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A STEREOSPECIFIC SYNTHESIS OF 10-OXA-9,11-ETHANO-PGH_1 DERIVATIVES

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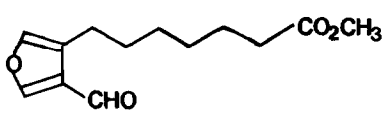
Abstract The reaction of the formylfuran 1 with maleic anhydride and *N*-methylmaleimide is reported as the key step in the synthesis of novel 10-oxa-9,11-ethano-PGH_1 analogues.

Analogues of the prostaglandin endoperoxides have attracted much attention recently owing to their biological activity and the involvement of the natural compounds in prostanoid biosynthesis [1,2] It has been reported, for example, that the PGH_1 analogue 2, having an oxygen atom at position C-10 and a 9,11-ethano bridge, exhibits potent vasodepressor and bronchoconstrictor activity *in vivo* [3]

In this connection we wish to describe the stereospecific conversion of the readily accessible formylfuran 1[4] into the novel 10-oxa-PGH_1 analogues 3 and 5 having a bulky 9,11-ethano bridge These analogues are important in establishing the specific structure requirement necessary for a biologically more selective compound with potential therapeutic value



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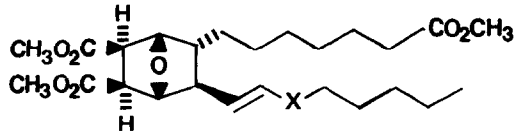
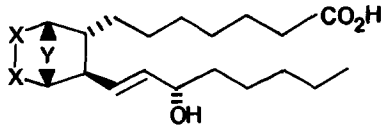
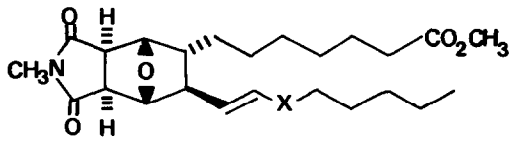


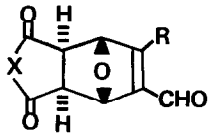
3 X = CHOH
4 X = CO



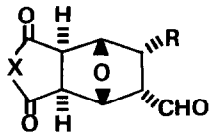
	X-X	Y
2	CH_2-CH_2	O
PGH_1	O-O	CH_2



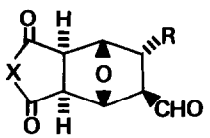
5 X = CHOH
6 X = CO



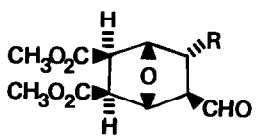
7 X = O
11 X = NCH_3



8 X = O
12 X = NCH_3



9 X = O
13 X = NCH_3



10
R = $(CH_2)_6CO_2CH_3$

Reaction of 1 with maleic anhydride (1.5 equivalents, ether, 23°, 4 days) afforded exclusively the crystalline *exo*-adduct 7 in 64% yield[5] [m p. 87-88°; NMR/$CDCl_3$ δ9.85 (1H, s, CHO), δ5.66 (1H, s, O≥CH), δ5.42 (1H, s, O≥CH), ν_{max}/cm^{-1} 1860, 1780, 1730, 1660; λ_{max}/EtOH 252 nm]. Catalytic hydrogenation of 7 (THF, Pd) gave a 99% yield of the reduced product 8 derived from the expected *cis*-addition of hydrogen to the least hindered *exo*-face[2,3] of 7 [NMR δ9.83 (1H, d, 2Hz, CHO), δ5.05 (1H, d, 5Hz, O≥CH), δ4 94 (1H, d, 5Hz, O≥CH)] Epimerisation of the formyl group of 8 into the thermodynamically favoured *exo,trans*-configuration was achieved cleanly and quantitatively with anhydrous potassium acetate (0.5 equivalents, $PhCH_3$, 100°, 3h) to give the *exo*-aldehyde 9 [NMR δ9.58 (1H, d, 2Hz, CHO), δ5.20 (1H, s, O-CH-CHCHO), δ4.95 (1H, d, 5Hz, O≥CH)]. Sequential treatment of 9 with THF-H_2O (3 2, 23°, 24h) followed by excess ethereal diazomethane (0°, 2min) afforded the triester 10 in 51% overall yield. Standard elaboration[2] of 10 using dimethyl 2-oxoheptylphosphonate gave the enone 4 (80%) which, after ketone reduction,[2] gave the required analogue 3 as a mixture of epimeric alcohols in 73% yield.

In contrast to maleic anhydride, the reaction of *N*-methylmaleimide with 1 (THF, 23°, 8 days) gave a 78 22 mixture of *endo*- and *exo*-adducts in 79% yield. This mixture could be isomerised in refluxing toluene (3h), however, to give exclusively the required *exo*-isomer 11 (80%) which after hydrogenation and subsequent isomerisation, as described above, afforded the intermediates 12 (99%) and 13 (100%) respectively. Elaboration of 13 gave the enone 6 (54%) which on reduction gave the analogue 5 as a mixture of epimeric alcohols in 73% yield.

Biological evaluation of these new analogues 3 to 6 will be reported at a later date [6]

REFERENCES AND NOTES

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2. M.F. Ansell, M.P.L Caton and P.C North, *Tetrahedron Letters, 22,* 1723 (1981).

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5. All intermediates were characterised by 100 MHz PMR, IR, UV (where applicable) and high resolution mass spectra. Detailed and unambiguous stereochemical assignments were made from PMR spectra with special reference to the multiplicity of the bridgehead proton signals. More specifically, this methine proton appears as a singlet when adjacent to a carbon bearing an *endo*-proton (i.e. J = OHz), and as a doublet when adjacent to a carbon bearing an *exo*-proton (J = 5Hz).[2,3]

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