Chemistry of Steroidal Tetrafluorocyclopropyl Enol Acetates[1]

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The chemical behavior of the α-tetrafluorocyclopropyl enol acetates **2** and **3** is reported. Treatment of these compounds with sodium hydroxide in methanol yields the rearranged cyclic product **6** as well as acyclic esters and ortho esters, depending on the reaction conditions. The structural and stereochemical assignments and spectral properties of the resulting new compounds are discussed.

Recently, a novel acyl migration was reported[2] which occurred during the course of difluorocarbene addition[3] to the ethynyl side chain of 17β-acetoxy-17α-ethynyl estratriene and androstane derivatives **1A** and **1B** (R = $COCH_3$) leading to the isomeric tetrafluorocyclopropyl enol acetates **2** and **3**. In this work we wish to report the unusual behavior of the tetrafluorocyclopropane system of adducts **2** and **3**.

To confirm that adducts **2** and **3** are indeed geometrical isomers,[2] we attempted to hydrolyze these compounds under a variety of alkaline conditions. The enol acetate moiety, however, turned out to be more resistant to alkaline treatment than the tetrafluorocyclopropyl group. As reported previously,[2] sodium hydroxide treatment of **2** and **3** in acetone, for example, gave the conjugated dienes **4** and **5**, resulting from the elimination of hydrogen fluoride (Chart I).

Hydrolysis of **2A** and **2B** with sodium hydroxide in aqueous methanol at room temperature afforded a major product **6** (*ca.* 40%), in which two of the fluorines were replaced by methoxyl groups. Two minor products, the open-chain unsaturated esters **8** (*ca.* 20%) and **9** (*ca.* 20%), were also isolated. Hydrolysis of the enol acetate **3B** under these conditions also provided compounds **6B** and **9B**, thus supporting the geometrical isomeric relationship between **2** and **3**.

The isolation of compound **8** from the hydrolyses of **2** and **4** and the absence of the geometric isomer of **8** among the hydrolysis products of **3** may indicate that the enol acetate is sterically more hindered in **2** and **4** than in **3**.

The structural assignment of the hydrolysis products **6A** and **6B** is based on the following physical and chemical evidence. The mass spectra of **6A** and **6B** (R = H) exhibited molecular ions of 434 and 440 mass units, respectively. They also showed fragment ions derived from the consecutive and combined losses of CH_3, CH_3OH, and HF, the expected cleavage products of the steroid skeletons, and weak but diagnostically significant fragment ions of *m/e* 344 and 350 ($M^+ - CH_3OCOOCH_3$), respectively. In the nmr spectra, in addition to the expected signals due to the protons on rings A and B, both compounds exhibited resonances corresponding to two nearly equivalent methoxyl groups. These results indicate that hydrolysis of the enol acetate was accompanied by the exchange of two fluorines with methoxyl groups, presumably *via* a successive elimination–addition mechanism[4] (*vide infra*).

The ^{19}F nmr spectrum of **6B** (R = p-BrC_6H_4CO) consists of the AB part of an ABX system with the following coupling constants: J_{AB} = 242.5 Hz, J_{AX} = 5.9 Hz, and J_{BX} = 1.6 Hz. The magnitude of J_{AB} is in good agreement with the expected value for geminal fluorines on a five-membered ring[5] while it is too high[6] for *gem*-difluorocyclopropyl derivatives.

In the low-field region of the pmr spectra both **6A** and **6B** exhibit a narrow doublet centered at 5.03 ppm (vinylic H) which is coupled (J = 1.5 Hz) to a proton which resonates in the 2.0-ppm region (C-17 H) as shown by double resonance experiments. This signal was absent in the spectrum of the hydrolysis product when **2B** (R = $COCH_3$) was treated with sodium deuterioxide in methanol-*O-d* yielding **7B** (R = H). This compound was shown to contain two deuteriums by mass spectrometric analysis. The AX and BX couplings in the ^{19}F nmr spectrum of **7B** (R = H) were also absent, showing only the AB pattern (J_{FF} = 245 Hz) of the geminal fluorines.

The deuteriums in **7B** (R = H) were unaffected by treatment with boiling alkaline methanol, and correspondingly no deuteriums could be incorporated onto a carbon atom in **6B** under base-catalyzed exchange conditions. This indicates the absence of any deuterium or hydrogen which is activated by enolization.

In the ir spectrum both **6A** and **6B** exhibited a strong absorption at 1660 cm^{-1} due to the double bond stretching of an enol ether moiety. Compound **6B** (R = H) was recovered unchanged when treated with sodium borohydride or lithium aluminum hydride. It is evident, therefore, that compound **6** contains no carbonyl function, which implies that the initial hydrolysis product of the enol acetate must have rearranged in forming **6**. This is further supported by the observation that **6B** (R = H) is unaffected by heating with sodium hydroxide in methanol, proving that it is not an intermediate in the formation of **8** and **9**, both of which could be derived from the expected cyclopropyl ketone.

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(1) Contribution No. 387 from the Institute of Organic Chemistry, Syntex Research.

(2) E. Velarde, P. Crabbé, A. Christensen, L. Tökés, J. W. Murphy, and J. H. Fried, *Chem. Commun.*, 725 (1970).

(3) For previous parts in this series see P. Crabbé, R. Grezemkovsky, and L. H. Knox, *Bull. Soc. Chim. Fr.*, 789 (1968); P. Crabbé, P. Anderson, and E. Velarde, *J. Amer. Chem. Soc.*, **90**, 2998 (1968); P. Anderson, P. Crabbé, A. D. Cross, J. H. Fried, L. H. Knox, J. Murphy, and E. Velarde, *ibid.*, **90**, 3888 (1968); P. Crabbé, H. Carpio, and E. Velarde, *Chem. Commun.*, 1028 (1971); and ref 2.

(4) T. C. Shields and P. D. Gardner, *J. Amer. Chem. Soc.*, **89**, 5425 (1967); T. C. Shields, B. A. Loving, and P. D. Gardner, *J. Chem. Soc. D*, 556 (1967); G. Camaggi and F. Gozzo, *J. Chem. Soc. C*, 178 (1970).

(5) R. E. Banks, M. G. Barlow, R. N. Haszeldine, M. Lapin, V. Mathews, and N. I. Tucker, *ibid.*, 548 (1968).

(6) K. L. Williamson and B. A. Braman, *J. Amer. Chem. Soc.*, **89**, 6183 (1967); M. G. Barlow, R. Fields, and F. P. Temme, *J. Chem. Soc. D*, 1671 (1968).

Compound **6** is acid sensitive; it decomposes on prolonged contact with silica gel. When stored at room temperature with hydrochloric acid in dioxane, it gives in high yield a difluoro keto ester (**11**) which still contains the four-carbon side chain, a carbonyl group at C-20, and the geminal fluorines. The structural assignment of **11** is fully supported by its ir and mass spectral data, and the observed A_2X_2 pattern in both pmr and ^{19}F nmr spectra (J_{HF} = 13.8 Hz) established unequivocally the vicinal relationship between the methylene (triplet at 3.32 ppm) and the difluoromethylene groups (triplet at −105.5 ppm relative to $CFCl_3$). Compound **11B** (R = H) upon treatment with sodium hydroxide in boiling dioxane was converted into 5α-pregnan-3β-ol-20-one **13B** (R = H), presumably *via* a β-diketo intermediate (**12**), which confirmed that the fluorines in **11** are adjacent to the ester group. Similarly, base treatment of **8B** and **9B** also afforded the pregnane derivative **13B**. The similarity of the chemical shifts of the C-18 protons in **11B** (R = H, 0.60 ppm) and in **13B** (R = H, 0.59 ppm) indicates that in **11** the C-17 side chain has the β configuration.

The structure most compatible with the chemical and physical characteristics of the major hydrolysis product of **2** and **3** is the substituted butenolide dimethyl ketal **6**. The absence of any coupling between the fluorines and the C-21 vinylic proton and the observed long-range coupling between the fluorines and the C-17 proton (which is probably α, although its stereochemistry has not been established) deserves some comments however. Williamson, *et al.*,[7] have shown that vicinal H–F couplings depend on bond angle, dihedral angle, and bond length. The small vicinal H–H coupling in the –CHCH=C fragment in five-membered rings[8] and the conformational dependence of the vicinal HF coupling in 3-fluoropropenes[9] indicate that a small (if not zero) H–F coupling in **6** is to be expected. The $^4J_{H_{17}-H_{21}}$ coupling (1.5 Hz) is within the range expected for allylic H–H couplings.

Homoallylic hydrogen–fluorine couplings of the order of 2.6–2.8 Hz have been observed in 1,1,1-trifluoro-2-butene in which the coupling nuclei are freely rotating.[10] The difference in the two $^5J_{H_{17}-F}$ values is apparently an indication that the side-chain ring exists mainly in a preferential conformation due to hindered rotation around the 17–20 bond.

A mechanistic scheme for the formation of the various hydrolysis products from the tetrafluorocyclopropyl derivative **2** is outlined in Chart II. The sequence begins with hydrogen fluoride elimination (**2** → **4**) and methanol addition (**4** → **16**) steps leading to the enol acetate **16**. The intermediacy of **4** has been confirmed by its conversion into **6**, **8**, and **9** upon treatment with sodium hydroxide in aqueous methanol. Elimination of the second fluorine atom in the form of hydrogen fluoride, or fluoride ion, is enhanced by the methoxyl group in **16**. The resulting cyclopropene (**17a**) or cyclopropyl carbonium ion (**17b**) intermediate yields the dimethoxydifluorocyclopropyl enol ether **18** in presence of methanol. This dimethoxy intermediate (**18**) can either hydrolyze to the corresponding ketone (**19**) or undergo further elimination–addition reactions leading to **20** (R′ = F or OCH_3). Similar exchange of functional groups *via* elimination–addition reactions have been well documented with halogenated cyclopropyl derivatives.[4,11]

Opening of the cyclopropyl ring[11] in **19** is facilitated by both the carbonyl group and by the electron-donating geminal methoxyl groups. Reclosure through the carbonyl oxygen leads then to the ring-enlarged rearrangement product **6**. Similar rearrangements have been reported previously in the formation of substituted butenolides under strongly[12] or mildly[13] acidic and thermal[12] conditions from various carbomethoxyl group containing cyclopropenyl derivatives.

When **18** undergoes further elimination–addition reactions prior to hydrolysis of the enol acetate, the ring opening in the resulting intermediate **20** follows a different course which involves the expulsion of a fluoride (when R′ = F) or a methoxyl group (when R′ = OCH_3). Instead of reclosure of the ring, the presumed intermediate **21**[14] leads to the open-chain products **8** and **9**, or **22** and **23**, depending on the presence or absence of water in the reaction medium. In addition to **22** and **23**, other ortho esters have been detected, but owing to their instability they were not isolated. The deuterium-labeled analogs of ortho ester **23** have been isolated, however, in both geometrically isomeric forms (**14** and **15** in Chart I) from the hydrolysis of **2B** (R = $COCH_3$) with sodium deuterioxide in anhydrous methanol-*O-d*. One of the undeuterated geometric isomers of **23A** was also isolated from the hydrolysis of a small amount of **2A** in anhydrous methanol. The other isomer and various other esters were also detected from this small-scale reaction, but they could not be obtained in sufficient quantity and purity for analysis.

The ortho esters **14B** (R = H) and **15B** (R = H) exhibited no molecular ions in their mass spectra, only $M^+ - OCH_3$, $M^+ - CH_3OH$ and $M^+ - CH_3OD$ peaks (*m/e* 435, 434, and 433). These assignments were supported by the observed unresolved metastable peaks in the region of *m/e* 404–406. The most diagnostic features in the mass spectra of the ortho esters **14B** and **15B** were the two very intense (70–100% relative intensity) peaks at 105 and 190 mass units. These peaks are due to trimethoxycarbonium ion (*m/e* 105) and to a fragment ion which results from the cleavage of the C-17 ↔ C-20 bond (α cleavage to the carbonyl group) the charge being retained on the carbonyl side (for cleavage pattern, see compound **23** in Chart II). These peaks were at 105 and 189 mass units in the mass spectrum of the undeuterated sample **23A**.

The structure assignment of these ortho esters was further substantiated by the nine-proton singlet at 3.20 ppm for the ortho ester methyl groups and three-proton singlets at 3.91 and 3.57 ppm, respectively, for

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[7] K. L. Williamson, Y.-F. Li Hsu, F. H. Hall, S. Swager, and M. S. Coulter, *J. Amer. Chem. Soc.*, **90**, 6717 (1968).

[8] A. A. Bothner-By, *Advan. Magn. Resonance*, **1**, 250 (1965).

[9] A. A. Bothner-By, S. Castellano, and H. Gunther, *J. Amer. Chem. Soc.*, **87**, 2439 (1965).

[10] R. N. Haszeldine, D. W. Keen, and A. E. Tipping, *J. Chem. Soc. C*, 414 (1970).

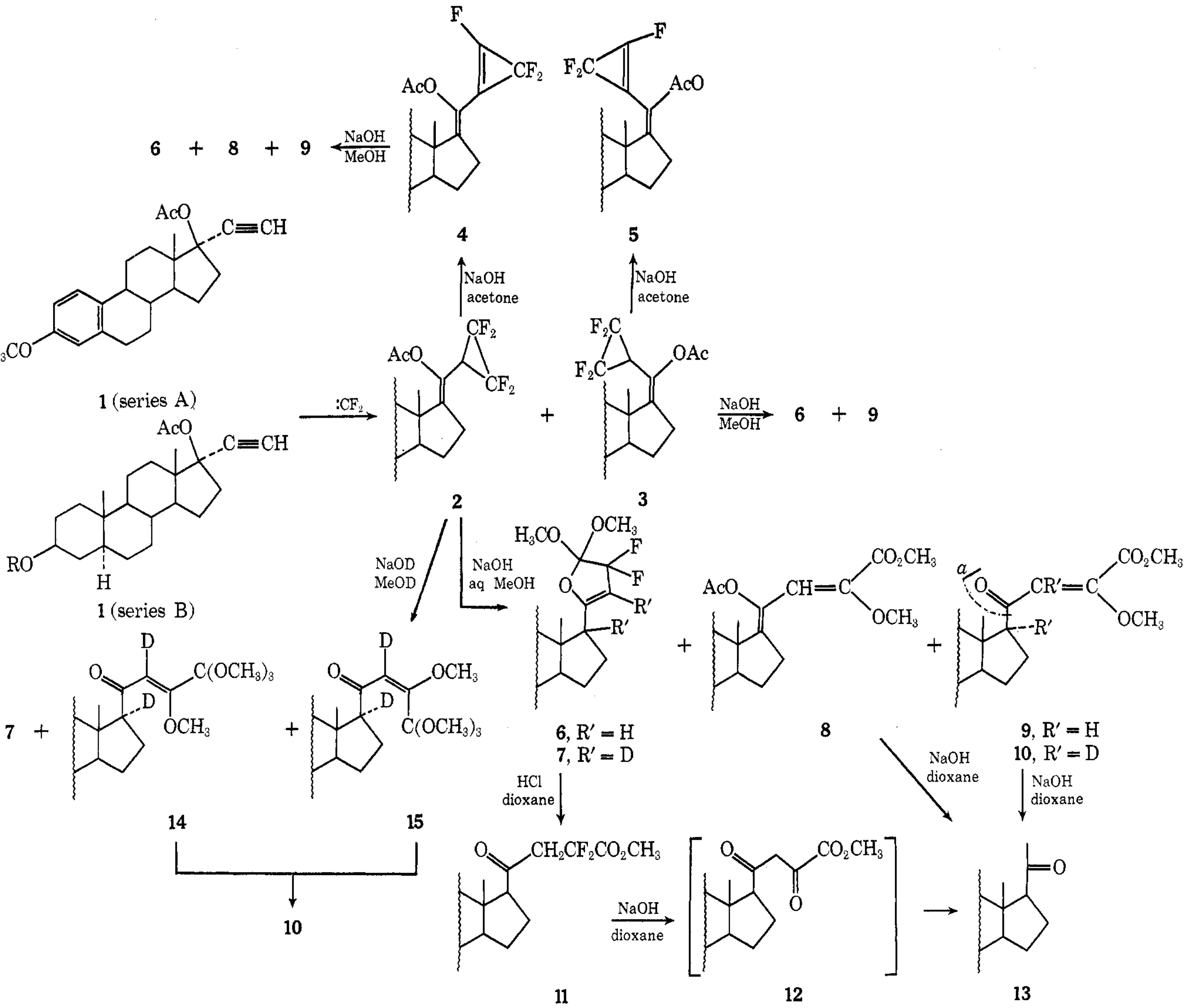
[11] U. Schöllkopf, E. Ruban, P. Tonne, and K. Riedel, *Tetrahedron Lett.*, 5077 (1970), and references cited therein.

[12] R. Breslow, R. Winter, and M. Battiste, *J. Org. Chem.*, **24**, 415 (1959).

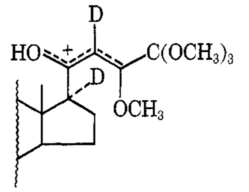
[13] L. Schrader, *Tetrahedron Lett.*, 2993 (1971).

[14] *Cf.* P. v. R. Schleyer, W. F. Sliwinski, G. W. Van Dine, U. Schöllkopf, J. Paust, and K. Fellenberger, *J. Amer. Chem. Soc.*, **94**, 125 (1972); W. F. Sliwinski, T. M. Su, and P. v. R. Schleyer, *ibid.*, **94**, 133 (1972), and related papers.

Chart I



the enol ether protons in the nmr spectra of **14B** and **15B**. The virtually identical chemical shifts (0.59–0.60 ppm) of the C-18 proton resonances in **13B** (R = H), **14B** (R = H), and **15B** (R = H) indicate that the stereochemistry of the C-17 side chain in all these compounds is most probably β. The cis stereochemistry of the enol ether with respect to the carbonyl group in **14** is tentatively assigned to the isomer which shows the more deshielded (3.91 ppm) enol ether signal. On treatment with aqueous methanol both ortho esters gave the same dideuterio methyl ester **10B** (R = H) whose physical characteristics are identical with those of the hydrolysis product **9B** (R = H) with the exception of the spectral differences due to the presence of the deuteriums. This indicates that the enol ethers can undergo isomerization to the thermodynamically more stable geometric form under the hydrolysis conditions. Since the two deuteriums were retained during the conversion of both cis and trans ortho ester **14** and **15** into the methyl ester **10**, the isomerization most probably proceeds *via* an enolate ion intermediate such as **24**, formed prior to hydrolysis of the ortho ester.



24

The spectral data of the hydrolysis products **8** and **9** are in good agreement with their assigned structures in both estratriene (**A**) and androstane (**B**) series. The C-18 proton resonance (0.59 ppm) of **9B** (R = H) is indicative of β-side-chain configuration. The stereoconfiguration of the side chain in **8** and **9** is presumably trans at the enol ether double bond, but this has not been established with certainty.[15] Conversion of both **8B** (R = H) and **9B** (R = H) into 5α-pregnan-3β-ol-20-one (**13B**, R = H) by sodium hydroxide treatment in boiling dioxane confirms the location of the methoxyl group at C-22.

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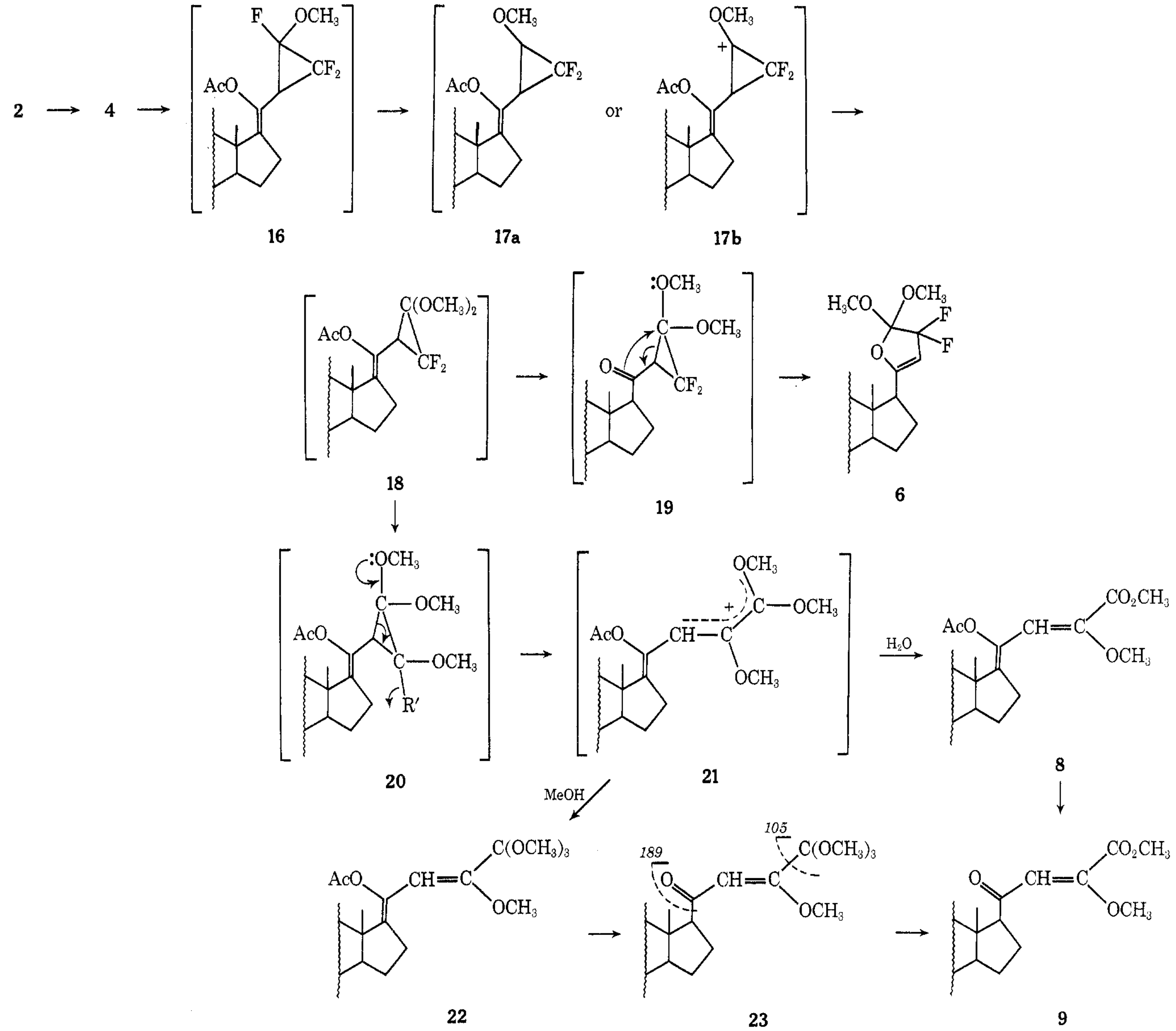
[15] In certain enol ethers the stereoconfiguration can be assigned on the basis of the chemical shift of the vinylic proton by calculating the shielding effect of the substituents which were found to be additive by U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell. *Tetrahedron*, **25**, 691 (1969), and in earlier reports cited therein. This method, however, was found to be unreliable when both methoxyl and carbonyl substituents are present on the double bond: S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

CHART II



Experimental Section[16]

Hydrolysis of 2A with Sodium Hydroxide in Aqueous Methanol. —The tetrafluorocyclopropyl adduct **2A** (400 mg) was dissolved in a solution (20 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 45 min at room temperature. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The product was purified by preparative tlc (hexane–ethyl acetate 85:15). The least polar fraction (173 mg, 43%) gave crystalline product **6A**: mp 111°; $[\alpha]_D$ +47°; λ_{max} 278–287 nm (ϵ 1687–1585); ν_{max} 1660, 1620, 1580 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.70 (18-H), 3.53 (2 OCH_3). 3.86 (3-OMe), 5.06 (vinylic H), 6.5–7.3 ppm (3 aromatic H); mass spectrum *m/e* 434 (M^+).

Anal. Calcd for $C_{25}H_{32}O_4F_2$: C, 69.08; H, 7.42. Found: C, 69.02; H, 7.63.

The two more polar fractions were tentatively identified as **9A** (90 mg, 20%; mp 85–90°; λ_{max} 262 nm (ϵ 8128); ν_{max} 1750, 1680, 1610 cm^{-1}) and **23A** (100 mg, 25%; oil; ν_{max} 1680, 1610 cm^{-1}) which were not further purified and characterized.

Hydrolysis of 2B with Sodium Hydroxide in Aqueous Methanol.—Adduct **2B** (R = $COCH_3$, 1.8 g) was dissolved in a solution (90 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred at room temperature for 45 min. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The product was chromatographed on Florisil (100 g). The fractions eluted with hexane–ether (9:1) afforded 650 mg (42%) of **6B** (R = H): mp 155–156°; $[\alpha]_D$ +8°; ν_{max} 1660 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.66 (18-H), 0.80 (19-H), 3.5 (2 OCH_3), 5.03 ppm (vinylic H); mass spectrum *m/e* 440 (M^+).

Anal. Calcd for $C_{25}H_{38}O_4F_2$: C, 68.14; H, 8.69; F, 8.62. Found: C, 68.16; H, 8.95; F, 9.20.

The fractions eluted with ethyl acetate gave 1 g of a mixture of compounds **8B** and **9B**. These esters were purified by tlc on silica gel in hexane–ethyl acetate (4:1). The less polar fraction gave 300 mg (20%) of **9B** (R = H): mp 140–142°; $[\alpha]_D$ −113°; λ_{max} 256 nm (ϵ 11,220); ν_{max} 3450, 1760, 1695, 1600 cm^{-1}; nmr (T-60) ($CDCl_3$) 0.60 (18-H), 0.80 (19-H), 3.73 and 3.86 (2 OCH_3), 5.50 ppm (vinylic H); mass spectrum *m/e* 418 (M^+).

Anal. Calcd for $C_{25}H_{38}O_5 \cdot CH_3OH$: C, 69.31; H, 9.39. Found: C, 68.92; H, 9.34.

The more polar compound was **8B** (R = H, 400 mg, 23%): mp 174–175°; $[\alpha]_D$ +9°; λ_{max} 230–232 nm (ϵ 10,470); ν_{max} 3450, 1740, 1720, 1630 cm^{-1}; nmr ($CDCl_3$) 0.80 (19-H), 0.910 (18-H), 2.35 (20-OAc), 3.71 (OCH_3), 3.91 (=$COCH_3$), 7.27 ppm (vinylic H); mass spectrum *m/e* 460 (M^+).

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[16] The nmr spectra were measured on a Varian HA-100 or T-60 spectrometer using tetramethylsilane as an internal reference. Proton chemical shifts are reported on the δ scale. The ^{19}F nmr spectra were recorded by computer averaging of transients using an IBM-1800. The lock signal was provided by an external capillary of $(CF_3)_2CO \cdot 3H_2O$. $CFCl_3$ was used as an internal standard; shifts to higher field are negative. The mass spectra were recorded on an Atlas CH-4 spectrometer equipped with an EFO-4B ion source; the ionizing energy was maintained at 70 eV.

Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.71. Found: C, 69.98; H, 8.95.

Hydrolysis of 3B with Sodium Hydroxide in Aqueous Methanol.—Adduct **3B** (R = $COCH_3$, 130 mg) was dissolved in a solution (5 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 1 hr at room temperature. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness. The crude product was chromatographed on Florisil (5 g). In fractions eluted with hexane–ether (9:1) 45 mg (39%) of **6B** (R = H) was isolated. The residue (40 mg) from the ethyl acetate fractions was purified by tlc in hexane–ethyl acetate (4:1) yielding 18 mg (18%) of **9B** (R = H). Both of these samples were identical with those obtained from the hydrolysis of **2B**; *vide supra.*

Hydrolysis of 2A with Sodium Hydroxide in Anhydrous Methanol.—Sodium hydroxide (100 mg) and then compound **2A** (10 mg) were dissolved in anhydrous methanol (5 ml). The solution was heated gently for 1 hr; then it was diluted with ether, washed with water, and dried (Na_2SO_4), yielding a glassy mixture of products.

Plate chromatography on silica gel in ether–benzene (1:9) after two developments gave five fractions. Elution of the least polar fraction (I) gave a crystalline product (2.9 mg, 13%) which proved to be identical with **6A**. With the exception of fraction IV, all other fractions were too small in quantity and were not sufficiently pure for characterization.

Fraction IV, upon elution with ether, gave a semicrystalline ortho ester (**23A**): 3.0 mg (30%); nmr ($CDCl_3$) 0.65 (18-H), 3.23 (3 OCH_3), 3.73 (aromatic OCH_3), 3.92 (enol ether), 6.02 (vinylic H), 6.6–7.25 ppm (3 aromatic H); mass spectrum *m/e* 458 (M^+), 189 and 105 (see compound **23** in Chart II). This ortho ester was converted into the conjugated methyl ester **9A** upon storing at room temperature for 48 hr in aqueous methanol containing trace of hydrochloric acid.

Hydrolysis of 2B with Sodium Deuterioxide in Methanol-*O-d*.—Sodium (52 mg) was treated with methanol-*O-d* (2 ml) which contained deuterium oxide (0.05 ml). After cooling a methanol-*O-d* solution (3 ml) of the tetrafluorocyclopropyl enol ether **2B** (R = $COCH_3$, 24 mg) was added and the reaction mixture was stored at room temperature for 1 hr. The solution was then diluted with ether, washed with water, and dried (Na_2SO_4). Evaporation of the solvent gave a glassy residue which was chromatographed on a silica gel plate in ether–benzene (1:1).

The least polar fraction (I), which exhibited the same R_f value as **6B** (R = H), contained the dideuteriobutenolide dimethyl ketal **7B** (R = H, 3 mg, 14%): mp 157–158° (aq MeOH); pmr ($CDCl_3$) 0.64 (18-H), 0.79 (19-H), 3.47 ppm (2 OCH_3); ^{19}F nmr ($CDCl_3$ with $CFCl_3$ internal standard) -104.4 and -103.4 ppm (AB pattern, J_{FF} = 245 Hz); mass spectrum *m/e* 442 (M^+), isotope composition 2% d_0, 14% d_1, and 84% d_2.

Elution of the two more polar fractions (II and III) with ether yielded two semicrystalline isomeric ortho esters tentatively identified as **14B** and **15B**, respectively. These ortho esters were analyzed without further purification since attempted recrystallizations led to decomposition.

Ortho ester **14B** (R = H) (fraction II, 6.5 mg, 29%): nmr ($CDCl_3$) 0.60 (18-H), 0.79 (19-H), 3.20 (3 × OCH_3), 3.91 ppm (enol ether); mass spectrum *m/e* 435 ($M^+ - OCH_3$), 434 (M^+ − MeOH), 433 (M^+ − MeOD), 190 (70%, analogous to *m/e* 189 fragment of compound **23**, Chart II) and 105 [100%, $C^+(OCH_3)_3$].

Ortho ester **15B** (R = H) (fraction III, 12 mg, 53%): nmr ($CDCl_3$) 0.60 (18-H), 0.78 (19-H), 3.20 (3 OCH_3), 3.57 ppm (enol ether); mass spectrum *m/e* 435 ($M^+ - OCH_3$), 434 (M^+ − MeOH), 433 (M^+ − MeOD), 190 (100%, analogous to *m/e* 189 fragment of compound **23**, Chart II) and 105 [83%, $C^+(OCH_3)_3$].

Both ortho esters **14B** and **15B** were dissolved in aqueous methanol (2 ml) which contained a trace of hydrochloric acid, and the solutions were stored at room temperature for 20 hr. Evaporation of the solvent under a stream of nitrogen gave the same hydrolysis product from both ortho esters which exhibited the same R_f value as **9B** (R = H). The residues were purified by chromatography on silica gel plates in ether–benzene (1:1) yielding the dideuterio ester **10B** (R = H): mp 140–142.5° (aq MeOH); nmr ($CDCl_3$) 0.595 (18-H), 0.79 (19-H), 3.71 and 3.85 ppm (2 OCH_3); mass spectrum *m/e* 420 (M^+), 144 and 116 (fragment a and a − CO as shown on compound **10**, Chart I); isotope composition 3% d_0, 15% d_1, and 82% d_2.

Hydrolysis of 4B with Sodium Hydroxide in Aqueous Methanol.—Compound **4B** (R = $COCH_3$, 10 mg) was dissolved in a solution (1 ml) of 2% sodium hydroxide in *ca.* 97% methanol. The mixture was stirred for 1 hr at room temperature. The product was isolated as described above and purified by tlc thus affording compounds **6B** (R = H), **8B** (R = H), and **9B** (R = H).

Reactions of 6B (R = H).—Compound **6B** (R = H) was recovered unchanged upon further treatment with sodium hydroxide in anhydrous or aqueous methanol at room temperature, as well as at boiling temperature.

A solution of **6B** (R = H, 10 mg) in methanol-*O-d* (5 ml) was saturated with 10% sodium deuterioxide in deuterium oxide. The solution was heated under reflux for 24 hr and then cooled, extracted with ether, washed with cold water, and dried (Na_2SO_4). The recovered crystalline product after the evaporation of the ether showed no deuterium content by mass spectrometric analysis.

Compound **6B** (R = H) was recovered unchanged when it was heated for 24 hr with sodium borohydride in isopropyl alcohol or from a 4-hr treatment with lithium aluminum hydride in boiling ether.

3β-(*p*-Bromobenzoate) Derivative of 6B (R = *p*-BrC_6H_4CO).—A solution containing **6B** (R = H, 80 mg) and *p*-bromobenzoyl chloride (100 mg) in pyridine (2 ml) was heated at 70° for 2 hr. After cooling, the mixture was poured into water, filtered, and washed to neutrality. Crystallization from methanol provided the pure sample of the *p*-bromobenzoate **6B** (R = *p*-BrC_6H_4CO): mp 175–178°; λ_{max} 244 nm (ϵ 19,500); ν_{max} 1600, 1650, 1720; nmr ($CDCl_3$) 0.66 (18-H), 0.86 (19-H), 3.50 (2 OCH_3), 5.83 (21-H), 7.40–8.10 ppm (aromatic H); mass spectrum *m/e* 622 (M^+).

Hydrolysis of 6B with Hydrochloric Acid.—A solution of **6B** (R = H, 155 mg) in dioxane (12 ml) and 10% hydrochloric acid (6 ml) was stirred for 4 hr at room temperature. The reaction mixture was diluted with ethyl acetate and washed with water to neutrality. Evaporation of the solvent and purification by tlc in hexane–ethyl acetate (7:3) yielded the difluoro keto ester **11B** (R = H, 108 mg, 72%): mp 165–167°; $[\alpha]_D$ +87°; ν_{max} 3510, 1790, 1710 cm^{-1}; nmr ($CDCl_3$) 0.60 (18-H), 0.79 (19-H), 3.32 [t, $J_{H,F}$ = 13 Hz —C(=O)CH_2CF_2—], 3.90 ppm [—C(=O)OCH_3]; mass spectrum *m/e* 426 (M^+).

Anal. Calcd for $C_{24}H_{36}O_4F_2$: C, 67.57; H, 8.50; F, 8.91. Found: C, 67.29; H, 8.64; F, 8.14.

3β-Hydroxy-5α-pregnan-20-one (13B, R = H). Method I.—A solution of **2B** (R = $COCH_3$, 200 mg) in *ca.* 95% dioxane (20 ml) containing 5% sodium hydroxide was heated under reflux for 45 min. The product was isolated by dilution with water and extraction with ethyl acetate. The organic layer was washed, dried, filtered, and evaporated to dryness, yielding **13B** (R = H, 95 mg, 90%): mp 193–195° (lit.[17] mp 194°); $[\alpha]_D$ +118°; ν_{max} 3400, 1700, 1690 cm^{-1}; nmr ($CDCl_3$) 0.59 (18-H), 0.79 (19-H), 2.08 ppm (21-H); mass spectrum *m/e* 318 (M^+).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 76.62; H, 10.07. Found: C, 76.28; H, 10.38.

Method II.—A solution of **11B** (R = H, 22 mg) in *ca.* 95% dioxane (2.5 ml) containing 5% sodium hydroxide was heated under reflux for 3 hr. The product was isolated as described above yielding **13B** (R = H, 14 mg, 87%), which was shown to be identical with an authentic sample by usual criteria.

Method III.—A mixture (40 mg) of compounds **8B** and **9B** dissolved in a 5% sodium hydroxide solution in *ca.* 95% dioxane (4 ml) was heated at reflux temperature for 10 hr. The product was isolated as usual thus affording compound **13B** (R = H, 40%), shown to be identical (mixture mp, ir, nmr, tlc) with an authentic sample.

Registry No.—**2A**, 36706-82-8; **2B**, 27741-56-6; **3B**, 27932-70-3; **4B**, 36706-85-1; **6A**, 36706-86-2; **6B**, 36706-87-3; **6B** (*p*-bromobenzoate), 36763-72-1; **7B**, 36706-88-4; **8B**, 36706-89-5; **9A**, 36706-90-8; **9B**, 36706-91-9; **10B**, 36706-92-0; **11B**, 36706-93-1; **13B**, 516-55-2; **14B**, 36706-95-3; **15B**, 36706-96-4; **23A**, 36706-97-5.

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[17] A. Butenandt and U. Westphal, *Chem. Ber.*, **69**, 443 (1936).