 4.59; F, 26.89.

Further elution gave 54.2 g of 1-acetoxy-5-methoxy-1,2-difluoromethylene-1,2,3,4-tetrahydronaphthalene (**7a**): colorless oil; λ_{max} 274 nm (ϵ 1860); ν_{max} 1760, 1590, and 1220 cm^{-1}; nmr 2.16 (OAc), 3.80 (OMe), 6.70–7.36 ppm (aromatic H).

Anal. Calcd for $C_{14}H_{14}O_3F_2$: C, 62.67; H, 5.26; F, 14.17. Found: C, 62.80; H, 5.41; F, 13.88.

Difluorocarbene Addition to 6-Methoxy-1-tetralone Enol Acetate (6b). A solution of 419.3 g (2.75 mol) of sodium chlorodifluoroacetate in 750 ml of anhydrous diglyme was added dropwise for 4 hr to 12 g (55 mmol) of **6b** in 200 ml of diglyme at reflux. Work-up as usual, followed by chromatography on Florisil, furnished two compounds. Elution with hexane–ether (19:1) gave 200 mg of the difluoromethyl ether **8b**: colorless oil; λ_{max} 232, 277, 284 nm (ϵ 12,600, 1800, 1700); ν_{max} 1610 and 1580 cm^{-1}; nmr 3.76 (OMe), 6.19 (pair of d, J_{HF} = 72 Hz, $OCHF_2$), 6.68–7.54 ppm (aromatic H); mass spectrum *m/e* 276 (M^+), 226 ($M^+ - CF_2$), 248 ($M^+ - C_2H_4$), 209 ($M^+ - OCHF_2$), 51 (CHF_2^+).

Anal. Calcd for $C_{13}H_{12}OF_4$: C, 56.53; H, 4.38. Found: C, 56.73; H, 4.56.

Further elution gave 11 g of 1-acetoxy 6-methoxy-1,2-difluoromethylene-1,2,3,4-tetrahydronaphthalene (**7b**): amorphous; λ_{max} 232, 278 nm (ϵ 11,220, 1862); ν_{max} 1760, 1605, and 1575 cm^{-1}; nmr 2.15 (OAc), 3.78 (OMe), 6.60–7.43 ppm (aromatic H).

Anal. Calcd for $C_{14}H_{14}O_3F_2$: C, 62.67; H, 5.26; F, 14.17. Found: C, 62.53; H, 5.51; F, 14.02.

Difluorocarbene Addition to 4-Keto-4,5,6,7-tetrahydrothianaphthene Enol Acetate (12). Sodium chlorodifluoroacetate (274.5 g, 1.8 mol) in 750 ml of anhydrous diglyme was added dropwise to a boiling solution of 14 g (72 mmol) of **12** in diglyme. After the usual procedure, the resulting product was chromatographed on Florisil. Elution with hexane–methylene chloride (1:9) afforded 170 mg of an oil which was purified by preparative tlc (ether–hexane, 1:24), yielding 100 mg of analytically pure 4,5-difluoromethylene-4,5,6,7-tetrahydrothianaphthene difluoromethyl ether (**13b**): amorphous; λ_{max} 236 nm (ϵ 5625); ν_{max} 1470 and 1445 cm^{-1}; nmr 6.26 (pair of d, J_{HF} = 72 Hz, $OCHF_2$), 7.14 ppm (aromatic H); mass spectrum *m/e* 252 (M^+), 224 ($M^+ - C_2H_4$), 202 ($M^+ - CF_2$), 51 (CHF_2^+).

Anal. Calcd for $C_{10}H_8OF_4S$: C, 47.66; H, 3.20; S, 12.72. Found: C, 47.89; H, 3.46; S, 12.84.

Further elution with hexane–methylene chloride (1:4) gave 13 g of 4-acetoxy-4,5-difluoromethylene-4,5,6,7-tetrahydrothianaphthene (**13a**). Recrystallization from ether–hexane afforded the pure sample: mp 54–55°; λ_{max} 236 nm (ϵ 6310); ν_{max} 3050, 1770, and 1210 cm^{-1}; nmr 2.18 (OAc), 6.97 (d, J = 5 Hz, 3-H), 7.13 ppm (d, J = 5 Hz, 2-H).

Anal. Calcd for $C_{11}H_{10}O_2SF_2$: C, 54.14; H, 4.13; S, 13.14. Found: C, 54.33; H, 4.28; S, 12.80.

Hydrolysis of 7a with Methanolic Sodium Hydroxide. A solution of 39 g of **7a** in 500 ml of 5% sodium hydroxide was allowed to reflux for 30 min. The reaction mixture was cooled to room temperature, poured into ice–water, neutralized with 5% hydrochloric acid, and extracted with ethyl acetate. The crude product which was obtained was chromatographed on silica gel. Elution with hexane–ethyl acetate (9:1) afforded 7,7-difluoro-11-methoxy-2,3-benzosuberone (**9a**) (10 g). The analytical sample was prepared by recrystallization from ether–hexane: mp 62–64°; λ_{max} 260, 314 nm (ϵ 5400, 1500); ν_{max} 1710 and 1590 cm^{-1}; nmr 2.90–3.13 (benzylic H), 3.88 (OMe), 6.86–7.33 ppm (aromatic H).

Anal. Calcd for $C_{12}H_{12}O_2F_2$: C, 63.71; H, 5.34. Found: C, 63.84; H, 5.52.

Further elution with hexane–ethyl acetate (3:7) yielded 16 g of 11-methoxy-2,3-benztropone (**10a**). Recrystallization from ether–hexane afforded the analytical sample: mp 52–54°; λ_{max} 234, 284 nm (ϵ 22,750, 6600); ν_{max} 1640 and 1580 cm^{-1}; nmr 3.95 (OMe), 6.67 (m, J_1 = 12 Hz, J_2 = 7 Hz, 6-H), 6.85 (dd, J = 12 Hz, 7-H), 7.00 (dd, J_1 = 7 Hz, J_2 = 1.5 Hz, 4-H), 7.06 (m, J_1 = 12 Hz, J_2 = 7 Hz, 5-H), 7.14 (dd, J_1 = 8.5 Hz, J_2 = 1 Hz, 10-H), 7.56 (t, J = 7.5 Hz, 9-H), 8.00 ppm (d, J = 12 Hz, 8-H); mass spectrum *m/e* 186 (M^+), 158 ($M^+ - CO$), 143 ($M^+ - C_2H_3O$), 115 (C_9H_7).

(36) L. F. Fieser and R. G. Kennelly, *J. Amer. Chem. Soc.*, 57, 1611 (1935).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.48; H, 5.67.

Treatment of 7b with methanolic sodium hydroxide was carried out essentially as described for **7a** to give **9b** and **10b**. The analytical sample of 7,7-difluoro-10-methoxy-2,3-benzosuberone (**9b**), obtained by recrystallization from ether–pentane, provided the pure sample: mp 46–47°; λ_{max} 230, 286 nm (ϵ 9550, 10,700); ν_{max} 1700 and 1600 cm^{-1}; nmr 2.90–3.16 (benzylic H), 3.86 (OMe), 6.75–7.86 ppm (aromatic H).

Anal. Calcd for $C_{12}H_{12}O_2F_2$: C, 63.71; H, 5.34; F, 16.80. Found: C, 63.79; H, 5.53; F, 16.58.

Recrystallization of 10-methoxy-2,3-benztropone (**10b**)[37] from methanol gave the analytical sample: mp 73–74°; λ_{max} 230, 276 nm (ϵ 24,350, 34,670); ν_{max} 1640, 1605, and 1575 cm^{-1}; nmr 3.96 (OMe), 6.33–8.13 ppm (aromatic H).

Base treatment of 13a was carried out as above. The analytical sample of 7,7-difluorothiophenosuberone (**14**) presented: amorphous; λ_{max} 224, 260 nm (ϵ 7812, 5720); ν_{max} 1690 and 1530 cm^{-1}; nmr 3.04–3.18 (benzylic H), 7.35 (d, $J_{8,9}$ = 6 Hz, 9-H), 7.42 ppm (d, $J_{8,9}$ = 6 Hz, 8-H); mass spectrum *m/e* 202 (M$^+$), 137 (M$^+$ − HC_2F_2), 110 (M$^+$ − $C_4H_6F_2$).

Anal. Calcd for $C_9H_8OF_2S$: C, 53.52; H, 3.99; S, 15.87. Found: C, 53.24; H, 4.17; S, 15.79.

The pure sample of 2,3-thiophentropone (**15**) showed: mp 46–47°; λ_{max} 238, 241, 324, 346, 360 nm (ϵ 21,380, 21,630, 8710, 7690, 6890); ν_{max} 1620, 1565, and 1505 cm^{-1}; nmr 6.23 (octet, $J_{5,4}$ = 11 Hz, $J_{5,6}$ = 6.5 Hz, $J_{5,7}$ = 2 Hz, 5-H), 6.99 (m, $J_{4,5}$ = 11 Hz, $J_{4,6}$ = 2 Hz, 4-H), 7.06 (m, $J_{6,7}$ = 11 Hz, $J_{5,6}$ = 6.5 Hz, $J_{4,6}$ = 2 Hz, 6-H), 7.48 (m, $J_{6,7}$ = 11 Hz, $J_{5,7}$ = 2 Hz, 7-H), 7.78 (d, $J_{8,9}$ = 6 Hz, 9-H), 7.92 ppm (d, $J_{8,9}$ = 6 Hz, 8-H).

Anal. Calcd for C_9H_6OS: C, 66.72; H, 3.73; S, 19.92. Found: C, 66.76; H, 3.74; S, 19.70.

Treatment of 7b with Ammonium Hydroxide. A mixture of 2 g of **7b**, dioxane (17.5 ml), and ammonium hydroxide (25 ml) was stirred at room temperature for 3.5 hr. The reaction mixture was poured into ice–water, neutralized with 5% aqueous hydrochloric acid, and extracted with ethyl acetate, thus affording an amorphous material which was purified by tlc (1:19, dioxane–benzene).

There was isolated 10-methoxy-7-fluoro-2,3-benzosuber-2-en-1-one (**16**) (160 mg, 12%) which after recrystallization from ether–pentane gave the analytical sample: mp 52–55°; λ_{max} 240, 312 nm (ϵ 12.590, 9035); ν_{max} 1640 and 1595 cm^{-1}; nmr 2.40–2.61 (m, 5-H), 2.94–3.06 (m, 4-H), 3.85 (OMe), 6.46 (m, J_{H_6F} = 20.5 Hz, $J_{6,5}$ = 5.5 Hz, 6-H), 6.66 (d, $J_{11,9}$ = 2.5 Hz, 11-H), 6.82 (dd, $J_{9,8}$ = 9 Hz, $J_{9,11}$ = 2.5 Hz, 9-H), 7.92 ppm (d, $J_{8,9}$ = 9 Hz, 8-H); mass spectrum *m/e* 206 (M$^+$), 178 (M$^+$ − CO), 163 (M$^+$ − C_2H_3O), 133 (M$^+$ − C_3H_2OF).

Anal. Calcd for $C_{12}H_{11}O_2F$: C, 69.97; H, 5.38; F, 9.22. Found: C, 69.78; H, 5.49; F, 9.35.

In addition, there was isolated 1.62 g (84%) of recovered starting material **7b**.

When this reaction was repeated for 16 hr under identical conditions, there was obtained 207 mg (14%) of **16** and 490 mg (29%) of **9b**: mp 45–47°; λ_{max} 228, 286 nm (ϵ 9770, 9120); ν_{max} 1700 and 1600 cm^{-1}; shown to be identical with an authentic sample by mixture melting point and ir and tlc analysis. Moreover, there was also isolated 100 mg (7%) of **10b**: mp 66–68°; λ_{max} 230, 276 nm (ϵ 19,500, 27,540); ν_{max} 1640, 1605, and 1575 cm^{-1}; identified by direct comparison (mixture melting point, tlc, and ir spectrum) with an authentic sample.

Treatment of 16 with methanolic sodium hydroxide was carried out essentially as described above for **7a** to give **10b**: mp 68–69°; λ_{max} 230, 276 nm (ϵ 20,420, 27,540); ν_{max} 1640, 1605, and 1575 cm^{-1}; the usual criteria (tlc, ir, and mixture melting point) showed this substance to be identical with an authentic sample (see above).

Zinc Treatment of 9b. A mixture of 2 g of **9b**, cupric acetate (200 mg), and zinc dust (4 g) in acetic acid (80 ml) was stirred at room temperature for 90 min.[38] The reaction mixture was filtered on Celite and then extracted with methylene chloride. Usual work-up afforded a mixture of two compounds which were separated by tlc (dioxane–benzene, 1:49).

After recrystallization from ether–pentane, there was obtained 745 mg (40.5%) of 7-fluoro-10-methoxy-2,3-benzosurberone (**9c**): mp 46–47°; λ_{max} 216, 254, 310 nm (ϵ 16,870, 6165, 2240); ν_{max} 1705 and 1590 cm^{-1}; nmr 2.20–2.60 (m, 5-H, 6-H), 2.90–3.20 (m, 4-H), 3.80 (OMe), 5.23 (m, J_{HF} = 50 Hz, J_{HH} = 6.5 Hz, 6-H), 6.90–7.33 ppm (aromatic H); mass spectrum *m/e* 208 (M$^+$), 180 (M$^+$ − CO), 149 (M$^+$ − $C_2H_3O_2$), 91 ($C_7H_7^+$).

Anal. Calcd for $C_{12}H_{13}O_2F$: C, 69.30; H, 6.30. Found: C, 69.18; H, 6.64.

The second product (940 mg, 56%) corresponded to the 10-methoxybenzosuberone (**9d**). The analytical sample was obtained by recrystallization from ether–pentane: mp 58–59°; λ_{max} 215, 252, 300 nm (ϵ 18,200, 6310, 2345); ν_{max} 1680 and 1580 cm^{-1}; nmr 1.66–2.90 (m, 6-H, 7-H), 2.60–2.80 (m, 5-H), 2.86–3.16 (m, 4-H), 6.90–7.33 ppm (aromatic H); mass spectrum *m/e* 190 (M$^+$).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.73; H, 7.63.

When the same reaction was effected for 24 hr the yield of **9d** was increased to 95%.

Preparation of 2α,3α-Difluoromethylene-3β,17β-dihydroxy-5α-androstane Diacetate (18). A solution of 130 g (0.85 mol) of sodium chlorodifluoroacetate in 260 ml of anhydrous diglyme was added dropwise during 3 hr to a refluxing solution of 5 g (13.4 mmol) of 3β,17β-dihydroxy-5α-androst-2-ene diacetate (**17**): mp 173–174°; [α]D +40°,[39] in 125 ml of diglyme under the usual conditions (see above). After concentration of the mixture *in vacuo* the ether–hexane solution of the resulting brown syrup was filtered through alumina–charcoal and evaporated. Recrystallization from methylene chloride–methanol gave the pure difluoromethylene adduct **18** (2.48 g): mp 197–199°; [α]D −5°; ν_{max} 1760 and 1730 cm^{-1}; nmr 0.80 (18-H), 0.88 (19-H), 2.25 ppm (3- and 17-OAc).

Anal. Calcd for $C_{24}H_{34}O_4F_2$: C, 67.87; H, 8.07; F, 8.95. Found: C, 68.08; H, 7.71; F, 8.69.

Reaction of 18 with methanol–potassium hydroxide was carried out as above. Recrystallization from methylene chloride–hexane afforded the pure sample (1.58 g, 79%) of 3,3-difluoro-17β-hydroxy-*A*-homo-5α-androstan-4-one (**19a**): mp 153–155°; [α]D +71°; CD (dioxane) $[\theta]_{353}$ ±0°; $[\theta]_{306}$ +5310°; $[\theta]_{245}$ ±0°; ν_{max} 3450 and 1744 cm^{-1}; nmr 0.74 (18-H), 0.88 (19-H), 1.5 (17-OH), 3.6 ppm (m, 17α-H); mass spectrum *m/e* 340 (M$^+$), 325 (M$^+$ − Me), 281 (M$^+$ − CH_2CH_2CHOH + H).

Anal. Calcd for $C_{20}H_{30}O_2F_2$: C, 70.55; H, 8.88; F, 11.16. Found: C, 70.56; H, 8.71; F, 11.25.

Acid Hydrolysis of 18. To 100 mg of **18** dissolved in 3 ml of absolute ethanol, 0.07 ml of 70% perchloric acid was added. The reaction mixture was stirred at room temperature for 16 hr. It was then poured into water and extracted with ethyl acetate. The crude extract was purified by preparative tlc (hexane–ethyl acetate, 9:1). After recrystallization from methylene chloride–hexane, there was obtained 60 mg of the *A*-homo-17β-acetate **19b**: mp 130–131°; [α]D +52°; ν_{max} 1745 and 1730 cm^{-1}; nmr 0.77 (18-H), 0.84 (19-H), 2.0 (OAc), 4.57 ppm (t, $J_{16,17}$ = 8 Hz, 17α-H).

Anal. Calcd for $C_{22}H_{32}O_3F_2$: C, 69.08; H, 8.43; F, 9.93. Found: C, 68.72; H, 8.30; F, 10.12.

Compound **19b** was also obtained by acetylation of **19a**.

Reaction of 19a with Acetic Anhydride. Treatment of 4 g of **19a** with 120 ml of acetic anhydride and 2.4 gof TsOH at reflux temperature for 8 hr was followed by extraction with ethyl acetate.

The reaction mixture was separated by preparative tlc. Two products were obtained. The less polar compound was the enol acetate **21** (50%).

Recrystallization of **21** from methylene chloride–methanol gave the pure enol acetate **21**: mp 166–169°; [α]D +52°; ν_{max} 1760 and 1730 cm^{-1}; nmr 0.78 (18-H), 0.89 (19-H), 2.01 (17-OAc), 2.16 (4-OAc), 4.60 (t, J = 7 Hz, 17α-H), 5.25 ppm (t, J = 4 Hz, 4a-H).

Anal. Calcd for $C_{24}H_{34}O_4F_2$: C, 67.77; H, 8.07; F, 9.16. Found: C, 68.00; H, 8.05; F, 9.30.

The more polar product (6%) was assigned structure **20**. After recrystallization from methylene chloride–hexane, compound **20** showed: mp 169–170°; [α]D +36°; λ_{max} 247, 254 nm (ϵ 9800, 10,000); ν_{max} 1765, 1740, and 1700 cm^{-1}; nmr 0.80 (18-H), 1.04 (19-H), 2.0 (17-OAc), 2.14 (4-OAc), 4.56 (m, 17α-H), 5.2 ppm (d, J = 7 Hz, 5a-H); mass spectrum *m/e* 404 (M$^+$), 362 (M$^+$ − CH_2-CO).

Anal. Calcd for $C_{24}H_{33}O_4F$: C, 71.25; H, 8.22; F, 4.69. Found: C, 71.44; H, 8.28; F, 4.89.

Alkaline Hydrolysis of the Enol Acetate 20. A solution containing 25 mg of 20 in methanol was treated with 1% sodium hydroxide at room temperature for 1 hr. The reaction mixture was diluted

(37) A. M. Khan, G. R. Proctor, and L. Rees, *J. Chem. Soc. C*, 990 (1966).

(38) (a) M. Hudlický, *Collect. Czech. Chem. Commun.*, **26**, 1414 (1961); (b) E. T. McBee, D. H. Campbell, and C. W. Roberts, *J. Amer. Chem. Soc.*, 77, 3150 (1955); (c) M. Hudlický, "Chemistry of Organic Fluorine Compounds," Pergamon Press, London, 1961, pp 264–265.

(39) J. Fajkos, *Collect. Czech. Chem. Commun.*, **23**, 1559 (1958).

with water and extracted with ethyl acetate to provide 9 mg of a product showing the typical uv and ir properties of a conjugated ketone: mp 167–175°; λ_{max} 248 nm (ϵ 11,200); ν_{max} 3450, 1675, and 1620 cm^{-1}.

Addition of Difluorocarbene to the Enol Acetate 21. A solution of 6 g of sodium chlorodifluoroacetate in 200 ml of anhydrous diglyme was added dropwise to a refluxing solution of 200 mg of compound **21** in 60 ml of diglyme. The solvent was removed *in vacuo* and the residue was purified by preparative tlc (hexane–ethyl acetate, 95:5) yielding 110 mg of starting material **21** and 75 mg of the adduct **22a** (33%). Recrystallization from methanol afforded the pure sample of **22a**: mp 258–259°; $[\alpha]D$ −50°; ν_{max} 1790 and 1740 cm^{-1}; nmr 0.77 (18-H), 0.925 (19-H), 2.00 (17-OAc), 2.07 (4-OAc), 4.65 ppm (m, 17α-H); mass spectrum *m/e* 474 (M^+), 414 (M^+ − HOAc).

Anal. Calcd for $C_{25}H_{34}O_4F_4$: C, 63.25; H, 7.22; F, 15.98. Found: C, 63.11; H, 7.38; F, 15.78.

Acid Treatment of the Difluorocyclopropyl Acetate 22a. A solution containing 50 mg of **22a** in 18 ml of methanol was refluxed for 15 min in presence of 5% hydrochloric acid. The reaction mixture was poured into cold water and extracted with ethyl acetate. After recrystallization from methylene chloride–ether, there was obtained 32 mg of the 17β-alcohol **22b**: mp 190–192°; $[\alpha]D$ −40°; ν_{max} 3300 and 1785 cm^{-1}; nmr 0.75 (18-H), 0.90 (19-H), 2.08 ppm (4-OAc); mass spectrum *m/e* 432 (M^+), 417 (M^+ − Me), 414 (M^+ − H_2O).

Anal. Calcd for $C_{23}H_{32}O_3F_4$: C, 63.81; H, 7.54; F, 11.08. Found: C, 63.85; H, 7.50; F, 10.95.

When the same reaction was performed for 40 min, the diol **22c** was obtained. Recrystallization from methylene chloride–ether gave the analytical sample: mp 204–207°; $[\alpha]D$ −13° (MeOH); ν_{max} 3450 and 3200 cm^{-1}; nmr 0.75 (18-H), 0.98 ppm (19-H); mass spectrum *m/e* 390 (M^+), 372 (M^+ − H_2O), 370 (M^+ − HF).

When the reaction mixture was refluxed for 24 hr under the same conditions, the starting material **22c** was recovered unchanged.

Acid Hydrolysis of the Difluorocyclopropanol 22c. A solution of 25 mg of **22c** in 3 ml of tetrahydrofuran was refluxed for 3 hr with 5% hydrochloric acid in aqueous tetrahydrofuran. After the usual extraction procedure, there was isolated 18 mg of 17β-hydroxy-3,3,4a,4a-tetrafluoro-*A*-bishomo-5α-androstan-4-one (**23**). Recrystallization from ether provided the analytical sample: mp 248–260° dec; $[\alpha]D$ −30°; CD (dioxane) $[\theta]_{300}$ ±0°; $[\theta]_{250}$ ±0°; $[\theta]_{219}$ −2400; ν_{max} 3500 and 1765 cm^{-1}; nmr 0.9 ppm (18 and 19-H); mass spectrum *m/e* 366 (M^+), 310 (M^+ − CF_2).

Anal. Calcd for $C_{21}H_{30}O_2F_4$: C, 64.59; H, 7.74; F, 19.46. Found: C, 64.60; H, 7.51; F, 19.56.

Addition of Difluorocarbene to 3β,17-Dihydroxy-5α-androst-16-ene Diacetate (24). The enol acetate **24**[40] (15 g, 0.402 mol) in 200 ml of diglyme was treated with a solution of 457.5 g (3.01 mol) of sodium chlorodifluoroacetate in 1500 ml of diglyme, for 6 hr. After usual work-up, the resulting brown oil was chromatographed on Florisil. Elution with hexane–methylene chloride (3:2) furnished a compound which was recrystallized from methylene chloride–methanol to afford 1.3 g of 3β,17β-dihydroxy-16α,17α-difluoromethylene-5α-androstane diacetate (**25**): mp 157–158°; $[\alpha]D$ −6°; ν_{max} 1760, 1735, and 1235 cm^{-1}; nmr 0.83 (18-H), 0.93 (19-H), 2.00, 2.08 (3- and 17-OAc), 4.66 ppm (3α-H).

Anal. Calcd for $C_{24}H_{34}O_4F_2$: C, 67.90; H, 8.07; F, 8.95. Found: C, 68.11; H, 8.07; F, 8.85.

Further elution with methylene chloride gave a crystalline product. Recrystallization from methylene chloride–methanol provided 7.5 g of 3β-hydroxy-16a-fluoro-*D*-homo-5α-androst-16(16a)-en-17-one acetate (**26a**): mp 194–195°; $[\alpha]D$ −29°; λ_{max} 234–236 nm (ϵ 7590); ν_{max} 1730, 1685, 1665, and 1240 cm^{-1}; nmr 0.83 (18-H), 1.06 (19-H), 2.02 (OAc), 4.35–5.00 (3α-H), 6.33 ppm (m, $J_{15\beta,16}$ = 3 Hz, $J_{15\alpha,16}$ = 6 Hz, J_{HF} = 15 Hz, 16-H).

Anal. Calcd for $C_{22}H_{31}O_3F$: C, 72.68; H, 8.86; F, 5.22. Found: C, 72.72; H, 8.85; F, 5.39.

Preparation of 26b from 25 was achieved as mentioned above for **7a**. The analytical sample of 3β-hydroxy-16a-fluoro-*D*-homo-5α-androst-16(16a)-en-17-one (**26b**) showed: mp 209–211°; $[\alpha]D$ −29°; λ_{max} 234 nm (ϵ 7300); ν_{max} 3400, 1690, and 1665 cm^{-1}; nmr 0.86 (18-H), 1.03 (19-H), 1.46 (OH), 3.7–3.9 (3α-H), 6.33 ppm (m, $J_{15\beta,16}$ = 3 Hz, $J_{15\alpha,16}$ = 6 Hz, J_{HF} = 15 Hz, 16-H).

Anal. Calcd for $C_{20}H_{29}O_2F$: C, 74.95; H, 9.13; F, 5.93. Found: C, 75.15; H, 9.10; F, 6.00.

Hydrolysis of 26a into 26b. Treatment of **26a** with a 2% methanolic sodium hydroxide solution followed by the usual extraction and isolation procedure afforded the 3-alcohol **26b**, shown by usual criteria to be identical with a sample obtained above.

Addition of Difluorocarbene to the Enol Acetate 27. Sodium chlorodifluoroacetate (99.5 g, 0.65 mol) in 200 ml of anhydrous diglyme was added by 25-ml portions at intervals of 30 min to a boiling solution containing 5 g (11.7 mmol) of 6,17α-dihydroxypregna-4,6-diene-3,20-dione diacetate (**27**) (mp 197–199°; λ_{max} 284 nm (ϵ 21,400))[41] in 200 ml of anhydrous diglyme. After usual work-up, the resulting product was purified by chromatography on preparative fluorescent chromatoplates. Recrystallization from acetone–hexane provided the pure sample of 6β,17α-dihydroxy-6α,7α-difluoromethylenepregn-4-ene-3,20-dione diacetate (**28**) (1.5 g): mp 208–210°; $[\alpha]D$ +11°; λ_{max} 248 nm (ϵ 13,180); ν_{max} 1770, 1730, 1680, and 1615 cm^{-1}; nmr 0.75 (18-H), 1.35 (19-H), 2.05 (21-H), 2.10 (6-OAc), 2.15 (17-OAc), 6.25 ppm (4-H).

Anal. Calcd for $C_{26}H_{32}O_6F_2$: C, 65.25; H, 6.74; F, 7.94. Found: C, 65.42; H, 6.92; F, 7.74.

Treatment of 28 with Methanolic Potassium Carbonate. A solution containing 1 g of **28** dissolved in methanol (90 ml) was treated with 10 ml of 1% aqueous potassium carbonate at room temperature for 90 min. The reaction mixture was diluted with water and extracted with ethyl acetate. The organic phase was washed with water, dried, filtered, and evaporated to give an amorphous residue which was crystallized from ethyl acetate to yield 600 mg (69%) of **29**: mp 117–119°; $[\alpha]D$ −103°; λ_{max} 262 nm (ϵ 9485); ν_{max} 1735, 1680, and 1660 cm^{-1}; nmr 0.78 (18-H), 1.28 (19-H), 2.07 (21-H), 2.14 (17-OAc), 6.25 (dd, J_1 = 26 Hz, J_2 = 4 Hz, 7-H), 6.35 ppm (4-H).

Anal. Calcd for $C_{24}H_{29}O_5F$, AcOEt: C, 66.64; H, 7.39; F, 4.56. Found: C, 66.73; H, 7.33; F, 4.76.

Difluorocarbene Addition to the *B*-Nor Steroid 30. **30**[42] in 100 ml of diglyme was treated with sodium chlorodifluoroacetate (25.5 mol) in diglyme at reflux. The reaction mixture was evaporated to dryness under high vacuum and purified by chromatography over neutral alumina. Elution with methylene chloride gave a material, which was purified by recrystallization from methylene chloride–hexane, thus providing the analytical sample, 19 g (82%) of **31a**: mp 177–178°; $[\alpha]D$ +33°; ν_{max} 1740 cm^{-1}; nmr 0.88 (18-H), 1.10 (19-H), 2.08 (OAc), 4.68 ppm (3α-H).

Anal. Calcd for $C_{21}H_{28}O_3F_2$: C, 68.82; H, 7.70; F, 10.37. Found: C, 68.87; H, 7.66; F, 10.10.

Hydrolysis of the 3-Acetate 31a into the Alcohol 31b. Compound **31a** (1.5 g) in methanol (30 ml) was hydrolyzed with 2% methanolic sodium hydroxide solution (1.3 ml). Recrystallization from methylene chloride–hexane afforded the analytical sample of **31b**: mp 166°; $[\alpha]D$ +24°; ν_{max} 3400 and 1740 cm^{-1}; nmr 0.83 (18-H), 1.0 ppm (19-H); mass spectrum *m/e* 324 (M^+).

Anal. Calcd for $C_{19}H_{26}O_2F$: C, 70.34; H, 8.08; F, 11.71. Found: C, 70.13; H, 7.96; F, 11.93.

Oxidation of the 3β-Hydroxy Derivative 31b into the Diketone 32. Compound **31b** was oxidized with Jones' reagent[20] (1.7 ml) in acetone (30 ml) at 0° for 20 min. The reaction mixture was poured into ice–water and extracted with methylene chloride, washed with water, dried, and evaporated to dryness to yield the diketone **32**. Recrystallization from methylene chloride–methanol provided 600 mg of the pure sample: mp 151–152°; $[\alpha]D$ +110°; ν_{max} 1740 and 1715 cm^{-1}; nmr 0.95 (18-H), 1.2 ppm (19-H); mass spectrum *m/e* 322 (M^+), 265 (M^+ − CH_2CH_2CO).

Anal. Calcd for $C_{19}H_{24}O_2F_2$: C, 70.71; H, 7.50; F, 11.78. Found: C, 70.77; H, 7.53; F, 11.85.

Base treatment of the diketone 32 (600 mg) at reflux with 4 ml of a 2% methanolic potassium hydroxide solution for 90 min afforded 480 mg (85%) of the diene dione **33**. Recrystallization from methylene chloride–methanol provided the analytical sample of 6-fluoroandrosta-4,6-diene-3,17-dione (**33**): mp 214–216°; $[\alpha]D$ +49°; λ_{max} 284 nm (ϵ 24,500); ν_{max} 1740, 1660, and 1610 cm^{-1}; nmr 0.93 (18-H), 1.16 (19-H), 5.76 (pair of d, J_1 = 14 Hz, J_2 = 2 Hz, 7-H), 6.1 ppm (4-H).

Anal. Calcd for $C_{19}H_{23}O_2F$: C, 75.46; H, 7.66; F, 6.28. Found: C, 75.28; H, 7.62; F, 6.48.

3α,20-Dihydroxy-5β-pregn-17(20)-ene Diacetates (34a and 34b).[22] A solution of 28 g of 3α-hydroxy-5β-pregnan-20-one in 500 ml of

(40) N. S. Leeds, D. K. Fukushima, and T. F. Gallagher, *J. Amer. Chem. Soc.*, **76**, 2943 (1954).

(41) We wish to thank Dr. St. Kaufmann, Syntex, S. A. (unpublished results), for this compound.

(42) (a) J. Joska and F. Šorm, *Collect. Czech. Chem. Commun.*, **23**, 1377 (1958); (b) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 1735 (1967).

acetic anhydride and 16.5 g of PTS was treated essentially as described for compound **1**. The residue (30 g) was purified by preparative tlc over neutral alumina (hexane–ethyl acetate, 9:1). Crystallization from methanol provided the trans enol acetate **34b**[43] in 10% yield which exhibited: mp 146–149°; $[\alpha]D$ +51°; ν_{max} 1740 cm^{-1}; nmr 0.88 (18-H), 0.93 (19-H), 1.86 (21-H), 2.01 (3-OAc), 2.08 (20-OAc), 4.72 ppm (3β-H).

Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.48; H, 9.61. Found: C, 74.31; H, 9.78.

The mother liquors of the crystalline trans enol acetate were purified by tlc and yielded 10% of the pure cis isomer **34a**[43] and 80% of the mixture. The homogeneous cis enol acetate **34a** was amorphous and showed the following constants: $[\alpha]D$ +57°; ν_{max} 1720 cm^{-1}; nmr 0.83 (18-H), 0.93 (19-H), 1.78 (21-H), 2.0 (3-OAc), 2.08 (20-OAc), 4.67 ppm (3β-H).[22]

Preparation of 3α,20-Dihydroxy-17α,20α-difluoromethylene-5β-pregnene Diacetate (36a). A solution of 20 g (15 mol equiv) of sodium chlorodifluoroacetate in 200 ml of anhydrous diglyme was added dropwise during 4 hr to a stirred solution of 3.4 g of the pure trans enol acetate **34b** in 100 ml of dry diglyme. The crude product was treated with activated charcoal to remove the color and crystallized from methylene chloride–methanol giving the trans adduct **36a**[43] in 80% yield: mp 138–140°; $[\alpha]D$ +32°; ν_{max} 1750 and 1735 cm^{-1}; nmr 0.92 (19-H), 1.0 (18-H), 1.61 (21-H), 1.99 (20-OAc), 2.00 (3-OAc), 4.70 ppm (m, 3β-H).

Anal. Calcd for $C_{26}H_{38}O_4F_2$: C, 68.99; H, 8.46; F, 8.39. Found: C, 68.97; H, 8.51; F, 8.43.

Preparation of the Cis Difluoro Adduct 35a. The corresponding cis adduct **35a**[43] of the amorphous pure cis enol acetate **34a** was prepared in the same manner and crystallized from methanol–water: mp 147–150°; $[\alpha]D$ ±0°; ν_{max} 1760 and 1740 cm^{-1}; nmr 0.92 (19-H), 0.98 (18-H), 1.41 (21-H), 2.00 (3-OAc), 2.04 (20-OAc), 4.70 ppm (m, 3β-H).

Anal. Calcd for $C_{26}H_{38}O_4F_2$: C, 68.99; H, 8.46; F, 8.39. Found: C, 68.87; H, 8.63; F, 8.62.

Acid Hydrolysis of 35a. (A) Hydrolysis of the 3-acetate **35a** with a 3% solution of perchloric acid in ethanol for 48 hr at room temperature provided the 3-hydroxy derivative **35b** in 70% yield. Recrystallization from methylene chloride–hexane afforded the analytical sample: mp 98–100°; $[\alpha]D$ −16°; λ_{max} 249–254 nm (ε 3630); ν_{max} 3220 and 1760 cm^{-1}; nmr 0.92 (19-H), 0.98 (18-H), 1.90 (OH), 2.06 ppm (21-Me).

Anal. Calcd for $C_{24}H_{36}O_3F_2$: C, 70.21; H, 8.84; F, 9.26. Found: C, 70.40; H, 8.95; F, 9.19.

(B) A solution containing 200 mg of **35a**, 2.5 ml of methanol, and 5 ml of a 5% hydrochloric acid solution in methanol was refluxed for 4 hr. The residue was purified by preparative tlc (benzene–dioxane, 98:2). The less polar fraction (82 mg, 45%) was the 3-alcohol **35b**. The second fraction corresponded to the conjugated ketone **37a** (39 mg, 25%) (see below). The most polar fraction was the diol **35c** (70 mg, 43%): mp 113–115°; $[\alpha]D$ −21°; ν_{max} 3350 cm^{-1}; nmr 0.90 (18-H), 0.96 (19-H), 1.30 (21-H), 2.03 ppm (20-OH); mass spectrum *m/e* 366 (M^+), 350 ($M^+ - H_2O$).

Anal. Calcd for $C_{22}H_{34}O_2F_2$: C, 71.72; H, 9.30. Found: C, 71.92; H, 9.49.

(C) A solution containing 200 mg of **35a** in 2.5 ml of methanol was added to 5 ml of a 5% hydrochloric acid solution in methanol. The reaction mixture was left at 40° for 26 hr. After extraction and evaporation of the solvent, the residue was purified by preparative tlc as above. There was isolated 70 mg (45%) of compound **37a** (*vide infra*), and 75 mg (46%) of the diol **35c** (see above).

Preparation of the Trans Enone 37a, Its Cis Isomer 37b, and the Difluoro Ketone 38. (A) **35a** (3 g) was refluxed for 1 hr with 30 ml of 2% sodium hydroxide in methanol. Chromatography on Florisil gave 5% of 3α-hydroxy-20-fluoro-21-methyl-5β-pregn-*cis*-17(20)-en-21-one (**37b**) which was recrystallized from methylene chloride–hexane: mp 176–177°; $[\alpha]D$ +93°; λ_{max} 252 nm (ε 9772); ν_{max} 3250 1705, and 1625 cm^{-1}; nmr ($CDCl_3$) 0.94 (18-H, 19-H), 2.24 (d, J_{HF} = 5.5 Hz, 22-H), 3.62 ppm (m, 3β-H); (benzene-d_6) 0.78 (18-H, 19-H), 2.02 (d, J_{HF} = 5 Hz, 22-H), 3.30 ppm (m, 3β-H).

Anal. Calcd for $C_{22}H_{33}O_2F$: C, 75.82; H, 9.54; F, 5.45. Found: C, 75.90; H, 9.34; F, 5.70.

The second compound, isolated in 48% yield, corresponded to the trans derivative **37a**. Recrystallization from methylene chloride–hexane afforded the analytical sample: mp 150–151°; $[\alpha]D$ +39°; λ_{max} 250 nm (ε 12,880); ν_{max} 3250, 1705, and 1625 cm^{-1}; nmr ($CDCl_3$) 0.95 (18-H, 19-H), 2.23 ppm (d, J_{HF} = 5.5 Hz, 22-H), 3.62 ppm (m, 3β-H); (benzene-d_6) 0.79 (18-H, 19-H), 2.03 (d, J_{HF} = 5 Hz, 22-H), 3.38 ppm (3β-H).

Anal. Calcd for $C_{22}H_{33}O_2F$: C, 75.82; H, 9.54; F, 5.45. Found: C, 76.02; H, 9.37; F, 5.56.

The third substance, isolated in 13% yield, corresponded to the difluoro ketone **38**. Recrystallization from methylene chloride–hexane gave the pure sample: mp 149–150°; $[\alpha]D$ +2°; CD (dioxane) $[\theta]_{345}$ ±0°; $[\theta]_{302}$ +1350; $[\theta]_{250}$ ±0°; ν_{max} 3250 and 1750 cm^{-1}; nmr ($CDCl_3$) 0.82 (t, *J* = 2 Hz, 18-H), 0.92 (19-H), 2.26 (t, *J* = 1.5 Hz, 22-H), 3.60 ppm (m, 3β-H); (benzene-d_6) 0.77 (19-H), 0.83 (t, *J* = 1.5 Hz, 18-H), 1.88 (t, *J* = 1.0 Hz, 22-H), 3.37 ppm (m, 3β-H).

Anal. Calcd for $C_{22}H_{34}O_2F_2$: C, 71.70; H, 9.30; F, 10.31. Found: C, 71.44; H, 9.16; F, 10.30.

(B) **35a** (114 mg) was dissolved in 2 ml of a 2% methanolic sodium hydroxide solution. The mixture was gently refluxed for 1 hr. The reaction mixture was concentrated *in vacuo* and extracted with ethyl acetate. Preparative tlc with hexane–ethyl acetate (9:1) yielded 2 mg of the cis compound **37b** and 100 mg of the trans derivative **37a**.

(C) **35a** (15 mg) and 1.5 ml of a 2% sodium hydroxide solution in methanol–water (94:6) were refluxed for 1 hr. The following compounds were isolated: 2 mg of the difluoro ketone **38** and 8 mg of the trans enone **37a**.

Base Treatment of 35b. A solution of 500 mg of **35b** and 100 mg of sodium hydroxide in 5 ml of methanol was heated at reflux for 30 min. There was obtained 120 mg (28%) of 3α-hydroxy-20-fluoro-21-methyl-5β-pregn-*cis*-17(20)-en-21-one (**37b**), which after recrystallization from acetone–hexane exhibited: mp 173–174°; $[\alpha]D$ +90°; λ_{max} 252 nm (ε 9740); ν_{max} 3250, 1710, and 1630 cm^{-1}; undepressed on admixture with an authentic sample (see above).

Second, 3α-hydroxy-20,20-difluoro-21-methyl-5β-pregnan-21-one (**38**) (50 mg; 12%) was isolated which was crystallized from ether–hexane: mp 149–151°; ν_{max} 3250 and 1740 cm^{-1}; undepressed on admixture with an authentic sample.

Third, 3α-hydroxy-20-fluoro-21-methyl-5β-pregn-*trans*-17(20)-en-21-one (**37a**) (220 mg; 52%) was obtained, which was recrystallized from ether–hexane: mp 148–150°; $[\alpha]D$ +41°; λ_{max} 250 nm (ε 12,590); ν_{max} 3250, 1705, and 1630 cm^{-1}; undepressed on admixture with an authentic sample (*vide supra*).

Hydrolysis of 36a into the 3β-Alcohol 36b. **36a** (100 mg) with 2 ml of 5% hydrochloric acid in acetone was stirred at room temperature for 20 hr. Recrystallization from acetone afforded the analytical sample of the alcohol **36b**, in 72% yield: mp 173–174°; $[\alpha]D$ +9° (dioxane); ν_{max} 3300 and 1760 cm^{-1}; nmr 0.9 (19-H), 1.0 (18-H), 2.03 (20-OAc), 2.06 (21-CH_3), ~3.40–3.76 ppm (3β-H); mass spectrum *m/e* 410 (M^+).

Anal. Calcd for $C_{24}H_{36}O_3F_2$: C, 70.21; H, 8.83. Found: C, 70.02; H, 8.93.

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(43) Compound **34a**, in which the acetate moiety is situated close to the 18-methyl group, is called cis. In its trans isomer **34b** the large acetoxy grouping is remote from the angular methyl. The same nomenclature applies to the corresponding difluoromethylene adducts **35** and **36**.