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A DIRECT STEREOSPECIFIC SYNTHESIS OF 9,11-ETHENO- AND 9,11-ETHANO-PGH_1 DERIVATIVES

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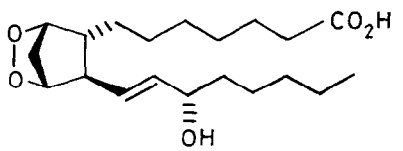
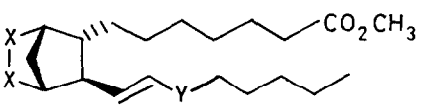
Abstract: The reaction of methyl 10-oxodec-8-ynoate with cyclopentadiene is reported as the key step in the synthesis of 9,11-etheno- and 9,11-ethano-PGH_1 derivatives.

The pivotal role of the labile prostaglandin endoperoxides in the biosynthesis of the classical prostaglandins, prostacyclin (PGI_2) and the thromboxanes has prompted the synthesis of several more stable analogues.[1] Some of these analogues have shown potential clinical utility in that they possess a highly selective inhibitory action on endoperoxide metabolism, while others exhibit potent agonist activity and thus facilitate pharmacological research in the area.[1]

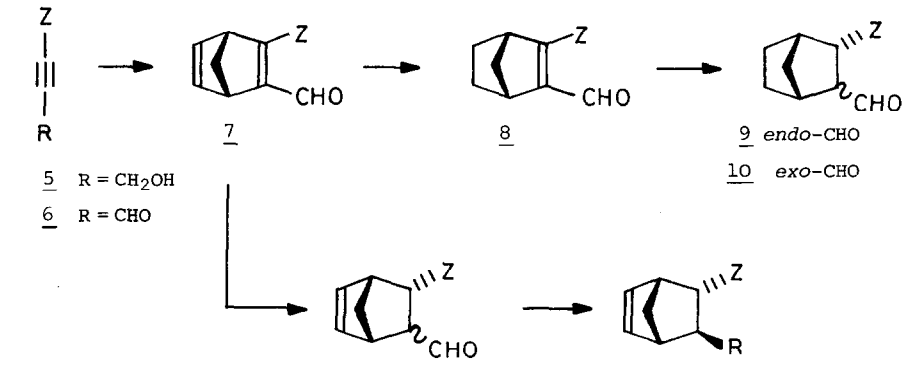
We describe herein a direct, stereospecific synthesis of 9,11-etheno-PGH_1 methyl ester 1, a known[2] specific inhibitor of PGE_1 synthetase. The synthesis avoids the production and subsequent separation of isomeric Diels-Alder adducts; a particularly tedious and scale-limiting feature of the previously reported syntheses.[2] Also described is the 9,11-ethano-PGH_1 analogue 2 and a stereoselective synthesis of the intermediates 13 and 14 which have recently been prepared non-stereoselectively and subsequently elaborated into $PGF_{1\alpha}$ via oxidative cleavage of their olefinic bond.[3]



PGH_1



	X-X	Y
1	CH=CH	CHOH
2	CH_2-CH_2	CHOH
3	CH=CH	CO
4	CH_2-CH_2	CO



Alkylation of the dilithio derivative of propargyl alcohol[4] with 7-bromoheptanoic acid (0.25 equivalents in THF-liquid ammonia, -40°, 20h), followed by esterification of the crude reaction product (excess CH_3OH, H_2SO_4 cat., reflux 3h) afforded the alcohol 5[5] in 81% overall yield [b.p. 126-130°/0.15 mm; NMR/$CDCl_3$ δ4.22 (2H, t, 2Hz, $HOCH_2C{\equiv}C$), δ3.65 (3H, s, CO_2CH_3); ν_{max}/cm^{-1} 3450 (OH), 2300, 2250 (C≡C), 1730 (CO_2CH_3)]. Oxidation of 5 using pyridinium chlorochromate (1.6 equivalents in CH_2Cl_2, 23°, 1.5h) or activated manganese dioxide (*ca.* 10 equivalents in CH_2Cl_2, 23°, 5 days) gave the aldehyde 6 in 70% and 88% yield respectively [b.p. 108-112°/0.35 mm; NMR δ9.17 (1H, s, CHO), δ3.65 (3H, s, CO_2CH_3); ν_{max} 2300, 2220, (C≡C), 1730 (CO_2CH_3), 1670 (CHO); λ_{max}/EtOH 225 nm]. Diels-Alder addition of 6 to a large excess of cyclopentadiene (75°, 40h) led to the key bicyclic intermediate 7 in 63% yield [NMR δ9.85 (1H, s, CHO), δ6.75 (2H, m, CH=CH), δ4.00 (1H, bs, >CH), δ3.65 (3H, s, CO_2CH_3), δ3.58 (1H, bs, >CH), δ2.70 (2H, t, 7Hz, $C{=}CCH_2$), δ2.32 (2H, t, 7Hz, $\underline{CH_2}CO_2CH_3$), δ2.05 (2H, m, <CH_2>); ν_{max} 1735 (CO_2CH_3), 1660 (CHO), 1615 (conj. C=C), 1580 (non-conj. C=C); λ_{max} 212, 249, 284 nm; m/e 262.1578 ($M^{+\cdot}$)]. Alternatively, the reaction could be catalysed by $BF_3.Et_2O$ (6:cyclopentadiene:$BF_3.Et_2O$ 1:6:0.15, benzene, 0°, 1.5h) to give 7 in 89% yield after chromatography (silica, petrol (b.p. 40-60°) - ether 1:1).

Catalytic hydrogenation of 7 (Pd cat., THF) using 2 equivalents of hydrogen gave the *endo, cis*-aldehyde 9 in 99% yield [NMR δ9.85 (1H, d, 3Hz, CHO); ν_{max} 1700 (CHO)]. The stereochemistry of 9 is expected from the *cis* addition of hydrogen to the least hindered *exo*-face[6] of the semi-reduced intermediate 8 [NMR δ9.80 (1H, s, CHO), no olefinic H; ν_{max} 1660 (CHO), 1610 (C=C); λ_{max} 261 nm] which could be isolated in 97% yield if the reaction was stopped after the absorption of only one equivalent of hydrogen. Isomerisation of 9 (10% 2M aqueous HCl in THF, 23°, 2h) gave a quantitative yield of the *exo,trans*-aldehyde 10 [NMR δ9.60 (1H, d, 2Hz, CHO); ν_{max} 1710 (CHO); m/e 266.1888 ($M^{+\cdot}$)]. Standard elaboration of 10 using the sodium salt of dimethyl 2-oxoheptylphosphonate (generated from the phosphonate:NaH 1.1:1, THF, 23°, 2h then

adding 0.95 equivalents of 10, 23°, 3h) led to a 66% yield of enone 4 which was reduced with lithium trisecbutylborohydride (1.15 equivalents in THF, -78°, 0.5h) to give the 9,11-ethano-PGH_1 analogue 2 as a mixture of isomeric C-15 alcohols in 69% yield [TLC:silica, petrol (b.p. 40-60°)-ether 1:1, R_f 0.36 and 0.39; m/e 364.2981 ($M^{+\cdot}$)].

The synthesis of the 9,11-etheno analogue 1 necessitated the selective reduction of the conjugated double bond of 7 in the presence of the non-conjugated double bond, the aldehyde group and the ester group. This highly selective reduction was achieved cleanly by treating a solution of 7 in DMF with an aqueous solution of chromous sulphate[7] (5.2 equivalents, 23°, 7h) which gave a mixture of the *endo,cis*-aldehyde 11 [NMR δ9.35 (d, 4Hz, CHO)] and the *exo,trans*-aldehyde 12 [NMR δ9.76 (d, 2.5Hz, CHO)] in a ratio of 76:24 in 95% yield.[8] Epimerisation of this mixture (2% 1OM aqueous HCl in THF, 23°, 16h) afforded a 97% yield of the required *exo*-isomer 12 [NMR δ9.76 (1H, d, 2.5Hz, CHO), δ6.15 (2H, m, CH=CH), δ3.65 (3H, s, CO_2CH_3) δ3.03 (1H, bs, >CH), δ2.88 (1H, bs, >CH), δ1.75 (1H, m, >CHCHO); ν_{max} 1730 (CO_2CH_3), 1710 (CHO); m/e 264.1730 ($M^{+\cdot}$)]. The stereochemistry of 12 was verified by ^1H NMR decoupling experiments,[9] by independent synthesis[10] and by hydrogenation (Pd cat., THF) which gave a quantitative yield of the saturated aldehyde 10 identical to that prepared above. Elaboration of 12 as described gave the enone 3 (65%) which was reduced to the desired analogue 1 as a mixture of isomeric C-15 alcohols in 74% yield [TLC:silica, petrol (b.p. 40-60°)-ether 1:1, R_f 0.33 and 0.38, m/e 362.2808 ($M^{+\cdot}$)].

Reduction of 12 (7.5 equivalents of $NaBH_4$, CH_3OH, 0°, 0.5h) gave a 98% yield of the alcohol 13 [NMR δ6.05 (2H, m, CH=CH), δ3.68 (2H, m, CH_2OH), δ3.65 (3H, s, CO_2CH_3), δ2.71 (2H, bs, >CH); ν_{max} 3450 (OH), 1730 (CO_2CH_3); m/e 266.1877 ($M^{+\cdot}$)] which on methylation (2 equivalents of NaH, DMSO then 20 equivalents of CH_3I, 23°, 15h) afforded the methoxy derivative 14 in 87% yield [NMR δ3.34 (3H, s, CH_2OCH_3)]. Both intermediates 13 and 14 are useful starting materials for the stereospecific synthesis of the 1-series prostaglandins and their analogues.[3]

Compounds 1 to 4, and other analogues derived from intermediates 10 and 12, exhibit an interesting biological profile which will be reported in a separate note.[11]

REFERENCES AND NOTES

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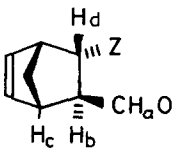
5. All compounds reported herein have been characterised by 100 MHz PMR, IR, UV (where applicable) and high resolution mass spectra on chromatographically homogeneous samples.

6. See for example E.J. Corey, R. Hartman and P.A. Vatakencherry, *J. Amer. Chem. Soc., 84,* 2611 (1962) and references cited therein.

7. A. Zurqiyah and C.E. Castro, *Organic Synthesis, 49,* 98.

8. Hydrogenation of this mixture gave the same ratio of the saturated aldehydes 9 and 10 respectively which could be isomerised as described to give 10 exclusively.

9. Irradiation of H_b (δ1.75) collapsed the H_a doublet into a singlet, thus confirming the assignment of H_b. The unusually high field shift of H_b is due to shielding by the olefinic bond, an effect only possible when H_b is *endo*.



12

Irradiation of H_b confirmed $J_{bc} = 0$ indicative of *endo*-H_b.
Irradiation of H_a revealed $J_{bd} = 5$ Hz, typical of a *trans*-H_b-H_d coupling; see J.C. Davis Jr. and T.V. van Auken, *J. Amer. Chem. Soc., 87,* 3900 (1965).

10. Treatment of the aldehyde 6 in DMF with 2 equivalents of aqueous chromous sulphate (23°, 25 min) afforded *trans*-methyl 10-oxodec-8-enoate in 95% yield [NMR δ9.50 (1H, d, 8Hz, CHO), δ6.85 and δ6.08 (2H, m, OHCC<u>H</u>=C<u>H</u>-, 16 Hz *trans*-coupling present); ν_{max} 1730 (CO_2CH_3), 1685 (CHO), 1635 (C=C), 990 (*trans*-CH=CH); λ_{max} 222 nm]. Reaction of this *trans*-enal with excess cyclopentadiene gave a mixture of two isomeric *trans*-adducts which were separated chromatographically (TLC, multiple development[3a]). The *exo*-formyl isomer so obtained was spectroscopically and chromatographically identical to 12 prepared stereoselectively via the adduct 7.

11. The financial support of a Science Research Council CASE award to P.C. North is gratefully acknowledged.

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