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A NOVEL SYNTHESIS OF 2,3-DINOR-6-OXO-PROSTAGLANDIN $F_{1\alpha}$

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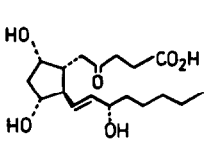
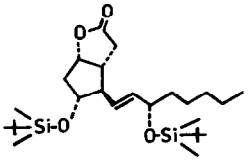
ABSTRACT

The synthesis of 2,3-dinor-6-oxo-prostaglandin $F_{1\alpha}$,the major metabolite of prostacyclin, from the prostaglandin lactone intermediate (2) is reported.

In vivo studies on the metabolism of prostacyclin in man have shown that 2,3-dinor-6-oxo-prostaglandin $F_{1\alpha}$ (1) is the major enzymatic metabolite.[1-3] As this diagnostic key metabolite is required for the development of analytical methods, several approaches have been described recently for the synthesis of 1.[4,5] This contribution will present a novel and alternate route to optically active 1.



1



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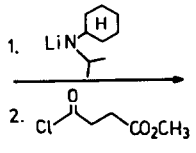

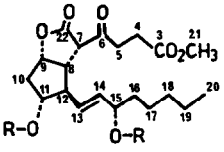

3 : R = Si

4 : R = H

The synthesis of the title compound starts from 2[6],readily available from Corey's lactone.[7] Lithium N-cyclohexyl-isopropylamide (3 equiv.) converts 2 into an intermediate lactone enolate (-78°C,THF,30 min) which is regioselectively acylated with methyl 3-chlorocarbonylpropionate (1.5 equiv.,1 h, -78°C) to give the new ß-keto lactone 3.[8] Removal of the silyl protecting groups (AcOH:H_2O/3:1,21°C,68 h) yields 4 (65%, $[\alpha]_D^{20}$=-16.7°(c 1.25,$CHCl_3$)). Saponification (1n LiOH,THF/H_2O,21°C,24 h) followed by decarboxylation ($LiHCO_3$/H_2O,200°C,45-60 min,sealed tube under argon) finally provided pure 1 after column chromatography (SiO_2-60,EtOAc:AcOH,99:1).[9]

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8. Isolated(43-49%)after flash-chromatography(SiO_2,EtOAc/n-hexane,1:5)as an inseparable mixture(ca.10:1)of 7-exo/endo isomers(prostanoic acid numbering used:N.A.Nelson,J.Med.Chem.17,911(1974))along with small amounts of enol tautomer(UV(n-hexane,$7.3\cdot10^{-4}$m):254 nm(ε 1400),203 nm(ε 3500)). TLC(SiO_2,EtOAc/n-hexane,1:5):R_f 0.40. Calc.for $C_{32}H_{58}O_7Si_2$(610.9) C 62.91%,H 9.57%;found C 62.88%,H 9.59%.$[\alpha]_D^{20.1}$=-24.9°(c 2.13,$CHCl_3$). IR(neat,cm^{-1}):2950,2930,2855,1770,1745,1725,1460,1360,1255,1170,1085,835, 775.MS(70eV,PI/EI,range m/e 400-650,rel.abund.(%)):m/e 553(57),539(8), 535(18),521(7),477(6),461(10),447(25),421(42),407(28),403(100).NMR data ($CDCl_3$,ppm from Me_4Si) for the major isomer,^{1}H-NMR(80 MHz,selected resonances):5.5-5.3(m,2H,H-13/14),4.98(m,J~2.9/7.8 Hz,1H,H-9),4.04(q,J~4.1 Hz, 2H,H-11/15),3.78(d,J=3.6 Hz,1H,H-7,disappears after the addition of CD_3OD), 3.68(s,3H,H-21),0.88($(CH_3)_3C$,s,18H); ^{13}C-NMR(20 MHz):201.3(C-6),173.1(C-3), 172.3(C-22),136.4(C-14),128.4(C-13),83.7(C-9),78.6(C-11),73.1(C-15),61.4 (C-7,'disappears' after the addition of CD_3OD),56.3(C-12),51.9(C-21),44.5 (C-8),40.4(C-10),38.4(C-16),36.6(C-5),31.8(C-18),27.9(C-4),25.1(C-17), 22.6(C-19),14.0(C-20);silyl:25.9,25.8($(CH_3)_3C$),18.3,18.1($(CH_3)_3C$),-4.2, -4.7,-4.8,-4.9(CH_3Si).

9. Isolated as an oil(62-65%) after column chromatography (SiO_2-60,EtOAc/ AcOH,99:1), $[\alpha]_D^{20.2}$=+16.9°(c 1.76,$CHCl_3$,measured after 24 h/20°C).Acidic work-up gives 1 as a mixture of at least two isomers(see Ref.5),TLC(SiO_2, R_f values):0.30(EtOAc/AcOH,98:2),0.24(EtOAc);0.80,0.74,trace at 0.63 (i-PrOH/n-hexane/AcOH,80:20:0.5),brilliant green spots were obtained after spraying with anisaldehyde/AcOH/H_2SO_4 followed by heating at 140°C. The identity of 1 was confirmed by full spectroscopic characterization (IR,NMR,MS(PI/EI,NI/CI,different derivatives)) and chromatographic comparison with authentic material.

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