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THE NOVEL STEREOSPECIFIC SYNTHESIS OF 11-OXAPROSTAGLANDIN $F_{2\alpha}$

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The current literature shows a considerable interest in the synthesis of novel prostaglandins with potential specific pharmacological properties free of undesirable side-effects, for example those where the C-9 and C-11 functionalities have been replaced by a hetero atom.[1] In a previous communication we described[2] the stereospecific synthesis of an 11-oxaprostaglandin from D-xylose.

Herein we wish to report the novel syntheses of the 11-oxaprostaglandin intermediates IXc and IXd, with known absolute stereochemistry at the chiral centres, from D-glucose and D-xylose respectively, via preparation of the corresponding branched-chain sugars. In addition, 11-oxa $PGF_{2\alpha}$ has been synthesised from the lactone IXc, thus completing the transformation of D-glucose into a prostaglandin analog.

Condensation[3] of 1,2:5,5-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose (I) [4], prepared from D-glucose, with the potassium salt of triethylphosphonoacetate, followed by reduction (H_2/Ni) of the mixture of cis- and trans-unsaturated branched-chain sugars, gave compound III[5] [71%; m.p. 90-91°; $[\alpha]_D^{23}$ + 67° (c 1,1 $CHCl_3$)]. The 100 MHz n.m.r. spectrum confirmed the allo configuration: δ 5,75 (H-1, d, $J_{1,2}$ = 4 Hz), 4,78 (H-2, t, $J_{2,3}$ = 4 Hz). Selective hydrolysis of III (AcOH/H_2O/70°) gave the corresponding 5,6-diol as a colourless oil (76%) which was directly converted (Ac_2O/pyridine/$CHCl_3$) to IVa [78%; m.p.; 53-54°; $[\alpha]_D^{22}$ + 80° (c 2,1 $CHCl_3$); δ 5,79 (H-1, d, $J_{1,2}$ = 4 Hz), 4,78 (H-2, t, $J_{2,3}$ = 4Hz), 2,02 and 2,04 (AcO-, 2s)].

Treatment of IVa with 80% AcOH (90°/3hr) yielded the γ-lactone Va as an oil (72%), characterised as the crystalline 1-β,5,6-tri-O-acetate VIa [m.p. 106-107°; $[\alpha]_D^{23}$ - 69° (c 1,7 $CHCl_3$); δ 6,34 (H-1, s), 4,93 (H-2, d, $J_{2,3}$ = 6 Hz), 2,04 2,10 and 2,11 (AcO-, 3s).] Acylation of Va (p-$O_2NC_6H_4COCl$/pyridine/$CHCl_3$) gave VIIa which was directly converted (HBr/CH_2Cl_2 followed by C_6H_5SK/EtOH) via the furanosylbromide to the phenylthio furanoside VIIIa [80%; m.p. 113-115°; $[\alpha]_D^{23}$ + 248° (c 1,2 $CHCl_3$); δ 5,76 (H-1, d, $J_{1,2}$ = 5 Hz), 5,20 (H-2, dd, $J_{2,1}$ = 5 Hz), 2,04 and 2,08 (AcO-, 2s)].

Desulfurisation of VIIIa (Ni/EtOH) yielded IXa as an oil [80%; $[\alpha]_D^{23}$ + 22° (c, 6,4 $CHCl_3$); δ 4,52 - 3,92 (H-1 and H-6, m), 3,85 (H-4, dd, $J_{3,4}$ = 7,5 Hz, $J_{4,5}$ = 5,5 Hz), 2,05 and 2,07 (AcO-, 2s).] Deacetylation of IXa (K_2CO_3/MeOH/H_2O followed by Dowex 50W H^+) gave

1,4-anhydro-3-C-(carboxymethyl-2,3-γ-lactone)-3-deoxy-D-allitol IXc as crystalline needles [98%; m.p. 134-135°; $[\alpha]_D^{27}$ - 26° (c 1,2 80% EtOH)].

In an analogous series of reactions 5-O-benzoyl-1,2-O-isopropylidene-α-D-erythro-pentofuranos-3-ulose (II)[6] was converted into 1,4-anhydro-3-C-(carboxymethyl-2,3-γ-lactone)-3-deoxy-D-ribitol IXd, obtained as an oil, via:

IVb : M.p. 86-87°; $[\alpha]_D^{22}$ + 57° (c 2,2 $CHCl_3$); δ 5,86 (H-1, d, $J_{1,2}$ = 4 Hz), 4,80 (H-2, t, $J_{2,3}$ = 4 Hz), 3,66 (OCH_3, s).

Vb : M.p. 114-115°; $[\alpha]_D^{24}$ - 47° (c 1,0 $CHCl_3$); δ 5,60 (H-1, s), 4,91 (H-2, d, $J_{2,3}$ = 6 Hz).

VIIb : M.p. 130-132°; $[\alpha]_D^{24}$ + 175° (c 1,4 $CHCl_3$); δ 6,63 (H-1, s), 5,19 (H-2, d, $J_{2,3}$ = 6 Hz).

VIIIb : M.p. 129-130°; $[\alpha]_D^{24}$ - 30° (c 1,2 $CHCl_3$); δ 5,81 (H-1, d, $J_{1,2}$ = 5 Hz), 5,23 (H-2, dd, $J_{2,1}$ = 5 Hz and $J_{2,3}$ = 7,5 Hz).

IXb : M.p. 130-133°; $[\alpha]_D^{24}$ + 4° (c 1,7 $CHCl_3$); δ 5,11 (H-2, m), 4,54-3,96 (H-1, H-4 and H-5,m), 3,08-2,44 (H-3, H-1', m).

Oxidation of IXc ($NaIO_4$/80% EtOH) gave the aldehyde IXe as an oil, which was immediately reacted with the sodio derivative of dimethyl 2-oxoheptylphosphonate[7] in DME to give the enone IXf [m.p. 65-67°; $[\alpha]_D^{22}$ + 34° (c 0,9 $CHCl_3$)][5]. Reduction ($Zn(BH_4)_2$/DME) gave a mixture of the epimeric alcohols IXg m.p. 94-97°; $[\alpha]_D^{22}$ + 4° (c 1,8 $CHCl_3$)][8]. Conversion of IXg into the tetrahydropyranyl ether IXh, followed by reduction (DIBAL/ϕCH_3/-60°) gave the lactol X as an oil

Wittig condensation of X with the 5-triphenylphosphoniovalerate ion in DMSO [7], followed by removal of the THP group with AcOH/H_2O (7:3) gave the C-15 epimeric alcohols XI. The more polar isomer XII [m.p. 66-67°; $[\alpha]_D^{26}$ + 59° (c 1,3 $CHCl_3$)] was obtained crystalline after purification by preparation layer chromatography (silica gel, 0,25 mm plates) with AcOH/AcOEt (2:98) and has been tentatively assigned the 15S configuration by analogy to the tlc behaviour of natural prostaglandins.

REFERENCES AND FOOTNOTES

1. I.T. Harrison and V.R. Fletcher, Tetrahedron Letters, 2729 (1974); I.T. Harrison, V.R. Fletcher and J.H. Fried, ibid., 2733 (1974); S. Hanessian, P. Dextraze, A. Fougerousse and Y. Guindon, ibid., 3983 (1974); I. Vlattas and L. DellaVecchia, ibid., 4267, 4455, 4459, (1974); I. Vlattas and A.O. Lee, ibid., 4451 (1974).

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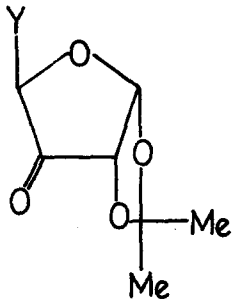
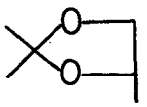


I Y = 

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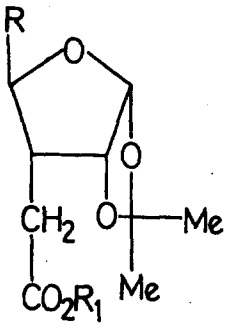
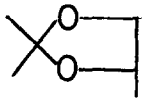


III R = 

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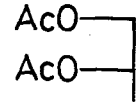
IVa R = 

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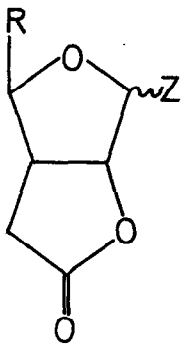
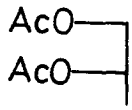
IVb R = $-CH_2OBz$

$R_1 = -CH_3$



Serie a: R = 

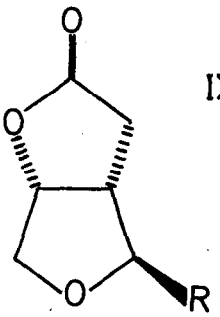
b: R = $-CH_2OBz$

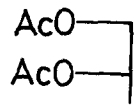
V Z = -OH

VI Z = β-OAc

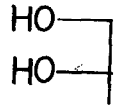
VII Z = $-OBz-pNO_2$

VIII Z = α-SPh



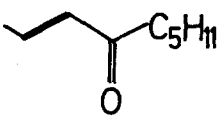
IX a: R = 

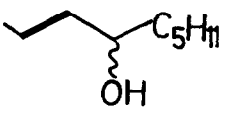
b: R = $-CH_2OBz$

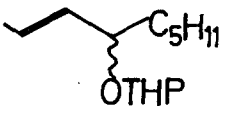
c: R = 

d: R = $-CH_2OH$

e: R = -CHO

f: R = 

g: R = 

h: R = 

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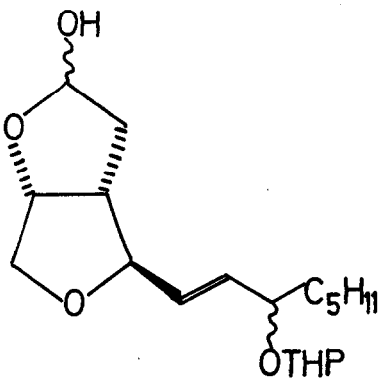

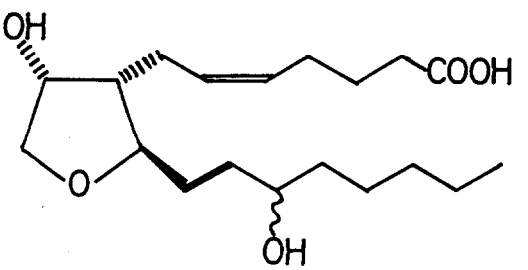

XI C-15: RS -OH

XII C-15: S -OH

5. All new compounds were homogeneous on tlc and gave satisfactory elemental analysis and infrared spectra. 100 MHz n.m.r. spectra were recorded in $CDCl_3$ solutions.

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8. The crystalline material probably represents one of the C-15 epimeric alcohols.