Tetrahedron Letters No. 9, pp 773 - 774, 1972. Pergamon Press. Printed in Great Britain.

PROSTAGLANDINS - A NEW TOTAL SYNTHESIS OF (±)-11-DEOXYPROSTAGLANDINS

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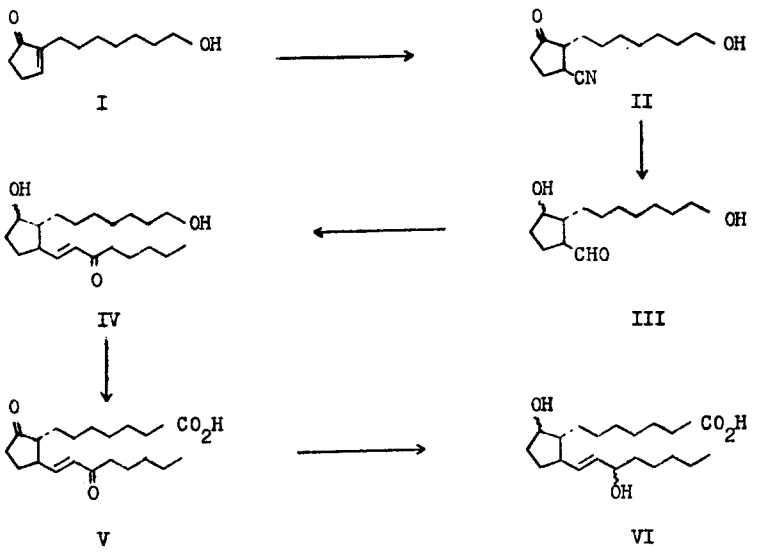
(Received in UK 19 January 1972; accepted for publication 27 January 1972)

Biologically active 11-deoxyprostaglandins are available by total synthesis[1-4] and from hydrogenation of prostaglandin A_1[5]. We wish to report a new route where the cyclopentenone I, readily prepared from cyclopentanone and 7-hydroxyheptanal, has been converted into these compounds by a simple sequence which avoids the use of protecting groups.

Alkylidene cyclopentanones are available in good yields from the reaction of aldehydes with a cyclopentanone enamine followed by hydrolysis[6]. We have found that this reaction can be extended to give alkylcyclopentenones if the crude hydrolysis products are heated at 100° with hydrochloric acid in n-butanol to effect isomerisation of the double bond to the endocyclic position. By this means 7-hydroxyheptanal, conveniently prepared from 6-cyanohexanol[7] by reaction with diisobutylaluminium hydride in ether-benzene, and cyclopentanone morpholine enamine were readily converted, without isolation of intermediates, into the required enone I: b.p. 135-140°/0.4mm; ν max. 1690, 1625, 795cm^{-1}; λ max. (EtOH) 227mμ, ε 9400; nmr ($CDCl_3$) 7.28δ (m, -CH=C<), 3.55δ (t, CH_2CH_2OH), 2.85δ (s, CH_2OH).

The enone I reacted with acetone cyanohydrin in aqueous methanol in the presence of sodium carbonate to give the nitrile II: n_D^{25} 1.4795; ν max. 2025, 1730cm^{-1}; the trans stereochemistry being assigned by analogy with earlier work[1-2]. Treatment with diisobutylaluminium hydride in ether-benzene at 10° and subsequent work-up with aqueous acetic acid yielded the hydroxyaldehyde III: b.p. 185-193°/0.1mm; ν max. 3400, 1705cm^{-1} which on Wittig coupling with hexanoylmethylene triphenylphosphorane[8] afforded the enone IV: λ max. (EtOH) 230mμ, ε 12,900. The latter was oxidised with 8N-Jones Reagent[9] at 15-25° to (±)-11-deoxy-15-dehydroprostaglandin E_1 V, which was purified by chromatography on silica gel: ν max. 1730, 1700, 1670, 1625, 980cm^{-1}; λ max. (EtOH) 228mμ, ε 12,300; nmr ($CDCl_3$) 9.68δ (s, COOH), 6.88δ (2d, J 16 c/s, J 7 c/s, CH=CHC=O), 6.17δ (d, J 16 c/s, CH=CHC=O), 0.98δ (t, J 5 c/s, CH_2CH_3).

11-Deoxyprostaglandins of the F_1 series can be prepared from V by suitable reduction procedures. Thus reaction with sodium borohydride in aqueous ethanol gave the (±)-11-deoxyprostaglandin F_1VI[1-2] as a mixture of stereoisomers, and hydrogenation at 400 psi over Raney nickel to the saturated diketo acid, followed by borohydride reduction afforded an epimeric mixture of the corresponding dihydro compound[3].



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