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SYNTHESIS OF (±) 11-DEOXYPROSTAGLANDIN E_1, $F_{1\alpha}$ and $F_{1\beta}$ AND ITS 15β-EPIMERS BY CONJUGATE ADDITION OF NITROMETHANE TO 2-(6'-CARBOMETHOXYHEXYL)-2-CYCLOPENTEN-1-ONE[1]

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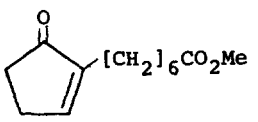
We wish to report an efficient synthesis of 11-deoxy PGE_1[9], 11-deoxy $PGF_{1\alpha}$, and 11-deoxy $PGF_{1\beta}$ and its 15β epimers *via* the key intermediate 2-(6'-carbomethoxyhexyl)-cyclopenten-1-one-3-carboxaldehyde (6).

Michael addition of nitromethane to the ketone 1[7a], catalyzed with tetramethylguanidine[2], at room temperature afforded the nitroketone 2 in 84% yield[3] [oil; ir 1750, 1551 cm^{-1}; nmr 3.62 (s, 3H, $O\underline{CH}_3$), 4.5 ppm (m, 2H, $-\underline{CH}_2NO_2$); m/e 254 ($285-OCH_3$).] Transformation of this compound into the cycloethylene ketal 3 was effected with ethylene glycol in benzene solution in the usual manner, to afford 3 in 95% yield [oil; ir 1745 (s), 1550 (s), 1360 cm^{-1}; nmr 2.18 (broad t, J=7, $C\underline{H}_2$ $COOCH_3$), 3.65 (s, 3H, $O\underline{CH}_3$), 3.89 (s, 4H, $O\underline{CH}_2\underline{CH}_2O$), 4.25-4.58 ppm (m, 2H, $-\underline{CH}_2NO_2$); m/e (329).] Treatment of a tetrahydrofuran solution of 3 with 0.1 N aqueous potassium hydroxide, generated the potassium nitronium salt 4. After removal of the organic solvent under reduced pressure, the resulting aqueous solution of 4 was buffered to pH 7 with magnesium sulfate and oxidized at 0-5°C with a dilute solution of potassium permanganate[4] to give 5. Esterification with diazomethane afforded the unstable aldehyde 6 [nmr 2.24 (broad t, J=7, $C\underline{H}_2$ $COOCH_3$), 3.61 (s, 3H, OCH_3), 3.90 (s, 4H, OCH_2CH_2O), 9.6 ppm (d, J=2, 1H, CH=O)], which, on reaction with the anion of dimethyl 2-oxoheptylphosphonate followed by zinc borohydride reduction[5], yielded a mixture of C-15 epimeric alcohols 7. Hydrolysis of this mixture in 65% aqueous acetic acid at room temperature, yielded a 1:1 mixture of carbinols 8 which was separated by chromatography on silica gel to yield the more polar 15α alcohol [ir 3470, 2960 (sh),

2935, 2860, 1740, 960 cm^{-1}; m/e (352); nmr 0.88 (broad t, J=6, 3H, CH_3), 2.25 (t, J=7, $\underline{CH}_2$ $COOCH_3$), 3.63 (s, 3H, OCH_3), 4.06 (m, 1H, $\underline{CH}$-O), 5.6 ppm (m, 2H, CH=CH) and the less polar 15β alcohol [ir, ms and nmr identical with 15α epimer.] Hydrolysis of these compounds with 0.1 N aqueous sodium hydroxide in tetrahydrofuran solution at room temperature yielded 11-deoxyprostaglandin E_1 (9)[6,7], 16% from 3 [mp 82.5-85°; ir 1720, 960 cm^{-1}; nmr 0.88 (broad t, J=6, 3H, CH_3), 2.29 (t, J=7, $\underline{CH}_2$ $COOCH_3$), 4.08 (m, 1H, $\underline{CH}$-O), 5.55 ppm (m, 2H, CH=CH); m/e (338) and 15-epi-11-deoxyprostaglandin E_1 (10), 19% from 3 [mp 53-56°; ir, nmr, and ms identical with that of 11-deoxy-PGE_1.

Reduction of 11-deoxy PGE_1 methyl ester with sodium borohydride gave a nearly quantitative yield of a mixture of 11-deoxy $PGF_{1\alpha}$ and 11-deoxy $PGF_{1\beta}$. Separation of this mixture of alcohols was accomplished by preparative thin layer chromatography on silica gel using an ethyl acetate/hexane system. The esters were hydrolyzed in tetrahydrofuran solution with 0.1 N aqueous sodium hydroxide to yield 11-deoxy $PGF_{1\alpha}$[8] 11 [mp 97-98.5°; ir 1695 (s), 975 (s) cm^{-1}; nmr 2.31 (t, J=7, $\underline{CH}_2$ $COOCH_3$), 4.00-4.30 (m, 2H, $\underline{CH}$OH), 5.18-5.49 ppm (m, 2H, $\underline{CH}$=$\underline{CH}$); m/e 340] and 11-deoxy $PGF_{1\beta}$ 12 [mp 69-70.5°; ir 1740 (s), 990 (s) cm^{-1}; nmr 2.3 (t, J=7, $\underline{CH}_2$ $COOCH_3$), 3.78-4.1 (m, 2H, $\underline{CH}$OH), 5.24 ppm (m, 2H, $\underline{CH}$=CH); m/e 322 (340-H_2O).] Similarly, 15-epi-11-deoxy-PGE_1 (10) was transformed into 15-epi-11-deoxy $PGF_{1\alpha}$ 13 [mp 102-103.5°; ir 1700 (s), 1640 (s), 970 (s) cm^{-1}; nmr 2.3 (t, J=7, $\underline{CH}_2$ $COOCH_3$), 4.3-4.95 (m, 2H, $\underline{CH}$OH), 5.35-5.5 ppm (m, 2H, $\underline{CH}$=$\underline{CH}$); m/e as the methyl ester 336 (354-18)] and 15-epi-11-deoxy $PGF_{1\beta}$ 14 [mp 59.0-60.5°; ir 1690 (s), 970 (s) cm^{-1}; nmr 2.9 (t, 2H, J=7, $\underline{CH}_2$ $COOCH_3$), 3.8-4.1 (m, 2H, $\underline{CH}$OH), 5.48 ppm (m, 2H, $\underline{CH}$=$\underline{CH}$); m/e as methyl ester (336) (354-18).][9]



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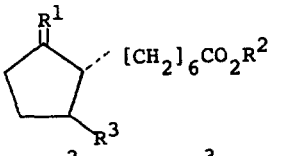
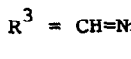
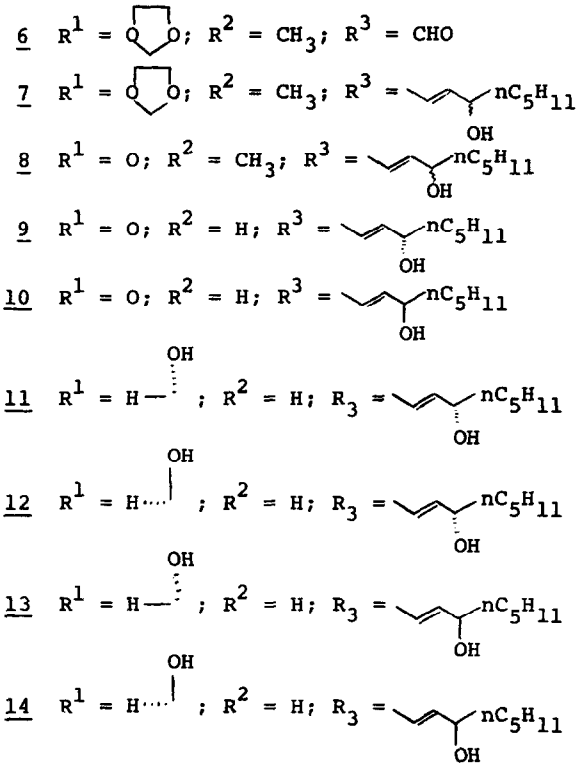


2 R^1 = O; R^2 = CH_3; R^3 = CH_2NO_2

3 R^1 =  ; R^2 = CH_3; R^3 = CH_2NO_2

4 R^1 =  ; R^2 = $K^{\oplus}$; R^3 = 

5 R^1 =  ; R^2 = H; R^3 = CHO



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3. The yields given throughout this paper are the minimum and the reaction conditions have not been optimized.

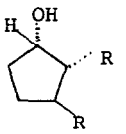
4. A. Shechter, F. T. Williams, Jr., J. Org. Chem., 27, 3699 (1972).

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

6. Assignment of configuration at C-15 has been based on direct comparison of alcohol (9) with an authentic sample of 15-(S)-15-hydroxy-9-oxa-prosta-13-trans enoic acid, prepared by hydrogenation of 15-(S)-15-hydroxy-9-oxa-prosta-10,13-trans-dienoic acid (PGA_1) with 5% Pd/C in methanol solution at -10 to -25°. These compounds showed no differences in their nmr, ms, ir and tlc behaviour.

7. The synthesis of (±)-11-deoxyprostaglandin F_1 as a mixture of stereoisomers has been reported, cf.: (a) J. F. Bagli, T. Bogri, R. Deghenghi, K. Wiesner, Tetrahedron Letters, 5, 465-470 (1966), and (b) M. P. L. Caton, E. C. J. Coffe, and G. L. Watkins, Tetrahedron Letters, 773 (1972).
(c) After completion of this work, two papers appeared in the literature describing the preparation of 9 and 10 by two different routes, cf.: C. J. Sih, R. G. Salomon, P. Price, R. Sood, and G. Peruzzotti, Tetrahedron Letters, 24, 2435-3437 (1972), and J. F. Bagli and T. Bogri, J. Org. Chem., 37, 2132 (1972).

8. (a) The configuration at C-9 was determined by C^{13} nmr studies. This analysis will be the subject of a separate report, M. Maddox, F. Alvarez, and L. Tökés, J.C.S. Chem. Comm., submitted for publication.
(b) It has been shown unambiguously that carbinolic proton signals at C-9 in 9α alcohols in trisubstituted cyclopentanes I appear consistently at low field in the nmr, relative to those in the 9β alcohols II:



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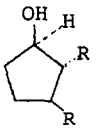

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cf.: J. F. Bagli and T. Bogri, Tetrahedron Letters, 5 (1967); J. F. Bagli and T. Bogri, J. Org. Chem., 37, 2132 (1972).

9. Throughout this paper all intermediates and final compounds are racemic. Satisfactory elemental analysis were obtained for all fully characterized compounds. Nmr spectra were obtained on Varian A-60 and HA-100 spectrometers in deuteriochloroform solution (10% w/v) containing tetramethylsilane as internal reference. Chemical shifts are reported as parts per million on the δ scale. We thank Dr. M. Maddox and Mrs. P. Nelson for these determinations. In the presentation of data, m = multiplet, s = singlet, t = triplet. The mass spectra were obtained with an Atlaswerke CH-4 spectrometer equipped with a direct inlet system. Spectra were measured at an ionizing potential of 3 KV. We thank Mr. B. Amos, Mr. J. Smith, and Dr. L. Tökés for assistance with these measurements.