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THE SYNTHESIS OF 3,4-DISUBSTITUTED FURAN PROSTANOIDS

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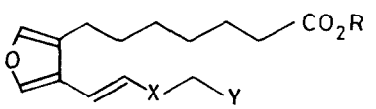
Abstract: The reaction of 4-phenyloxazole with methyl 10-oxodec-8-ynoate is reported as the key step in the synthesis of 3,4-disubstituted furan prostanoids.

The enzyme mediated reaction of oxygen with poly-unsaturated fatty acids to give prostaglandin endoperoxides (e.g. PGH_1) has long been established as the key step in prostaglandin biosynthesis.[1] In connection with work on PGH_1 analogues,[2] our attention was turned to the novel 3,4-disubstituted furan prostanoid 1. Furans are known to undergo a facile 2 + 4 cycloaddition with oxygen to give bicyclic endoperoxides[3] and we reasoned that the reaction of 1 with oxygen *in vivo* may give the short-lived (cf. PGH_1) intermediate 2 of close structural similarity to PGH_1.

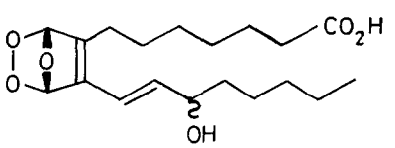
Thus, 1 could exhibit interesting biological activity by competing for oxygen thereby inhibiting PGH formation. Alternatively the adduct 2 may exhibit PGH_1 agonist activity or selectively inhibit any one of the PGH_1 metabolites.[1] The additional possibility of 1, like some other heterocyclic prostanoids,[4] having intrinsic biological activity prompted us to synthesize it together with other related analogues.



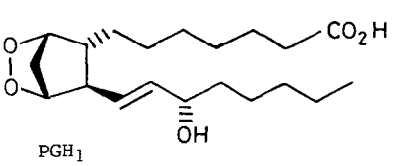
1 X = CHOH; Y = $(CH_2)_3CH_3$; R = H

3 X = CO; Y = $(CH_2)_3CH_3$; R = CH_3

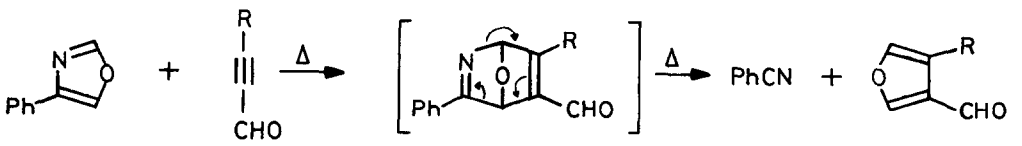
4 X = CHOH; Y = OPh; R = CH_3



2



PGH_1



5 6 R = $(CH_2)_6CO_2CH_3$ 7

The synthesis of 1 was achieved via the aldehyde 7 prepared by an interesting one-pot Diels-Alder, retro Diels-Alder reaction of methyl 10-oxodec-8-ynoate[2] 6 with 10 equivalents of 4-phenyloxazole[5] 5 (200°, 3.5h) which gave 7 in 73% yield[6] [b.p. 175-180°/0.1mm (short-path); m.p. 40-41°; NMR/$CDCl_3$ δ9.97 (1H, s, CHO), δ8.02 (1H, s, -OCH=), δ7.25 (1H, s, -OCH=), δ3.65 (3H, s, CO_2CH_3); ν_{max}/cm^{-1} 1730 (CO_2CH_3), 1690 (CHO); λ_{max}/EtOH 207, 217, 259 nm; m/e 238.1203 (M^+)]. This method should find wide applicability to the direct conversion of readily available acetylenic aldehydes[2] into relatively inaccessible 3,4-disubstituted formyl furans.[7]

Standard elaboration of 7 using dimethyl 2-oxoheptylphosphonate gave the enone 3 (92%) which, after ketone reduction[2] followed by ester hydrolysis (excess LiOH, THF-H_2O, 24h, 0°), afforded 1 as a mixture of isomeric alcohols in 77% yield from 3. Similarly, elaboration of 7 using dimethyl 2-oxo-3-phenoxypropylphosphonate[8] gave, after ketone reduction, the phenoxy analogue 4. The ability of these prostanoids to act as a diene in 2 + 4 cycloaddition reactions was demonstrated by the methyl ester of 1 which on treatment with N-methylmaleimide at room temperature gave the expected adduct in 70% yield.

Biological evaluation of analogues 1 and 4 is currently in progress and will be reported at a later date.[9]

REFERENCES AND NOTES

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3. J. Hamer (Ed.) '1,4-Cycloaddition reactions', Academic Press, New York, 1967, p.288.
4. For leading refs. see M.P.L. Caton and K. Crowshaw, *Progr. Med. Chem.*, *15*, 384 (1978).
5. Prepared in one step from phenacyl bromide; H. Bredereck and R. Gompper, *Chem. Ber.*, *87*, 700 (1954). The oxazole was purified via its hydrochloride salt. The excess oxazole was recovered by distillation after reaction with 6.
6. All intermediates were characterised by 100 MHz PMR, IR, UV and mass spectra.
7. For related examples of this approach see R. Lakhan and B. Ternai, *Adv. Heterocyclic Chem.*, *17*, 190 (1974); J. Hutton, B. Potts and P.F. Southern, *Synth. Commun.*, *9*, 789 (1979).
8. J. Bowler and N.S. Crossley, *Brit. Pat.*, 1350971.
9. The financial support of a Science Research Council CASE award to P.C. North is gratefully acknowledged.

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