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SYNTHESIS OF (±)- AND 15-EPI-(±)-10,10-DIMETHYLPROSTAGLANDIN E_1

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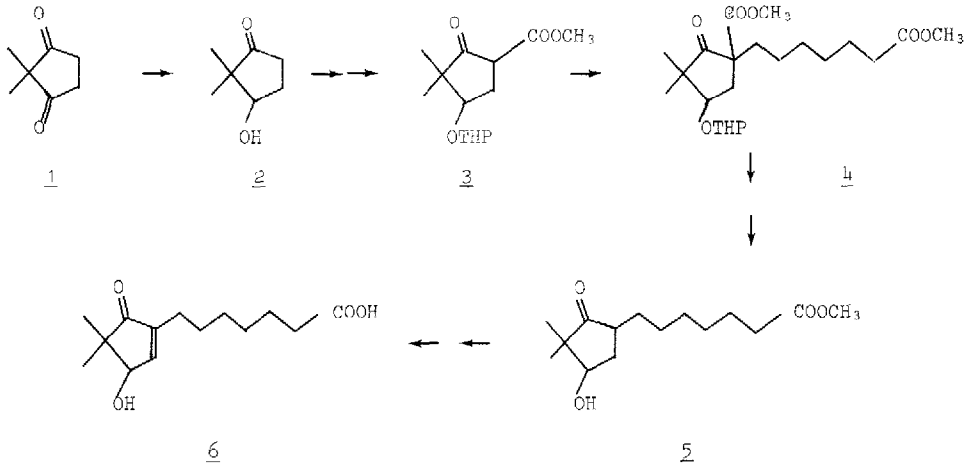
The therapeutic usefulness of E-type prostaglandins (PGs) is compromised by the rapid metabolic oxidation[1] of the C-15 hydroxyl group, and by the pH-sensitive β-ketol group which easily dehydrates[2] to give A-type PGs[3]. We report herein the synthesis of a PG E analogue, 10, 10-dimethyl PG E_1, which does not suffer from the latter type of instability[4].

2,2-Dimethyl-1,3-dione (1)[5,6] was reduced (H_2, 30°C, 1 atm., PtO_2, 2-propanol) to the ketol (2) b.p. 73°C/0.2mm (94% yield). Compound (2) was converted to its tetrahydropyranyl ether (dihydropyran, methylene chloride, trace of p-toluenesulfonic acid) and then alkylated with methyl carbonate (2 equiv.) and sodium hydride in benzene to give (3). Treatment of (3) with methyl-7-bromo-heptanoate (1.2 equiv.) and sodium hydride (1.2 equiv.) in dimethylformamide at reflux for two hours gave (4) which after base (20% ethanolic KOH, reflux 20 minutes) then acid (30% methanolic HCl, reflux two hours) treatment yield the PG precursor (5).



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Bromination of (5) with bromine (1 equiv.) in chloroform containing 0.01 % hydrogen bromide, followed by dehydrobromination with sodium hydroxide (3 equiv.) in methanol gave the cyclopentenone (6) in an overall yield of 32 % from ketol (2). Compound (6) has m.p. 65-66°C (from diisopropyl ether); λ max. (EtOH) 223 nm, ε 7300. Esterification of (6) with diazomethane followed by reaction with nitromethane in methanol containing sodium methoxide (2 equiv.) gave a mixture of epimers (7) and (8) which was easily separated (silica gel, 1:1 diethyl ether/pentane). Compound (7), m.p. 85-88°C, was obtained in 51 % yield based on unreacted (6); the less polar (8), an oil, was obtained in 30 % yield. The stereochemistry of these compounds was established by 90 MHz H^1 n.m.r. (Table)[7].

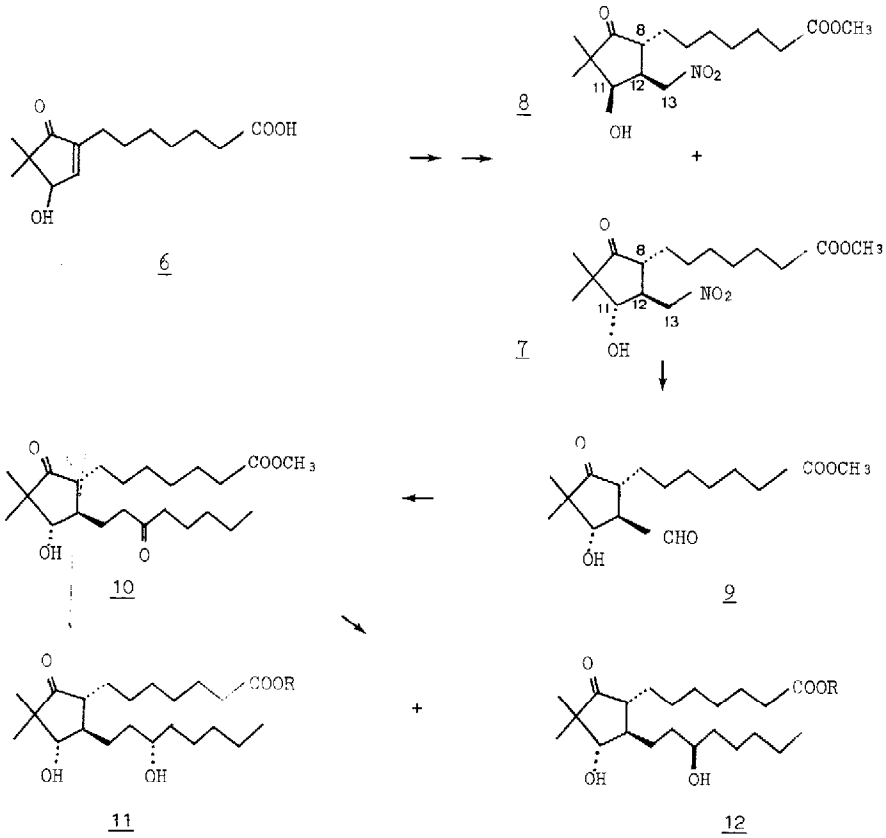
TABLE

90 MHz n.m.r. spectra obtained in $CDCl_3$ solution at room temperature.

	Compound (7)	Compound (8)
	Chemical shift (ppm)	
H - 8	2.08	2.18
H - 11	3.84	4.0
H - 12	2.62	2.9
H - 13	4.7	4.88
H - 14		4.5
	Coupling Constants (Hz)	
$J_{8,12}$	12	12
$J_{11,12}$	10	4
$J_{12,13}$	5.5	9.5
$J_{12,13'}$		4.8

Compound (7) was converted to aldehyde (9) in 86 % yield by a modified Nef reaction[8]. In the n.m.r., the H-11 doublet moves downfield to 4.1 ppm, and the coupling constant $J_{11,12}$ of 9 Hz shows that the stereochemistry of the nitromethylene precursor has been retained. Wittig-Horner reaction of (9) with the sodium salt of dimethyl 2-oxoheptylphosphonate[9] gave (10) in

64 % yield after silica gel chromatography. A coupling constant of 16 Hz ($J_{13,14}$) establishes the trans configuration of the double bond. Selective reduction of the C-15 ketone function of (10) was obtained using lithium tri-sec-butylborohydride (L-Selectride, 1 equiv.) in tetrahydrofuran at -78°C. The two epimers (11a),m.p. 50-52°C (42 % yield) and the less polar (12a), an oil (30 % yield) were easily separated by silica gel chromatography and have virtually identical 90 MHz n.m.r. spectra. Assignment of the configurations at C-15 is based on the relative polarities on silica gel of (11a) and (12a) and of (11b) and (12b), compared with those of PG E_1, 15-epi-PG E_1 and their methyl esters. Biological potencies of the final compounds provide support for these assignments[10]. The esters (11a) and (12a) were saponified in methanolic potassium hydroxide at reflux, followed by acidification and extraction to yield racemic 10,10-dimethyl PG E_1 (11b), m.p. 99-101°C, and its less polar C-15 epimer (12b), an oil, each in greater than 95 % yield.



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4) Since the completion of this work a synthesis of 10,10-dimethylprostaglandin F_1 (as its methyl ester) has been reported: O.G. PLANTEMA, H. de KONING and H.O. HUISMAN. Tetrahedron letters,2645 (1975).

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6) Each numbered compound has been characterised by H^1 n.m.r. spectra. Compounds 6, 7, 8, 11a, 11b, 12a and 12b have been additionally characterised by elemental analyses (crystalline compounds) and high resolution mass spectra. The yields quoted are for pure products.

7) For comparison see:
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10) When tested on the isolated rat uterus compounds (11a) and (11b) showed a weak muscular agonistic activity (about 1/1000 that of PG $F_{2\alpha}$); at the same concentration the 15 epimers (12a) and (12b) were inactive.