

A typical alkylation experiment was performed as follows. A suspension of 1 mol of thallous cyclopentadienide in 400 ml of dry ether at -20° (N_2) was treated gradually with 1 mol of chloromethyl methyl ether with stirring. After 5 hr the insoluble thallous chloride was removed by rapid filtration from the precooled (to -40°) mixture and washed with a small amount of pentane.⁷ Concentration of the ether solution under reduced pressure ($<0^{\circ}$) afforded the monoalkylated cyclopentadiene II containing 0–3% of the isomer IV by nmr analysis. Reaction of the cyclopentadiene II so obtained with 2-chloroacrylonitrile (4 equiv) and cupric fluoroborate⁸ (0.3 equiv) at 0° for 18 hr followed by addition of brine containing some sodium tartrate, extraction with ether, and concentration *in vacuo* afforded an oily product (80–90% yield) containing 75–85% of the desired adduct III by vpc analysis.⁹ Alkaline hydrolysis of this crude product dissolved in 1 l. of dimethyl sulfoxide was accomplished by addition of a hot solution of 2.5 mol of potassium hydroxide in 45 ml of water and maintenance at 30 – 35° for 1.5 hr. Addition of water to the reaction mixture, extraction with ether, and distillation of the organic extract through a spinning band column afforded pure ketone I,^{2a} bp 68° (0.5 mm), in 50–55% yield based on thallium cyclopentadiene and overall for three steps.^{10,11}

The procedure outlined here for the methoxymethylation of cyclopentadiene without prototropic rearrangement is advantageous for the following reasons: (1) availability of the reagent, (2) simple isolation of the monoalkylated cyclopentadiene II without the need for aqueous treatment, (3) suitability for large-scale synthesis. The benzyloxy analogs of II and I have been obtained similarly starting from chloromethyl benzyl ether and thallous cyclopentadienide. To our knowledge these are the first carbon-substituted cyclopentadienes to be prepared from the thallium derivative. Further studies on the utility of thallous cyclopentadienide for the synthesis of alkylated cyclopentadienes and 7-substituted bicyclo[2.2.1]heptane derivatives are in progress.

Caution. Certain hazards are associated with the above procedures.^{12,13}

(7) The thallous chloride ($>97\%$ recovery) was readily converted to thallous sulfate by treatment with sulfuric acid, thereby permitting efficient recycling of thallium.

(8) Commercial cupric fluoroborate was powdered (exclusion of moisture) and dried over KOH at 25° for 1 day and then over P_2O_5 at 25° for >5 days.

(9) The analysis was performed using a 10 ft \times 0.125-in. column containing 5% silicone (SE-30) at 135° .

(10) The conversion of III to I in 80% yield by alkaline hydrolysis described previously^{2a} refers to chromatographically purified III.

(11) The higher boiling fraction contains chloronitrile(s) in the bicyclo[3.2.0]heptane series. These are resistant to the hydrolysis conditions which convert III to I.

(12) Thallium and its compounds are highly toxic and must be handled with great care; see, for example, E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970). 2-Chloroacrylonitrile is also an unusually hazardous substance, and inhalation of vapors or contact with the skin must be avoided. Severe skin irritation and blistering have been experienced with this substance in a number of laboratories.

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Stereospecific Total Synthesis of Prostaglandins E_3 and $F_{3\alpha}$

Sir:

This communication reports the first synthesis of prostaglandins E_3 and $F_{3\alpha}$ in optically active, naturally occurring form.¹ The optically active hydroxy lactone I (oil, $[\alpha]^{25}_D -10^{\circ}$ in $CHCl_3$), readily available from previously described intermediates,² was converted to the tetrahydropyranyl (THP) derivative II^{3a} (1.5 equiv of dihydropyran and *ca.* 1 mol % *p*-toluenesulfonic acid in methylene chloride at 25°) and thence to the primary alcohol III³ (hydrogen at 1 atm with 5% palladium/carbon in 20:1 ethanol–acetic acid at 25°) and the aldehyde V³ (Collins oxidation⁴) (85–90% of V overall from I).⁵ The aldehyde V was converted stereospecifically to the unsaturated alcohol VI by means of the β -oxido ylide reagent^{6,7} derived from the hydroxy phosphonium salt (S)-(+)-XII as follows. The (S)-(+)-phosphonium salt XII was treated at -78° in tetrahydrofuran solution under nitrogen with 2 equiv of methylolithium, and the mixture was brought to and maintained at -25° for 30 min, cooled to -78° , and treated with the aldehyde V. After 5 min at -78° the reaction mixture was brought to 0° for 30 min, and the product was separated by addition of pH 4 citrate buffer and extraction. The desired alcohol VI^{3a} was then isolated in 35% yield by chromatography on silica gel (R_f 0.60 using ethyl acetate). As expected from the fact that optically pure phosphonium salt XII was used, none of the epimeric allylic alcohol was present in the reaction product.

The synthesis of the (S)-(+)-phosphonium iodide was carried out starting from readily available and inexpensive natural (S)-(-)-malic acid *via* (S)-(-)-1,2,4-butanetriol⁸ and the corresponding acetonide VII,³ $[\alpha]^{25}_D -1.29^{\circ}$ (*c* 4.6, CH_3OH). Collins oxidation⁴ of VII gave the aldehyde VIII³ in 99% yield further transformed into the *cis*-olefin IX³ in 70% yield by reaction with propyldienetriphenylphosphorane in tetrahydrofuran (-78° for 30 min, 0° for 30 min, and 25° for 30 min); $[\alpha]^{25}_D +25.7^{\circ}$ (*c* 1.0, $CHCl_3$). *Anal.* Found for IX: C, 70.75; H, 10.64. Hydrolysis of IX in 2 *N* hydrogen chloride in methanol at reflux for 4 hr gave 96% yield of the diol X,³ $[\alpha]^{25}_D +9.0^{\circ}$ (*c* 1.0, $CHCl_3$), which was converted to a primary monotosylate³ (80% yield) with 1 equiv of *p*-toluenesulfonyl

(1) A synthesis of racemic prostaglandin E_3 methyl ester has been outlined by U. Axen, J. L. Thompson, and J. E. Pike, *Chem. Commun.*, 602 (1970).

(2) E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971).

(3) Satisfactory (a) nuclear magnetic resonance and infrared spectra and (b) mass spectra were obtained for this oily intermediate after chromatographic purification; only one component could be detected by thin-layer chromatography using several solvent systems.

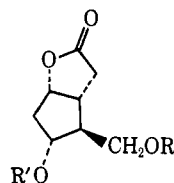
(4) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(5) The intermediate III was also obtained from the methyl ether corresponding to the benzyl ether I [E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *J. Amer. Chem. Soc.*, **92**, 397 (1970); **91**, 5675 (1969)] by the sequence (1) acetylation, (2) methyl ether cleavage with boron tribromide, (3) acetate saponification, (4) selective trichloroacetylation of the primary alcohol function in IV, (5) etherification of the secondary alcohol function with dihydropyran, and (6) saponification of trichloroacetate. The intermediate diol IV was crystalline, mp 115.5 – 116° , $[\alpha]^{25}_D -43.8^{\circ}$ (*c* 1.04, CH_3OH). *Anal.* Found: C, 55.66; H, 7.02.

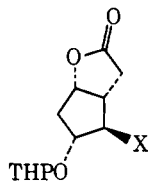
(6) E. J. Corey and H. Yamamoto, *ibid.*, **92**, 226, 3523 (1970).

(7) E. J. Corey and H. Yamamoto, *ibid.*, **92**, 6636 (1970).

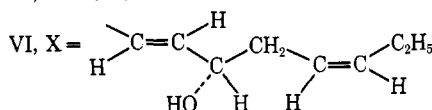
(8) P. W. Feit and O. T. Nielsen, *J. Med. Chem.*, **9**, 416 (1966).



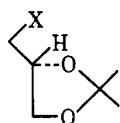
- I, R = CH₂C₆H₅; R' = H
 II, R = CH₂C₆H₅; R' = THP
 III, R = H; R' = THP
 IV, R = H; R' = H



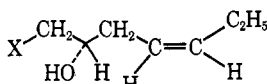
V, X = CHO



VI, X =

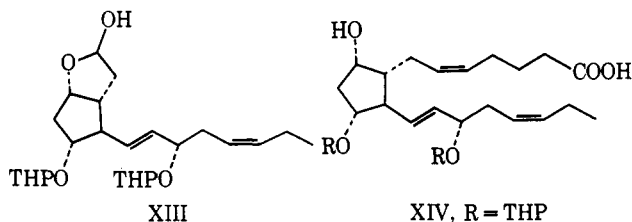


VII, X = CH₂OH
 VIII, X = CHO



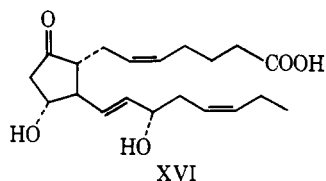
IX, X =

X, X = OH
 XI, X = I
 XII, X = (C₆H₅)₃P⁺



XIII

XIV, R = THP
 XV, R = H



XVI

chloride in pyridine at -20° for 5 hr and 0° for 12 hr and thence to the iodo alcohol XI³ (NaI in acetone, 96% yield), $[\alpha]^{25}_{\text{D}} +12.4^{\circ}$ (c 1.0, CHCl₃). Prolonged reaction of XI with 2 equiv of triphenylphosphine in benzene at $40-45^{\circ}$ (8–20 days) afforded cleanly the (*S*)-(+)-phosphonium iodide XII³ as a solid foam, $[\alpha]^{25}_{\text{D}} +45.8^{\circ}$ (c 1.0, CHCl₃).

Reaction of the allylic alcohol VI with dihydropyran as described for II yielded the corresponding bis-THP derivative,³ $[\alpha]^{25}_{\text{D}} -40.5^{\circ}$ (c 0.84, methanol), which was transformed in >98% yield to the lactol XIII^{3a} by exposure to 2 equiv of diisobutylaluminum hydride in toluene at -60° for 20 min; $[\alpha]^{25}_{\text{D}} -35.9^{\circ}$ (c

1.06, CHCl₃). Treatment of the lactol XIII with the Wittig reagent derived from 5-triphenylphosphonovale-ric acid⁵ in dimethyl sulfoxide⁹ produced stereospecifically the 11,15-bistetrahydropyranyl derivative of prostaglandin F_{3α} (XIV),^{3a} $[\alpha]^{25}_{\text{D}} -4.9^{\circ}$ (c 0.82, CHCl₃), in 66% yield. This derivative was converted by hydrolysis in acetic acid–water–tetrahydrofuran, 19:11:3, at 45° for 1 hr into prostaglandin F_{3α} (XV),³ $[\alpha]^{25}_{\text{D}} +29.6^{\circ}$ (c 0.54, tetrahydrofuran), homogeneous in five different solvent systems^{10,11} on silica gel and silica gel–silver nitrate. Oxidation of XIV with 1.1 equiv of chromic acid–acetone (Jones) reagent at -10° for 25 min followed by removal of the tetrahydropyranyl groups and chromatography on silica gel using 10% methanol–chloroform led to prostaglandin E₃ (XVI),³ $[\alpha]^{25}_{\text{D}} -48.9^{\circ}$ (c 1.2, tetrahydrofuran), spectroscopically and chromatographically identical with prostaglandin E₃ of natural origin.¹² The mass spectrum of the methyl ester diacetate methoxy oxime of XVI provided additional confirmation of structure.¹³

All of the known primary prostaglandins have now been prepared by chemical synthesis in biologically active, naturally occurring form, and our original objective of the synthesis of these substances from a common intermediate has been achieved.

Acknowledgment. This research was assisted financially by a grant from the National Institutes of Health.

(9) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(10) N. H. Andersen, *J. Lipid Res.*, **10**, 316 (1969).

(11) K. Gr  n and B. Samuelsson, *ibid.*, **5**, 117 (1964).

(12) We are indebted to Dr. Bengt Samuelsson, Department of Medical Chemistry, Royal Veterinary College, Stockholm, and Dr. John Pike the Upjohn Co., for reference samples of naturally derived prostaglandin E₃.

(13) K. Gr  n, *Chem. Phys. Lipid*, **3**, 254 (1969).

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New Reagents for Stereoselective Carbonyl Reduction. An Improved Synthetic Route to the Primary Prostaglandins

Sir:

This communication describes three significant improvements in the previously described synthesis¹ of primary prostaglandins, including the application of a new reagent for stereoselective carbonyl reduction. Successive alkylation of cyclopentadiene with chloromethyl benzyl ether using the thallium method,² cupric fluoroborate catalyzed addition of 2-chloroacrylonitrile,² and hydrolysis using potassium hydroxide in dimethyl sulfoxide² afforded the bicyclic ketone I.³ Crude I was subjected to reaction with *m*-chloroperbenzoic acid–sodium bicarbonate in methylene chloride at 0 to -10° to form a lactone¹ which was directly

(1) (a) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, **91**, 5675 (1969); (b) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970).

(2) E. J. Corey, U. Koelliker, and J. Neuffer, *ibid.*, **93**, 1489 (1971).

(3) The only purification step involved was the filtration of I through a fivefold amount of silica gel.