Tetrahedron Letters No. 49-50, pp 4343 - 4346, 1974. Pergamon Press. Printed in Great Britain.

CYCLOPENTANONES. XI[x]. A NOVEL PREPARATION OF A PROSTANOID SYNTHON STARTING FROM A 3-ALKYL-1,2,4-CYCLOPENTANETRIONE

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The compound XIX generally known as Corey's lactone[1] is an important key intermediate for the synthesis of prostaglandins. Our investigation[2,3] on the potentiality of 3-alkyl-1,2,4-cyclopentanetriones (such as I in the mono enol form) as starting materials for prostaglandin synthesis has led to an independent preparation of this synthon.

Compound II [m.p. 53° : I.R. : 1700, 1625, 1120 cm^{-1}; U.V. (CH_3OH) : λ_{max} = 261 nm; Rf = 0.33 with ether-benzene 1:1] was obtained from I in 80 % yield (after recrystallisation from n.pentane) by a general and already described method[3,4]. An organozinc reaction of II with crotyl bromide (3 eq.) in tetrahydrofuran and subsequent refluxing in HMPA[5] followed by acid hydrolysis (1 N HCl : 1 hr) produced III in 81 % yield after column chromatography (silicagel : isooctane-ether 7:3) [$M^{+\cdot}$ at m/e 208; I.R. : 1745, 1710, 1640 cm^{-1}; U.V. (CH_3OH) : λ_{max} = 245 nm; Rf = 0.53 with ether-benzene 1:1]. Reduction with zinc-acetic acid in methylene chloride at -20°C gave a mixture of the isomeric cyclopentenolones IV and IV' in high yield, sufficiently pure and both usable the next reaction [$M^{+\cdot}$ at m/e 210; I.R. : 3400, 1710, 1650 cm^{-1}; U.V. (CH_3OH) : λ_{max} = 230 nm; Rf = 0.32 with ether-benzene 1:1]. A key step in the synthesis is the reduction of these enolones with lithium (8 eq) in liquid ammonia-tetrahydrofuran in the presence of a hydroxylic proton donor.

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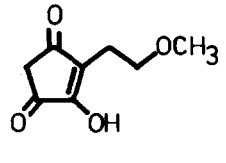
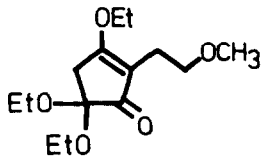
[x] Part X : ref. 3.

[+] Bursary of the I.W.O.N.L.

[≠] Aspirant of the N.F.W.O.



I



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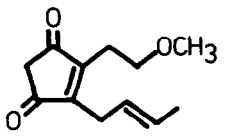

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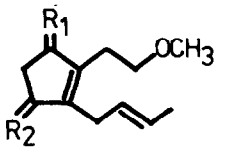
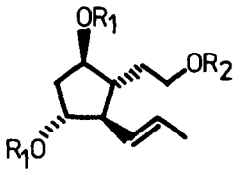
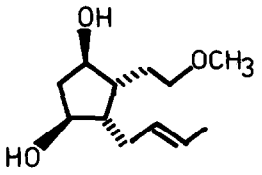


IV, R_1=O ; R_2 

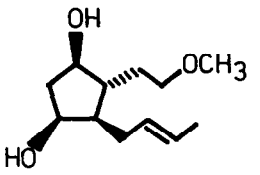
IV, R_1  ; R_2=O



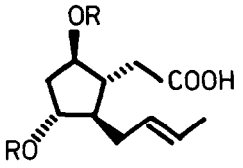
V, R_1=H ; R_2=CH_3
VIII, R_1=Ac ; R_2=CH_3
IX, R_1=Ac ; R_2=H



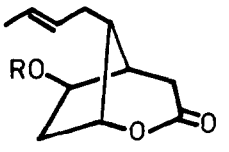
VI



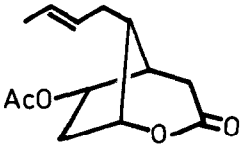
VII



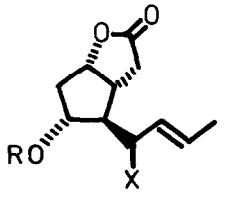
X, R = Ac
XI, R = H



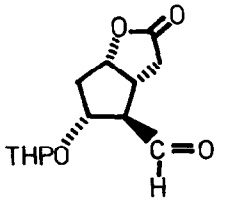
XII, R = H
XIII, R = Ts



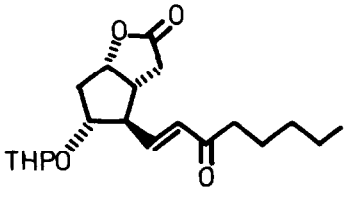
XIV



XV, R = H ; X = H
XVI, R = THP; X = H
XVII, R = THP; X = Br
XVIII, R = THP; X = OH



XIX



XX

This reduction has a fairly high degree of stereoselectivity[6,7] as only three of the possible diastereoisomers are formed. The all-trans isomer* V is the only desired one for our purpose and can be obtained as the most abundant isomer (60 %)

* For configurational assignement of 1,4-dihydroxy-2,3-dialkylcyclopentanes see references 5 and 6.

when phenol[8] (8 eq) is the hydroxylic co-solvent; VI and VII are present for respectively 25 % and 15 %. After column chromatographic separation (silicagel : ethyl acetate; Rf = 0.38 with same eluent) the overall yield (from III) of the isomer V is 35 %. The di-acetate VIII [$(M-HO\bar{A}c)^{+\cdot}$ m/e 238, $(M-2\ HOAc)^{+\cdot}$ m/e 178; I.R. : 1745, 1250, 1115, 970 cm^{-1}; Rf = 0.86 with ethyl acetate] was formed (acetic anhydride - pyridine) in an almost quantitative yield. The methyl ether was cleaved with borontribromide (4 eq) in methylene chloride (-20° for 4 days; yield : 70 %) to the alcohol IX [I.R. : 3450, 1750, 1250, 970 cm^{-1}; Rf = 0.33 with ether-benzene 1:1]. Oxydation of IX with Jones reagent at -5° for 1 hr followed by removal of the acetate functions (40 % HCl, 80°, 3 hr) led to the dihydroxy-acid XI [Rf = 0.22 with ethyl acetate]. Treatment of XI with a catalytic amount p.toluene sulphonic acid in benzene (azeotropic distillation) and column chromatography (silicagel : ethyl acetate - benzene 1:1) produced the δ-lactone XII (overall yield from IX : 62 %) [$M^{+\cdot}$ at m/e 196 : I.R. : 3440, 1730, 965 cm^{-1}; Rf = 0.66 with ethyl acetate - benzene 7:3]. Inversion of the hydroxyl function as the tosylate XIII with tetraethyl ammonium acetate (4 eq in acetone at 60°, 16 hr) yielded the expected acetate XIV [$(M-HOAc)^{+\cdot}$ at m/e 178; I.R. : 1740, 1250, 970 cm^{-1}]. Acid hydrolysis (40 % HCl, 80°, 3 hr) followed by continueous extraction with ether and column chromatography (silicagel : ethyl acetate - benzene 1:1) led in an overall yield of 65 % (from XII) to the δ-lactone XV [$M^{+\cdot}$ at m/e 196 : $(M-H_2O)^{+\cdot}$ at m/e 178; I.R. : 3400, 1765, 970 cm^{-1}; Rf = 0.31 with ethyl acetate benzene 1:1]. The corresponding tetrahydropyranyl ether XVI [$(M-THP)^{+}$ m/e 195, $(M-OTHP)^{+}$ m/e 179; I.R. : 1760, 1130, 1080, 1040, 965 cm^{-1}; Rf = 0.75 with ethyl acetate - benzene 1:1], was formed (yield : 85 % after column chromatography on silicagel with ethyl acetate - benzene 2:8) with 1 eq. dihydropyran in methylene chloride and p.toluene sulphonic acid as catalyst. Treatment of XVI with NBS in refluxing carbon tetrachloride for 20 min produced the unstable bromide XVII (one spot on TLC). That no bromination on the methyl group had taken place was ensured by integration of the ^{1}H-NMR signals $C\underline{H}_3$-CH= (δ = 1.62) and HO-C$\underline{H}$-C= (δ = 4.15) in the corresponding alcohol XVIII. No allylic rearrangement could be detected, although the latter would not affect the ultimate out come. The alcohol XVIII, obtained by silver carbonate on celite in acetone (0°, 1 hr) was directly oxidised to the aldehyde XIX with sodium periodate

(4 eq)-osmium tetroxide (catalytic amount) in water - dioxane (20°, 6 hr). The unstable[1] aldehyde XIX was without purification treated with the sodio derivative of dimethyl-2-oxoheptylphosphonate by an already described method[1] yielding the enone XX [$(M-THP)^+$: m/e 265; (M-OTHP) : 249; I.R. : 1765, 1680, 1630 cm^{-1}; U.V. (CH_3OH) : λ_{max} = 226 nm; Rf = 0.71 with ethyl acetate]. The overall yield of XX starting from XVI was 42 % after purification on silicagel ethyl acetate - benzene (1:1) as eluent.

The remaining transformations for the synthesis of prostaglandins starting from XX are adequately described in the literature[1].

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