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# A NOVEL SYNTHESIS OF (±)-PROSTAGLANDIN $D_2$

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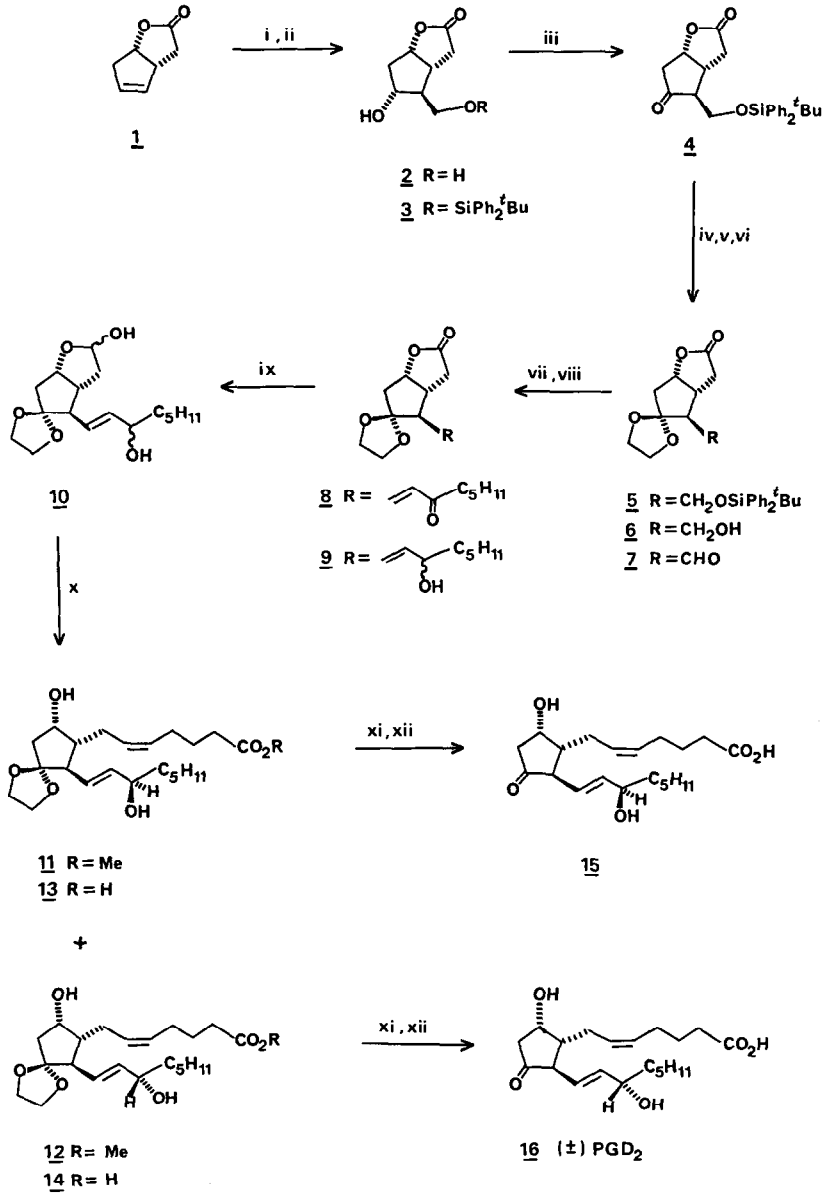
Summary: A novel, efficient synthesis of (±)-Prostaglandin $D_2$ 16 from (3aα,4α,5β,6aα)-Hexahydro-5-hydroxy-4-(hydroxymethyl)-2H-cyclopenta[b]furan-2-one 2 is reported.

Prostaglandin $D_2$ ($PGD_2$) is a potent inhibitor of ADP- and collagen-induced aggregation in human platelet rich plasma and is therefore of interest as an anti-thrombotic agent. Four routes[1-4] to $PGD_2$ have been reported previously, one from $PGF_{2\alpha}$[1] and three de novo syntheses[2-4]. Three of the processes[1-3] suffer from concurrent production of quantities of $PGE_2$ whereas the fourth[4] involves a lengthy protection and deprotection sequence. We wish to report here a novel, efficient synthesis of (±)-$PGD_2$ 16 from the readily available bicyclic lactone 2. Our synthetic route differs from those previously reported in that the C-11 carbonyl functionality is introduced early in the reaction sequence and carried through the remaining steps as an ethylene ketal group.

Bicyclic lactone 2 was obtained easily and in good yield via a Prins reaction on olefin 1[5]. Selective protection of the primary alcohol group ($Ph_2{}^tBuSiCl$/imidazole/DMF; 83%) gave silyl ether 3[6] (m.p. 90-95°) which upon oxidation with Jones reagent furnished the labile ketone 4 as an oil [99%; IR ($CHBr_3$) 1778, 1750cm$^{-1}$][7]. We were unable to purify ketone 4 by chromatography; however, introduction of the ethylene ketal moiety was carried out in good yield on the crude material. Thus 4 in neat ethylene glycol (10ml/gm of 4) was treated with an excess of boron trifluoride etherate (2ml/gm of 4) at room temperature for 4h to furnish key intermediate 5[8] [74%; IR ($CHBr_3$) 1765cm$^{-1}$; $^1$H n.m.r. ($CDCl_3$) δ 1.05 (9H,m,$^t$Bu), 2.06 (1H,m,H-4), 2.10 (1H,m,6-endo H), 2.33 (1H,dd,6-exo H), 2.55 (1H,dd,3-endo H), 2.8 (1H,dd,3-exo H), 2.95 (1H,m,H-3a), 3.6-4.0 (6H,m,ketal $CH_2$ and $CH_2OSi$), 4.95 (1H,td,H-6a), 7.3-7.8 (10H,m,Ar)] as a solid (m.p. 73-75°)[9]. Removal of the silyl protecting group ($^nBu_4N^+F^-$/THF; 88%) followed by oxidation of the resulting alcohol 6 [m.p. 83-85°; IR ($CHBr_3$) 3600, 3540 (br), 1770cm$^{-1}$] with pyridine-sulphur trioxide complex in DMSO provided aldehyde 7 (93%; m.p. 85-86°) [IR ($CHBr_3$) 2730, 1770, 1720cm$^{-1}$; $^1$H n.m.r. ($CDCl_3$) δ 2.2 (2H,AB,H-6), 2.5 (1H,dd,3-endo H), 2.9 (1H,dd,3-exo H),

Scheme




Reagents :- i) Ref. 5 ii) $Ph_2{}^tBuSiCl$/ Imidazole/DMF/ $5^o$/1·5h iii) *Jones Reagent*/Acetone/ $5^o$/ 0·75h iv) HO–(CH2)2–OH/ $BF_3{\cdot}Et_2O$/ $20^o$/4h v) $^nBu_4N^+F^-$/THF/$20^o$/1h vi) $C_5H_5N{-}SO_3$ /DMSO/$Et_3N$/$CH_2Cl_2$/ $5^o$/ 1h vii) $^nBu_3P{=}CHCOC_5H_{11}$ (17)/THF/$20^o$/2h viii) $NaBH_4$/THF:EtOH (1:1)/$-15^o$/15h ix) Dibah/$CH_2Cl_2$/$-70^o$/2h x) $Ph_3P^+(CH_2)_4CO_2H\ Br^-$/$KO^tBu$/ THF/$20^o$/1h then $CH_2N_2$/$Et_2O$ xi) 2N NaOH/MeOH/$20^o$/5h xii) AcOH:$H_2O$ (4:1)/$20^o$/20h

2.98 (1H,d,H-4), 3.5 (1H,m,H-3a), 4.07 (4H,m,ketal-$CH_2$), 5.04 (1H,m,H-6a), 9.78 (1H,s,CHO)]. The ω-side chain was introduced into aldehyde 7 using the tri n-butyl phosphorane[10] 17 in THF at room temperature.

Enone[11] 8 was reduced with sodium borohydride to give an inseparable mixture of epimeric alcohols 9 [82%; IR ($CHBr_3$) 3595, 1770$cm^{-1}$] as an oil. Reduction of hydroxy lactone 9 with diisobutylaluminium hydride (dibah) to the corresponding lactol 10 (m.p. 83-84°) followed by first condensation with the potassium salt of the ylid derived from 4-(carboxybutyl)triphenyl phosphonium bromide ($KO^tBu$/THF) and then treatment with diazomethane gave a chromatographically separable mixture of isomeric esters[12] 11 (33%) and 12 (43%).

The most polar (by t.l.c.) ester 12 was hydrolysed (2N NaOH/$CH_3OH$) to ketal acid 14 [76%; IR ($CHBr_3$) 3590, 1710$cm^{-1}$] which upon exposure to aqueous acetic acid smoothly afforded racemic $PGD_2$ 16 (74%) as colourless crystals (m.p. 85-87°)[13,15].

The C-15 isomer 15[14] of (±)-$PGD_2$ was similarly obtained (hydrolysis 95%, deprotection 70%) as an oil from the least polar (by t.l.c.) ketal ester 11 via acid 13 [m.p. 78-80°; IR ($CHBr_3$) 3590, 1720$cm^{-1}$].

References and Notes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4. N. H. Anderson, S. C. Imamoto and D. H. Picker, Prostaglandins, 1977, 14, 61.
5. I. Tomoskozi, G. Kovacs, I. Szekely, V. Simonidesz, M. Lovasz, B. Keresztes, J. Remport, I. Stadler, Z. Visky and C. Szantay, U.S. Patent 4126622 (1978).
6. IR ($CHBr_3$) 3580, 1761$cm^{-1}$; $^1H$ n.m.r. ($CDCl_3$) δ 1.1 (9H,s,$^tBu$), 1.95-2.05 (2H,m,6-endo H,H-4), 2.15 (1H,d,OH), 2.41 (1H,dd,3-endo H, J=18,2Hz), 2.43 (1H,dt,6-exo H,J=14,7,7Hz), 2.6 (1H,m,H-3a), 2.71 (1H,dd,3-exo H,J=18,10Hz), 3.63 and 3.74 (2H,both dd,$CH_2$OSi), 4.18 (1H,qd,H-5,J=6,6,6Hz), 4.9 (1H,dt,H-6a,J=2.5,7,7,Hz), 7.4-7.7 (10H,m,Ar).
7. High field (250MHz) $^1H$ n.m.r. spectrum was in accord with the assigned structure. ($CDCl_3$) δ 1.06 (9H,s,$^tBu$), 2.2 (1H,m,H-4,J=8.5,4,3Hz), 2.56 (1H,m,3-endo H,J=18,1Hz), 2.64 (1H,m,6-exo H,J=19.5,5.5Hz), 2.86 (1H,m,6-endo H,J=19.5,1Hz), 2.94 (1H,m,3-exo H,J=18,8Hz), 3.27 (1H,m,H-3a,J=8,8,5.5,1Hz), 3.81 and 4.07 (2H,ABX,$CH_2$OSi,J=10,3 and 10,4Hz), 5.18 (1H,t,H-6a,J=6,6Hz).

8. The composition of all new compounds was confirmed by elemental analysis.
9. The corresponding thioketal has recently been described. E. J. Corey and K. Shimoji, Tetrahedron Lett., 1983, 169.
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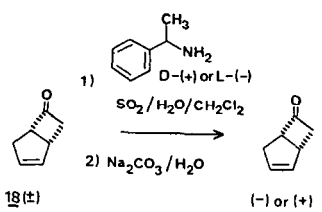
11. M.p. 61-62°; IR ($CHBr_3$) 1770, 1690$cm^{-1}$; $^1H$ n.m.r. ($CDCl_3$) δ 3.94 (4H,m,ketal $CH_2$), 5.01 (1H,m,H-6a), 6.25 (1H,d,CH=CH-C=O), 6.76 (1H,dd,CH=CH-C=O).
12. Esters 11 and 12 were separated by column chromatography on silica gel with ether/methanol (97:3) as eluent. Ester 11 obtained as an oil; t.l.c. ($SiO_2$, column eluent) Rf 0.56; IR ($CHBr_3$) 3590, 1725$cm^{-1}$; $^1H$ n.m.r. ($CDCl_3$) δ 2.34 (2H,t,H-2), 2.55 (1H,m,H-12), 3.69 (3H,s,$OCH_3$), 3.75-4.0 (4H,m,ketal $CH_2$), 4.12 (1H,q,H-15), 4.21 (1H,q,H-9), 5.45 (2H,m,cis olefin), 5.58 (2H,m,trans olefin). Ester 12 obtained as an oil; t.l.c. ($SiO_2$, column eluent) Rf 0.41; IR ($CHBr_3$) 3600, 1730$cm^{-1}$; $^1H$ n.m.r. ($CDCl_3$) δ 2.55 (1H,m,H-12), 3.69 (3H,s,$OCH_3$), 3.76-4.00 (4H,m,ketal $CH_2$), 4.12 (1H,q,H-15), 4.20 (1H,t,H-9), 5.43 (2H,m, cis olefin), 5.60 (2H,m,trans olefin).
13. The t.l.c., $^1H$ n.m.r (250MHz) and IR spectra were all in close agreement with those of natural $PGD_2$. Our melting point (85-87°; from ether/petroleum ether, b.p. 40-60°) is significantly higher than that reported by Hayashi[2] (m.p. 68°).
14. IR ($CHBr_3$) 3590, 1745, 1710$cm^{-1}$; $^1H$ n.m.r ($CDCl_3$) δ 2.84 (1H,dd, H-12), 4.2 (1H,q,H-15), 4.55 (1H,q,H-9), 5.4-5.74 (4H,m, all olefinics). T.l.c. ($SiO_2$, ether containing acetic acid) Rf 0.43 cf. (±)-$PGD_2$ 16, Rf 0.35.
15. The synthetic route described in this paper may also be applied to the preparation of natural $PGD_2$ since we have now developed a practical and efficient method for resolving ketone 18 (the most convenient precursor of lactone 1) via α-methylbenzylamine/bisulphite addition complexes. Details of this process will be published shortly.




18(±) (-) or (+)

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