In a subsequent preparation, dry hydrogen chloride gas was passed through the ethereal solution of **6** and ethyl malonate. The ethereal solution of ethyl malonate was carefully decanted from the oily hydrochloride of **6**. The hydrochloride was washed with ether and then liberated to the free amine by the action of an excess of triethylamine in ether. The ethereal solution was then filtered and distilled as before. Compound **6** was again obtained in a 39% yield with slightly less resinification in the distilling flask.

Anal. (picrate, mp 85–86.5°). Calcd for $C_{20}H_{28}N_4O_{11}$: C, 48.00; H, 5.64; N, 11.20. Found: C, 47.86; H, 5.46; N, 11.40.

Attempted Preparation of Alkylated Azetidines in Ether. Attempted Preparation of 2-(1-*tert*-Butyl-3-azetidinyl)indane-1,3-dione (4).—To a solution of 0.52 g (3.56 mmol) of indane-1,3-dione and 0.085 g (3.54 mmol) of sodium hydride in 25 ml of ether, which had been stirred for 15 min, was added 1.00 g (3.53 mmol) of **1**. The mixture was stirred for 30 hr. Water was added, and the ethereal layer was separated and dried (magnesium sulfate). Evaporation of the ether yielded 0.95 g of white solid identified as **1** by pmr spectroscopy.

Attempted Preparation of Diethyl (1-*tert*-Butyl-3-azetidinyl)-malonate (6).—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 4.00 g (0.025 mol) of ethyl malonate. After *ca.* 20 min 7.00 g (0.025 mol) of **1** was added. After 48 hr the mixture was filtered and the ether was removed *in vacuo*. The pmr spectrum of the crude product indicated little if any **6**.

Preparation of Ethyl (1-*tert*-Butyl-3-azetidinyl)acetoacetate (7).—To a solution of sodium ethoxide prepared from 0.57 g (0.0248 g-atom) of sodium and 1.14 g (0.0248 mol) of ethanol in 100 ml of ether was added 3.35 g (0.025 mol) of ethyl acetoacetate. After stirring for *ca.* 20 min, 7.00 g (0.025 mol) of **1** was added. After stirring for 48 hr the mixture was filtered, and the ether was removed from the filtrate *in vacuo*. The pmr spectrum indicated 8–9% of the azetidine to be **7**, the remainder unreacted **1**.

Registry No.—**1**, 17358-65-5; **5**, 34910-31-1; **5** picrate, 34910-32-2; **6**, 34910-33-3; **6** picrate, 34910-34-4; **7**, 34910-35-5.

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A Solvolytic Fission of a Carbon–Fluorine Bond Induced by Triethyl Orthoformate in 6β-Fluoro-17α-acetoxyprogesterone[1]

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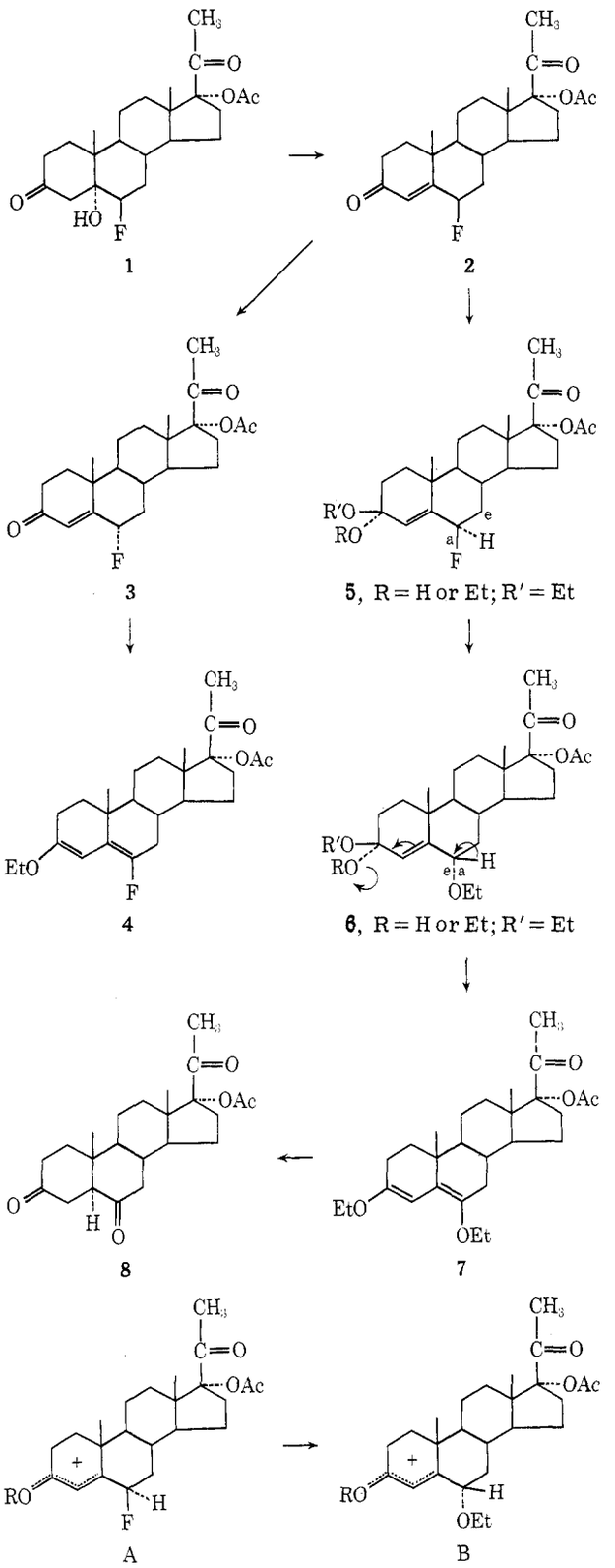
In the course of a series of synthetic transformations, we became interested in the preparation of 3-ethoxy-6-fluoro-17α-acetoxypregna-3,5-dien-20-one (**4**) from 6β-fluoro-17α-acetoxyprogesterone (**2**). Treatment of **2** with triethyl orthoformate in dichloromethane solution in the presence of *p*-toluenesulfonic acid dihydrate at room temperature gave a new compound in 79% yield which differed from the expected dienol ether **4**. The structure of this new compound was established as 3,6-diethoxy-17α-acetoxypregna-3,5-dien-20-one (**7**) based on its physical properties and conversion to the corresponding 3,6-diketone **8** on treatment with acid. Formation of this interesting product may be explained as follows. It is known that 6β-fluoro-3-keto steroids require very severe conditions for epimerization to the corresponding 6α-fluoro isomers, such as treatment with hydrogen chloride in acetic acid for a period of several hours.[2] This indicates that loss of an equatorial



(1) This paper represents Contribution No. 391 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, Calif.

(2) A. Bowers, L. Cuellar Ibañez, and H. J. Ringold, *Tetrahedron*, **7**, 138 (1959).

proton in a cation such as A (R = H) to give a fluorodienol analogous to **4** is slow. In the present experiment, initial formation of A (R = Et) or the ketal or hemiketal **5** is apparently followed by preferential solvolysis of the axial fluorine atom at C-6 to yield the 6α-ethoxy intermediate [**6** or B (R = Et)]. This intermediate then collapses to **7** by loss of the axial C-6 proton.

It is noteworthy that the 6α-fluoro isomer **3** yields the enol ether **4** as expected.[3]

Experimental Section[4]

6β-Fluoro-17α-acetoxyprogesterone (2).—A suspension of 900 mg of 5α-hydroxy-6β-fluoro-17α-acetoxyprogesterone[2] (**1**) in 10 ml of dichloromethane containing 1 ml of pyridine was cooled to 0° and then 900 mg of thionyl chloride was added. The mixture was stirred at 0° for 30 min and then diluted with 100 ml of water. The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with water to neutrality and dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crystalline residue was crystallized once from acetone–hexane and twice from dichloromethane–hexane to yield 650 mg of **2**: mp 184°; $[\alpha]D$ −18°; uv 233 mμ (ε 13,180); nmr 0.78 (18-H), 1.30, 1.32 (19-H, J = 2.5 Hz), 2.08, 2.11 (21-H + 17α AcO), 4.61, 5.02 (6α-H, J = 48 Hz), 5.83, 5.92 ppm (4-H, J = 4 Hz). *Anal.* Calcd for $C_{23}H_{31}O_4F$: C, 70.74; H, 8.00; F, 4.84. Found: C, 70.78; H, 8.32; F, 4.32.

3,6-Diethoxy-17α-acetoxypregna-3,5-dien-20-one (7).—A solution of 1 g of 6β-fluoro-17α-acetoxyprogesterone in 10 ml of dichloromethane was treated at room temperature with 30 mg of *p*-toluenesulfonic acid dihydrate and 0.9 ml of triethyl orthoformate. The reaction mixture was stirred for 2 hr at room temperature and then 5 drops of pyridine was added and the mixture was washed with water, dried over anhydrous sodium sulfate, and filtered. The solvent was removed under reduced pressure, and the residue was dissolved in 10 ml of dichloromethane and filtered through 15 g of sil ca gel, eluting with the same solvent (500 ml). The solvent was removed under reduced pressure to yield 900 mg of **7**, homogenous on tlc (25% ethyl acetate–75% hexane).

This material was crystallized from dichloromethane–methanol to yield an analytical sample: mp 104–106°; $[\alpha]D$ −119°; uv 322 mμ (ε 716), 246 (19,326); ν_{max} 1735, 1770, 1250 cm^{-1}; nmr 0.68 (18-H), 0.96 (19-H), 2.11 (21-H), quartets centered at 3.75 and 3.85, and triplets centered at 1.26 and 1.32 (C-6 and C-3 EtO groups) and 5.68 ppm (4-H). *Anal.* Calcd for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07; O, 17.99. Found: C, 72.88; H, 9.01; O, 18.24.

This product proved to be unstable on standing. A small sample was dissolved in a mixture of 95% tetrahydrofuran–5% water and treated with a few drops of concentrated hydrochloric acid. After 30 min, no starting material was present and a more polar, nonultraviolet-absorbing compound corresponding to diketone **8** was detected by tlc analysis. Not enough sample was available for full characterization of this compound.

Registry No.—**2**, 336-79-8; **7**, 35048-85-2.

Acknowledgments.—Thanks are due to Dr. John Fried for very helpful discussions during the preparation of this manuscript.

(3) P. Crabbé and J. Iriarte, unpublished results.

(4) Melting points are corrected. Optical rotations were measured in chloroform solution unless stated otherwise using an O. C. Rudolph and Sons Model 80 polarimeter. Ultraviolet spectra were measured in methanol using a Cary Model 14 spectrometer. Nmr spectra were recorded on a Varian A-60 spectrometer using deuteriochloroform as solvent. Chemical shifts are recorded in parts per million (ppm). Infrared spectra were measured using a Perkin-Elmer Model 137 spectrophotometer. We wish to thank Dr. L. Throop's staff for these measurements.

Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

A Total Synthesis of Prostaglandins $F_{1\alpha}$ and E_1

Summary: A synthesis of prostaglandins $F_{1\alpha}$ and E_1 has been accomplished starting from the lactone **1** *by a route in which the carboxylic side chain is added first and the remaining side chain subsequently; key intermediates include the hydroxy acid* **2**, *the aldehyde* **3**, *and the ketone* **4**.

Sir: In previous papers we have reported the synthesis of the six primary prostaglandins from a common intermediate by a route in which the seven-carbon carboxyl-bearing side chain was elaborated after the eight-carbon hydroxylic side chain.[1,2] We now describe a modification of this approach in which the side chains are introduced in the reverse order. The modified synthetic scheme can advantageously be applied to the synthesis of a new range of prostanoid structures which are of biological and medical interest.

Conversion of the readily available (−)-hydroxy lactone **1**[2] to the tetrahydropyranyl (THP) derivative and reduction with 1.1 equiv of diisobutylaluminum hydride in toluene at −78° for 1.0 hr yielded the oily lactol **2**[3,4] which was condensed with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid[5] and sodio methylsulfinylcarbanide[5] in dimethyl sulfoxide to form the hydroxy acid **3**[4,6] (83% from **1** after silica gel column chromatography using ethyl acetate as eluent). Treatment of the hydroxy acid **3** with excess diazomethane in ether afforded the hydroxy ester **4**[3,4] which was acetylated using 2.25 equiv of acetic anhydride in pyridine at 50°. Hydrogenation of the resultant acetoxy ester **5**[3,4] was carried out in 5% acetic acid–absolute ethanol as solvent under 1 atm of hydrogen for 48[7] hr with 5% palladium on carbon

(1) E. J. Corey, R. Noyori, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **92**, 2586 (1970).

(2) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *ibid.*, **93**, 1490 (1971); see also E. J. Corey, T. Ravindranathan, and S. Terashima, *ibid.*, **93**, 4327 (1971).

(3) Unless designated, the crude product was used without purification.

(4) Infrared and nmr (at 60 MHz) spectra were in agreement with the assigned structure.

(5) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969).

(6) Satisfactory mass spectral data were obtained on this oily compound.

(7) The first equivalent of hydrogen is rapidly consumed (2 hr), whereas the second equivalent is slowly consumed over the remaining 46 hr. Alternatively, the hydrogenation can be monitored by thin layer chromatography using 2:1 benzene–ether as eluent with the ether **5** and alcohol **6** having R_f 0.80 and 0.20, respectively.