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).

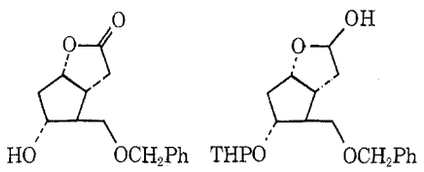
(3) Unless designated, the crude product was used without purification.

(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).

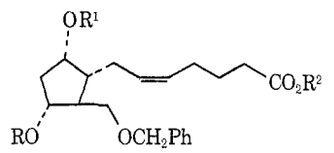
(6) Satisfactory mass spectral data were obtained on this oily compound.

(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.

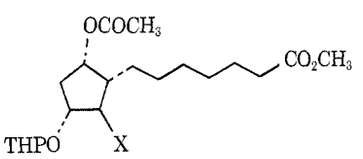


1 $[\alpha]^{20}D$ −7.2° (*c* 1, $CHCl_3$)

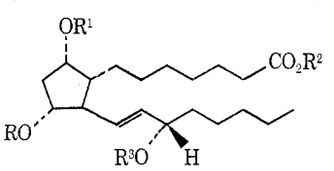
2 $[\alpha]^{20}D$ +7.2° (*c* 0.8, $CHCl_3$)



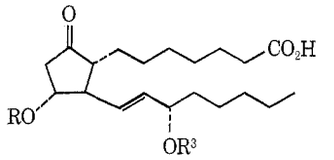
3, R = THP; R^1 = H; R^2 = H
4, R = THP; R^1 = H; R^2 = CH_3
5, R = THP; R^1 = $COCH_3$; R^2 = CH_3



6, X = CH_2OH
7, X = CHO
8, X = CH=CHCO(n-C_5H_{11})
9, X = CH=CHCHOH(n-C_5H_{11})



10, R = R^3 = H; R^1 = $COCH_3$; R^2 = CH_3
11, R = R^1 = R^2 = R^3 = H
12, R = R^3 = THP; R^1 = $COCH_3$; R^2 = CH_3
13, R = R^3 = THP; R^1 = R^2 = H



14, R = R^3 = THP
15, R = R^3 = H

(Engelhard Industries, Inc.) (amount, 0.10 times weight of substrate **5**) to afford the oily alcohol **6**[3,4] (82% from **3**). Oxidation of the alcohol **6** using the Collins reagent generated *in situ*[8] in methylene chloride at 0° produced the unstable oily aldehyde **7** which was immediately treated with the sodio derivative of dimethyl 2-oxoheptylphosphonate[9] in dimethoxyethane at 25° for 2.0 hr to form stereospecifically the oily trans enone **8**[4,6] (83% from **6** after silica gel column chromatography using 1:1 methylene chloride–ethyl acetate as eluent). Treatment of the enone **8** with excess zinc borohydride[5] in dimethoxyethane at 25° for 3.0 hr afforded a mixture of epimeric alcohols **9**[3,4,10] (ratio ~1:1). Hydrolysis of **9** using 2:1 acetic acid–water at 40 ± 2° for 2.5 hr afforded the 11α,15α-dihydroxy prostanoid **10**[11,12] and its 15β epimer (>95% yield from **8**). Separation of the desired 15α epimer **10**[4,6] from the mixture was accomplished by silica gel column chromatography using 4:1 ether–cyclohexane as eluent. Further, the 15β epimer of **10** could be used in the synthesis, since it reverts to the precursor **8** upon oxidation with activated manganese dioxide in methylene chloride followed by pyranylation with dihydropyran (1.5 equiv) in methylene chloride containing *p*-toluenesulfonic acid (0.01 equiv) at 25° for 5 min.

Optically active prostaglandins $F_{1\alpha}$ and E_1 were obtained from the 11α,15α-dihydroxy prostanoid **10** in the following manner. Cleavage of **10** with 1.0 *N* aqueous sodium hydroxide (3 equiv) in methanol–tetrahydrofuran at 25° for 1.5 hr afforded crystalline prostaglandin $F_{1\alpha}$ (**11**), >95% yield from **10** which was homogeneous by thin layer chromatographic analysis). Recrystallization from ethyl acetate–cyclohexane afforded prostaglandin $F_{1\alpha}$ (**11**) as colorless needles, $[\alpha]^{20}D$ +25.0° (*c* 1.1, THF), mp and mmp[13] 100–101.5°. The ir and nmr spectra and chromatographic behavior of the two samples of prostaglandin $F_{1\alpha}$ were identical.

The dihydroxy prostanoid **10** was converted to the bistetrahydropyranyl derivative **12**[3,4] using dihydropyran (3 equiv) in methylene chloride containing *p*-toluenesulfonic acid (0.01 equiv) at 25° for 20 min. Cleavage of **12** with 1.0 *N* aqueous sodium hydroxide (3 equiv) in methanol–tetrahydrofuran afforded the bis-THP ether of prostaglandin $F_{1\alpha}$ (**13**)[3,4] which was oxidized by Jones reagent at −20° affording the bis-THP ether of prostaglandin E_1 (**14**).[3,4] Hydrolysis of **14** using 2:1 acetic acid–water at 40 ± 2° for 5 hr afforded crystalline prostaglandin E_1 (**15**, 55% yield from **10**). Recrystallization from ethyl acetate–cyclohexane afforded colorless microcrystals, $[\alpha]^{20}D$ −57.0° (*c* 0.9, THF), mp and mmp[13] 113.5–114.0°. The spectra and chromatographic properties of the two samples of prostaglandin E_1 were identical.

We anticipate that a number of improvements in the synthetic approach described above may be realizable, including the use of other protecting groups which will render many of the intermediates crystalline and the use of modified procedures[14] for the stereoselective introduction of the chiral center at C-15.

(8) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(9) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *J. Amer. Chem. Soc.*, **90**, 3247 (1968).
(10) Although the epimeric mixture was separable by thin layer chromatography, clean separation could not be effected by column chromatography.
(11) We have found this term to be convenient for describing prostanoic acid relatives; see E. J. Corey, T. Ravindranathan, and S. Terashima, *J. Amer. Chem. Soc.*, **93**, 4326 (1971).
(12) For nomenclature with regard to stereochemical orientation, see B. Samuelsson, *Angew. Chem., Int. Ed. Engl.*, **4**, 410 (1965).
(13) The authentic sample was obtained by total synthesis as described in ref 1.
(14) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1490 (1971).

MEDICAL RESEARCH LABORATORIES
CHAS. PFIZER AND COMPANY, INC.
GROTON, CONNECTICUT 06340
THOMAS K. SCHAAF

DEPARTMENT OF CHEMISTRY
HARVARD UNIVERSITY
CAMBRIDGE, MASSACHUSETTS 02138
E. J. COREY*

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