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CYCLOPENTANONES. VIII*

A STEREOSELECTIVE SYNTHESIS OF (dl) 8-epiPROSTAGLANDIN $F_{1\alpha}$.

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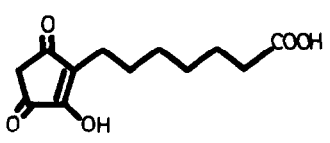
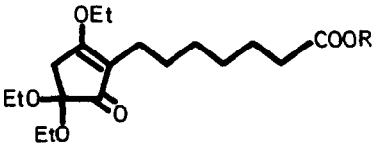
A previous paper[1] described the potentiality of 3-alkyl-1,2,4-cyclopentanetriones (in the mono enol form I) as starting materials for the synthesis of the prostaglandin skeleton. In this communication we wish to report the synthesis of prostaglandins of the F_1 series. A key intermediate is compound IIa which allows specific reaction at the 2-carbonylfunction of I. Compound IIa was obtained (yield 72 %) by refluxing I with triethyl orthoformate in dry ethanol and p.toluene sulphonic acid as a catalyst and slowly distilling of the ethyl formate (18 hrs), followed by the hydrolysis (1 eq. 0.1 N NaOH at r.t.) of the intermediate ester IIb. The acid IIa [I.R.; 1725, 1700, 1625, 1050 cm^{-1} : U.V. (CH_3OH); λ_{max} = 263 nm (ε = 14.800) : R_f = 0.49 with ethyl acetate-isooctane-acetic acid 60:40:8] was extracted, at pH 6, with ether; the crude compound was sufficiently pure for the next step. A Grignard reaction of IIa with 1-octyne (4-eq.) in tetrahydrofuran and subsequent hydrolysis at pH 6 yielded III, which was smoothly converted to IV, by sodium borohydride in a phosphate buffer solution (water-ethanol 1:1) at pH 8. After acid hydrolysis (0.1 N HCl; r.t.; 15 min) the crude reaction product was purified by C.C.D. (ether/phosphate buffer pH 8.15, water-methanol 1:1); after 120 transfers compound IV (K = 1.1) was collected in a over-all yield (from IIa) of 48 % [M^+ at m/e 334; I.R.; 3400, 2230, 1720, 1715, 1635 cm^{-1} : U.V. (CH_3OH); λ_{max} = 263 nm (ε = 16.000): P_f = 0.51 with ethyl acetate-isooctane-acetic acid 60:40:8].

Reduction of IV in the di-anion form (prior treatment with two eq. sodium hydride in THF) with an excess lithium in liquid ammonia-ethanol (90 eq)-THF in

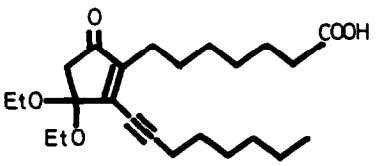
* Part VII : ref. 2.



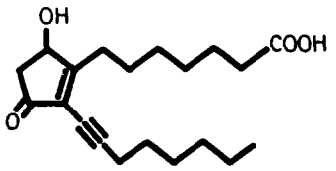
I



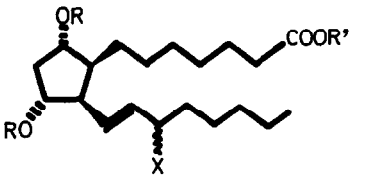
IIa R=H
IIb R=Et



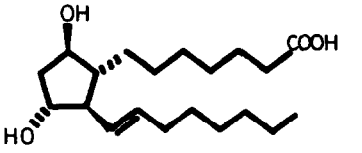
III



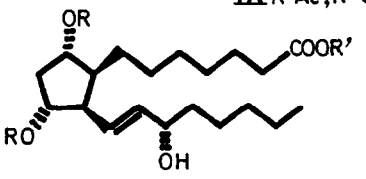
IV



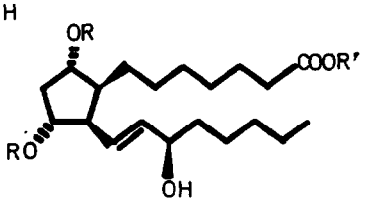
V R=R'=X=H
VII R=X=H; R'=CH3
VIII R=Ac; R'=CH3; X=H
IX R=Ac; R'=CH3; X=H



VI



X R=Ac R'=CH3
XI R=H R'=CH3
XII R=R'=H



XIII R=Ac R'=CH3
XIV R=H R'=CH3
XV R=R'=H

the presence of sodium ethoxide (20 eq) and working up with ammonium chloride yielded the 2,3-dialkyl-1,4-cyclopentanediols in a total yield of 56 % after purification by column chromatography (silicagel and benzene-dioxane 5:4 as eluent) The diastereoisomers[≠] formed were separated by C.C.D. (ether/phosphate buffer pH 9, water-methanol 3:1). After 1340 transfers V (K = 0.35; 75 %), VI (K = 0.27; 15 %) were collected. Two other products were also found; a diastereoisomer with unknown configuration, but two hydroxyl function in cis position (K = 0.5; 5 %) and a side chain saturated product (K = 0.47; 5 %) with the same configuration as

≠ For the stereochemistry of the lithium-liquid ammonia reduction of 2,3-dialkyl-4-hydrocyclopentenones and configurational assignment by NMR see ref. 2.

The relative R_f values (silicagel and benzene-dioxane 5:4 are 0.30 (V); 0.29 (VI); 0.37 and 0.29.

The diastereoisomer V was further purified as the methyl ester (VII) by column chromatography on silicagel and ethyl acetate as eluent [(VII : M^+ (diTMS ether) m/e 498; I.R. ; 3400, 1750 and 970 cm^{-1}; R_f = 0.33 (silicagel with ethyl acetate)].

Compound VII, was converted by acetic acid anhydride-pyridine (r.t. 8 hrs) to VIII which was purified by column chromatography (silicagel and isooctane-chloroform 60:40). [$(M-2xHOAc)^+$ at m/e 318; I.R.; 1740, 1240 and 965 cm^{-1} : R_f = 0.75 (ethylacetate 1 % acetic acid as eluent)].

Treatment of VIII with NBS (reflux in CCl_4 for 30 min) yielded IX which was directly converted to a mixture of the epimers X and XIII, with silver carbonate on celite[3] (freshly prepared) in aceton for 1 hr at 0°C.

Separation of the two 15-epimers X and XIII (ratio ca. 6:4) was accomplished by column chromatography on silicagel and chloroform - ethyl acetate (7:3) as eluent (total yield 60 % from V); on the basis of chromatographic and TLC behaviour[4] the more polar epimer is assigned as X (R_f = 0.37; silicagel, chloroform-ethyl acetate 7:3) and the less polar as XIII (R_f = 0.44) [X and XIII ; $(M - 2xHOAc)^+$ at m/e 334; I.R.; 3420, 1745, 975 cm^{-1}]. Hydrolysis of X with potassium carbonate in methanol (r.t., 4 hr) yielded after column chromatography (silicagel and acetone-ethyl acetate 1:1) the methyl ester of (dl) 8-epi $PGF_{1\alpha}$ [XI : M^+(tri TMSether) at m/e 586; I.R.; 3420, 1745 and 975 cm^{-1}][5]. Further hydrolysis with potassium carbonate in water-methanol[6] yielded (dl) 8-epi $PGF_{1\alpha}$ [XII : I.R.; 3420, 3000-2600, 1710 and 975 cm^{-1}.; ^{1}HNMR (300 MHz, CD_3OD); 8-H δ = 2.03 (m), 10-Hα δ = 2.46 ($J_{8H\alpha,H\beta}$ = 15.0 Hz δ = 5.39 ($J_{13,14}$ = 15.22, $J_{12,13}$ = 8.85), 14-H δ = 5.48 ($J_{14,15}$ = 6.55)].

The 15-β epimer XV was obtained in the same way from XIII. The relative mobilities on TLC (silicagel; ethylacetate, acetic acid, isooctane, water (106, 12, 24, 50) are 0.39 (XI), 0.22 (XII) 0.41 (XIV) and 0.29 (XV).

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