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THE STEREOSPECIFIC SYNTHESIS OF AN 11-OXAPROSTAGLANDIN ANALOG FROM D-XYLOSE

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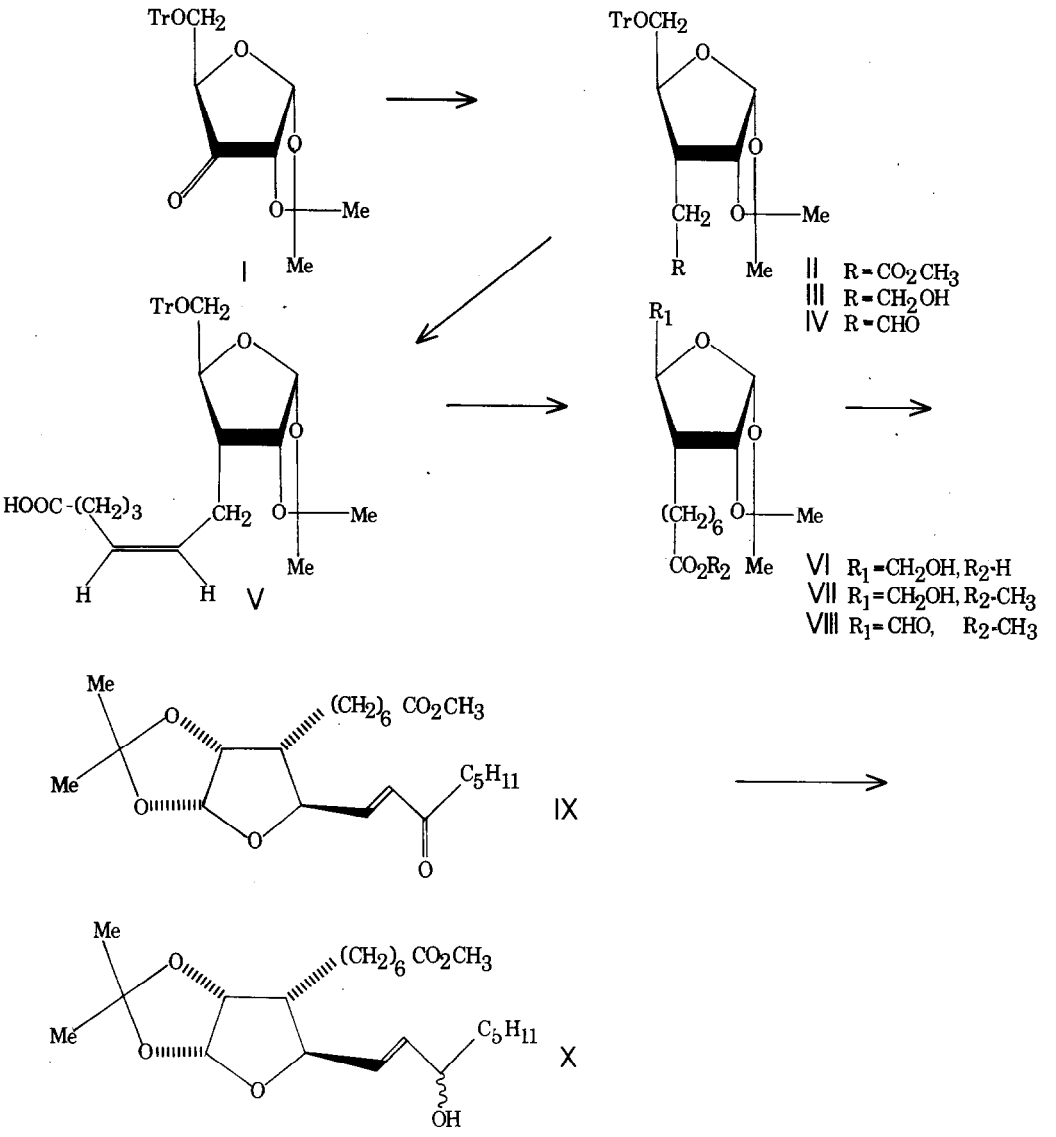
The syntheses of prostaglandins and prostaglandin analogs have been the subject of numerous reports.[1] Recently, the syntheses of some 9- and 11-oxaprostaglandins have been described.[2]

It occurred to us that 3-deoxy-D-ribofuranose sugars, suitably branched at C-3, could serve as intermediates from which 11-oxaprostaglandins, with the chains at C-8 and C-12 in correct absolute stereochemical relationship, could be synthesised. In addition the hydroxyl group at C-2 of the ribofuranose also has the desired absolute stereochemistry required at C-9 of several prostaglandins. The stereospecific synthesis of these branched-chain sugars is well documented.[3,4] We wish to report the stereospecific synthesis of the prostaglandin analog (X), starting from D-xylose; the synthesis of more generally useful intermediates from D-glucose and D-xylose is the subject of an accompanying report.

Condensation[4] of 1,2-O-isopropylidene-5-O-trityl-α-D-erythro-pentofuranos-3-ulose (I)[5], prepared from D-xylose, with potassium salt of trimethyl phosphonoacetate, followed by reduction with nickel catalyst gave compound II** (92%;m.p. 114-15°; $[\alpha]_D^{23}$ + 34° (c 1,2 $CHCl_3$); M^+488; ν_{max} ($CHCl_3$) 1745 cm^{-1}. The assigned ribo configuration was confirmed[3,4] by its 100 MHz n.m.r. spectrum: δ 5,88 (H-1, d, $J_{1,2}$ = 4 Hz), 4,80 (H-2, t, $J_{2,3}$ = 4 Hz). Reduction of II ($LiAlH_4$/THF) yielded III as a syrup, [84%; $[\alpha]_D^{23}$ + 36° (c 1,8 $CHCl_3$); M^+460; δ 5,88 (H-1, d, $J_{1,2}$ = 4 Hz), 4,68 (H-2, t, $J_{2,3}$ = 4 Hz), 1,86 (OH, s, exchangeable with D_2O)],

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


TrOCH2
Me
I
II R=CO2CH3
III R=CH2OH
IV R=CHO
HOOC-(CH2)3
H
V
R1
VI R1=CH2OH, R2=H
VII R1=CH2OH, R2=CH3
VIII R1=CHO, R2=CH3
(CH2)6 CO2CH3
C5H11
IX
OH
X

which was oxidized (CrO_3/pyridine)[6] to the aldehyde IV [82%; m.p. 136-38°; $[\alpha]_D^{23}$ + 49° (c 1,2 $CHCl_3$); ν_{max} ($CHCl_3$) 1720 cm^{-1}; δ 9,66 (CHO, s), 5,87 (H-1, d, $J_{1,2}$ = 4 Hz), 4,78 (H-2, t, $J_{2,3}$ = 4 Hz)].

Wittig reaction of IV with sodium 5-triphenylphosphoranylidenepentanoate[7] gave the unsaturated acid V, [83%; m.p. 164,5-165,5°; $[\alpha]_D^{22}$ + 48° (c 1,3 $CHCl_3$); ν_{max} ($CHCl_3$) 1705 cm^{-1}; δ 5,33 (C$\underline{H}$ = C$\underline{H}$, m)], which was reduced (H_2/Pt/AcOH) to the detritylated saturated acid VI [93%; m.p. 99-100°; $[\alpha]_D^{23}$ + 63° (c 1,2 $CHCl_3$); ν_{max} ($CHCl_3$) 3500, 1715 cm^{-1}]. Esterification (CH_2N_2/Et_2O/EtOH) of VI gave compound VII as a syrup [100%; $[\alpha]_D^{22}$ + 57° (c 2,3 $CHCl_3$); ν_{max} ($CHCl_3$) 3500, 1750 cm^{-1}; δ 5,80 (H-1, d, $J_{1,2}$ = 4 Hz), 4,65 (H-2, t, $J_{2,3}$ = 4 Hz), 3,68 (OCH_3, s), 2,75 (OH, t, J = 6 Hz exchangeable with D_2O)].

Oxidation of VII (DCC/CF_3COOH/DMSO/C_6H_6)[8] gave the aldehyde VIII (72%) as an oil which was treated with the sodio derivative of dimethyl 2-oxoheptylphosphonate[7] in THF to yield the enone IX as an oil [80%; $[\alpha]_D^{23}$ + 32° (C 0,9 $CHCl_3$); ν_{max} ($CHCl_3$) 1730, 1690 cm^{-1}; δ 0,92 ($CH_2C\underline{H}_3$, t, J = 7 Hz), 1,36 and 1,56 ($(CH_3)_2C$, 2s), 2,34 ($C\underline{H}_2CO_2CH_3$, t, J = 7 Hz), 2,57 ($C\underline{H}_2C{=}O$, t, J = 7 Hz), 3,69 ($CO_2C\underline{H}_3$, s), 4,34 (H-12, dd, $J_{12,8}$ = 9,5 Hz, $J_{12,13}$ = 5,5 Hz), 4,68 (H-9, t, $J_{8,9}$ = 3,5 Hz), 5,87 (H-10, d, $J_{9,10}$ = 3,5 Hz), 6,36 (H-14, dd, $J_{14,13}$ = 15,75 Hz, $J_{14,12}$ = 1 Hz), 6,75 (H-13, dd, $J_{13,14}$ = 15,75 Hz, $J_{13,12}$ = 5,5 Hz)].

Reduction of the enone (IX) ($Zn(BH_4)_2$/DME) yielded the C-15 epimeric alcohols (X) as an oil [84%; $[\alpha]_D^{23}$ + 31° (c 5,6 $CHCl_3$); ν_{max} ($CHCl_3$) 3610, 3440, 1740 cm^{-1}; δ 1,52 and 1,33 ($(CH_3)_2C$, 2s), 2,09 (OH, s, exchangeable with D_2O), 2,31 ($C\underline{H}_2CO_2CH_3$, t, J = 7 Hz), 3,66 ($CO_2C\underline{H}_3$, s), 4,0-4,22 (H-12, H-15, m), 5,42-5,92 (H-13, H-14, m), 4,6 (H-9, t, $J_{9,8}$ = 4 Hz), 5,78 (H-10, d, $J_{10,9}$ = 3,8 Hz)].

This route illustrates that 11-oxaprostaglandins analogs can be synthesised stereospecifically in high yield from sugars, <u>via</u> branched-chain sugars.

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