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A HIGHLY STEREOSELECTIVE SYNTHESIS OF A POTENTIAL PRECURSOR OF THE 10,10,-DIMETHYLPROSTAGLANDINS

Paul Jefferson, Edward McDonald* and Paul Smith
University Chemical Laboratory, Lensfield Road,

Cambridge, CB2 1EW.

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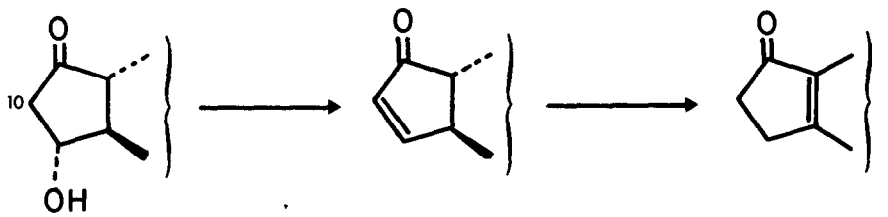
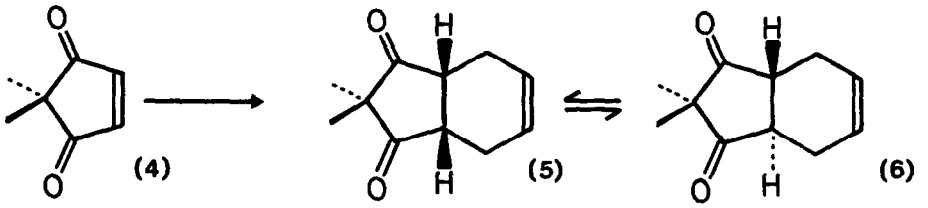
Prostaglandin analogues disubstituted at C-10 are of particular interest because they are protected against the normal chemical and metabolic degradations[1] which convert PGE's (1) to PGA's (2) and subsequently to PGB's (3). Two syntheses of 10,10-dimethylprostaglandins have been reported[2, 3], each



(1) (2) (3)

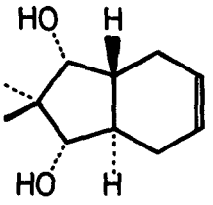
requiring separation of diastereoisomers at more than one point. Our approach is quite different and we now report a highly stereoselective synthesis of the key intermediate (7).

Reaction of the enedione[4] (4) with excess butadiene (PhH, 80°, 48 h., sealed tube) gave the adduct (5) which could be partially epimerised to (6) in the presence of pyridine. Reduction of (5) using $LiAlH(OMe)_3$ (THF, 0°) gave in

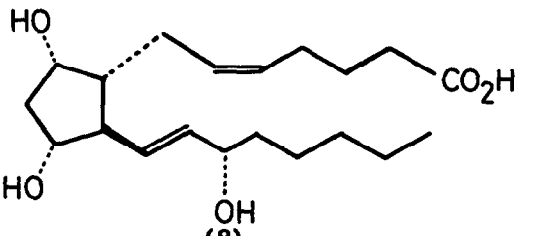


(4) (5) (6)

>80% yield a single crystalline diol (7), m.p. 93-95° whose relative stereochemistry corresponds exactly to that of PGF2α (8).

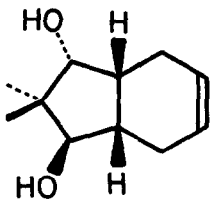


(7)

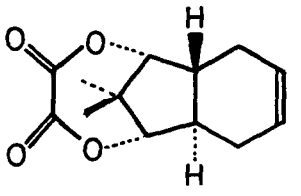


(8)

The structure of the reduction product could be partially defined by its ^{1}H-n.m.r. spectrum which showed <u>two</u> C<u>H</u>(OH) resonances at δ 3.53 (d, J=9Hz) and 3.71 (d, J=6Hz) and two <u>CH</u>$_3$ singlets at δ 0.90 and 1.04. Of the six possible diols which may be derived from (5) or (6), only (7) and (9) have diastereotopic -OH groups and therefore non-equivalent -C<u>H</u>(OH) protons. Furthermore, although the C-Me groups of (7) and (9) are diastereotopic in both compounds, the observed chemical shift non-equivalence of 0.14 ppm seems to fit better for (7) than for (9)‡, and this assignment was confirmed when the reduction product was successfully converted to the cyclic oxalate (10).



(9)

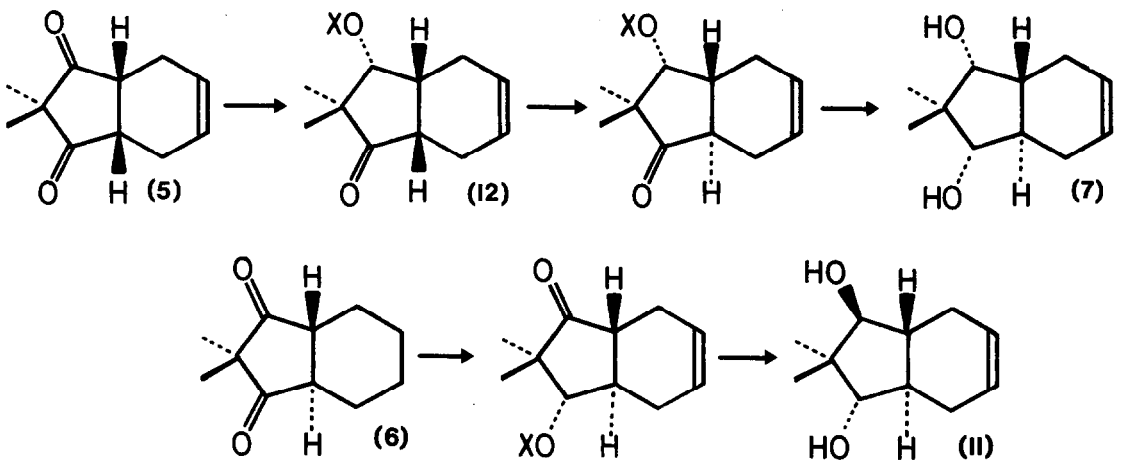


(10)

‡ Isomer (9) was isolated in 24% yield from reduction of (5) by $NaBH_4$/EtOH. Its n.m.r. spectrum has <u>two</u> CH(OH) resonances at δ 3.34 (d, J=5Hz) and 3.61 (d, J=3Hz) and a <u>single</u> C-Me peak at δ 1.02 (6H) which splits into two 3-H singlets on adding Eu(fod)$_3$.

When the trans-fused diketone (6) was reduced with $LiAlH(OMe)_3$ under identical conditions to those used for (5), the diol isolated in good yield was not (7) but an isomer believed to be (11). Clearly (6) is not an intermediate in the remarkable transformation of (5) to (7), and the necessary epimerisation must occur after the first reduction.

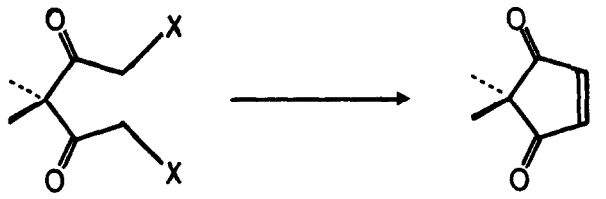
Two pathways are possible for each of the reductions (5) to (7) and (6) to (11) but consideration of molecular models leads us to favour those illustrated in the scheme. Here each of the reduction steps corresponds to delivery of



X = $Al(OMe)_3$

hydride at the most accessible face of the various carbonyl groups (torsional strain playing an important role in each case).[5] Presumably the carbonyl group of intermediate (12) is sufficiently hindered that enolisation is faster than reduction by the bulky reagent $LiAlH(OMe)_3$.[6] Enolisation of (12) should certainly be favoured by the ideal location of the C-H bond, which is virtually coplanar with the π-orbital of the carbonyl group.

Having found the literature preparation[4] of the enedione (4) unsatisfactory, we have developed a simpler route from 4,4,-dimethylpentane-1,-3-dione[7] (13). Bromination of (13) ($Br_2/AlCl_3/Et_2O$, 0°) gave the dibromide (14) and treatment of the freshly-prepared crude product with base (Et_3N,CH_3CN, 40°) effected cyclisation and elimination to the required enedione (4). The cyclisation step here is of the 5-endo-trig type. In a closely related system Baldwin recently reported[8] the failure of this type of reaction, with 5-exo-trig cyclisation (to an enol ether) occurring instead.



(4)

(13) X = H

(14) X = Br

Further elaboration of the key intermediate (7) towards the 10,10-dimethylprostaglandins will be reported in due course.

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