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PROSTAGLANDINS:TOTAL SYNTHESIS OF PGD_2 "via" 1,3 CYCLOPENTANEDIONE.

GIANFRANCO CAINELLI[a*], DARIA GIACOMINI[a], MAURO PANUNZIO[a*], GIORGIO MARTELLI[b] and GIUSEPPE SPUNTA[b].

a) Istituto Chimico "G.Ciamician" Università and C.S.F.M.-C.N.R. Via Selmi 2 I 40126 Bologna (Italy)
b) Istituto dei Composti del Carbonio Contenenti Eteroatomi e Loro Applicazioni C.N.R. Via Tolara di Sotto 89 I 40064 Ozzano Emilia Italy

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Abstract: A practical total synthesis of PGD_2 starting from an acyclic precursor is reported. A novel efficient inversion of stereochemistry at C_9 tosylate group "via" a SN_2 displacement by tetrabutylammonium nitrate is described.

Prostaglandins (PGs) of the D series and their metabolites, whose biological significance was little appreciated earlier, have recently been revaluated in view of their potent ability to inhibit blood platelet aggregation[1a], their antitumor activity[1b], and other unique physiological properties[1c,d]. Although much effort has been devoted to their synthesis[2], few of them avoid an oxidative step for the introduction of the C_{11} carbonyl function. Of particular synthetic interest, from this point of view, is, in our opinion, the base-induced cyclization of γ-keto-esters which lead directly to cyclopentanones suitably functionalized with proper side chains at the desired position for further elaboration into PGD_2.

(A)

The drawback of this method is the lack of reliable chemoselective methods of discriminating between the two ring carbonyls. Recently we have reported an attractive solution to this problem which allowed the synthesis of the highly substituted cyclopentane system as in (A)[3]. The solution proposed includes a sequential bis-acetalization-selective mono-de-acetalization of the cyclopentanedione (A). We wish to report here an application of this synthetic procedure to the synthesis of PGD_2.

The readily available cyclopentanedione (2), easily obtained from γ-ketoester (1) via base-induced cyclization[3c], was easily converted to the monoethylene acetal (3) in 70% overall yield by the following sequence:

a) acetalization by exposure to an excess of ethylene glycol in the presence of a catalytic amount of p-toluenesulfonic acid (PTSA) in benzene at reflux for 8 hours, b) selective deprotection of the C_9 carbonyl group by stirring the product with SiO_2 and a catalytic

amount of aqueous H_2SO_4 in methylene dichloride for 5 hours[4].

The 9-keto group of (3) was reduced with K-Selectride in THF at -78°C, conditions which selectively produce the 9 α-hydroxyl in similar compounds[5], to give exclusive formation of the desired alcohol (4) in 70% yield. The configuration of the hydroxyl group, resulting from the attack of hydride from the less hindered side, was shown by ^{13}C and ^{1}H NMR (see below).

An alternative route to compound (4) starting from (3) involves a convenient procedure for the inversion of stereochemistry at C_9 recently developed in these laboratories. Thus reduction of (3) in ethanol at 0°C with sodium borohydride proceeds stereospecifically to give the β-alcohol (5) in quantitative yield.[6] Analysis of the 90 MHz ^{1}H NMR and FT 80 ^{13}C NMR spectra shows the absence of the corresponding 9 - α - alcohol.

Indeed the (C-9) H in 9-α-hydroxy PG's is known to occur at approx. 0.3 ppm upfield from the corresponding signal in 9-β-hydroxy PG's[8]. Moreover the ^{13}C NMR spectra of (4) and (5) showed the signals of C-8 and C-9 to be more shielded in (4) than in (5) (Prostane numbering)[9]. The β-hydroxy-acetal thus obtained was converted into its corresponding tosylate (6) by p-toluenesulfonyl chloride in pyridine. Exposure of the tosylate (6) to $But_4N^+NO_3^-$ in pentane at 120°C in a sealed tube for 5 hours afforded the nitric ester (7) "via" SN_2 displacement in quantitative yield.[10] It is worth mentioning that no trace of elimination products could be detected. Reduction of the 9- α -nitric ester by Zn/CH_3COOH gave the α-hydroxyacetal (4), whose structure was confirmed by comparison with authentic sample obtained by an alternative route[3c], in 70% yield starting from (3).

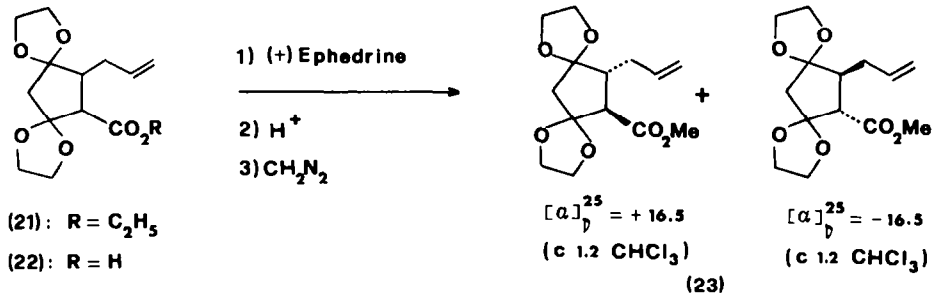
Protection of the hydroxy group (t-butyldimethylsilylchloride--imidazole--dimethylformamide-(DMF))[11], gave the silyl ether (8) which upon reduction with lithium aluminum hydride (LAH) in anhydrous ethyl ether afforded the alcohol (9) as an oil in 90% yield. Finally acetylation of (9) by treatment with a slight excess of acetic anydride in pyridine and a catalytic amount of dimethylamine pyridine (DMAP) at 0°C for 2 h, furnished quantitatively the acetate (10) as an oil.

The next phase of the synthesis is the attack of the necessary ring appendages. To this purpose the key intermediate (10) was oxidatively converted into the aldehyde (11) by exposure to a stream of ozone in CH_2Cl_2 solution at -78°C until a deep blue solution was obtained, followed by the reduction of the resulting ozonide with Zn/CH_3COOH. The aldehyde (11), without further purification, was then allowed to react in dimethylsulfoxide with the sodium salt of (4-carboxybutyl)triphenyl-phosphonium bromide[12] obtained by treatment with sodium methylsulfinylmethide, to give the coupled product (12) which was subjected to mild basic hydrolysis and sequential esterification by diazomethane to afford the ester (14) in 43% yield starting from (11). CrO_3/Pyridine oxidation of (14) led to the aldehyde (15) which was then converted to the α-β unsaturated ketone (16) by means of the sodium salt of dimethyl (2-oxohepthyl)phosphonate following a well known standard procedure. Completion of the synthesis was then effected by a three step procedure: a) sodium borohydride reduction of the 15-ketone which afforded a mixture of epimeric C(15) alcohols (17) and (18); b) separation by preparative t.l.c. of the most polar alcohol; c) hydrolysis of the latter to PGD_2 methyl ester by exposure to HF_{aq}/CH_3CN[13].

In order to complete the synthesis of PGD_2 purely from optically active precursors, we have now developed a practical and efficient method for resolving cyclopentanedione bis-acetal[3c] (21) "via" the formation of the (+) ephedrine salt of the corresponding acid (22) and

conversion to the optically active intermediate (23) (SCHEME II), which can be transformed into the optically active natural PGD_2 following the route reported in this paper. Details of this process will be reported shortly elsewhere.

SCHEME II



(21): R = C_2H_5
(22): R = H

$[\alpha]_D^{25}$ = + 16.5 (c 1.2 $CHCl_3$)

$[\alpha]_D^{25}$ = - 16.5 (c 1.2 $CHCl_3$)

(23)

EXPERIMENTAL

I.r. spectra were recorded as film on a Perkin-Elmer 710 B spectrophotometer. ^1H and ^{13}C n.m.r. spectra were determined in $CDCl_3$ or C_6D_6 solutions on Varian EM 390 and Varian FT 80 instruments respectively; chemical shifts are expressed as δ-values in p.p.m. from internal standard $SiMe_4$. Mass spectra were taken on a Varian Mat 112 S instrument (70 eV). T.l.c. was performed on silica gel sheets (Kieselgel 60 F_{254} - Merck) and column chromatography on a Chromatospac Prep. 10 (Jobin-Ivon instrument) using silica gel (H 60 Merck).

Materials.--Commercially available starting materials were used without prior purification, unless otherwise stated. THF was obtained anhydrous and oxygen-free by distillation over sodium benzophenone ketyl under argon. Methylene dichloride was distilled over P_2O_5. Diisopropylamine was refluxed over molecular sieves (Type 4A, Fluka) and distilled at atmospheric pressure. Dimethyl sulfoxide (DMSO) was distilled at reduced pressure over CaH_2. (4-Carboxybutyl) triphenyl-phosphonium bromide and dimethyl-(2-oxo-heptyl)-phosphonate were purchased from Aldrich.

Preparation of compounds.

2,3-trans-3,4-trans-2-Ethoxycarbonyl-3-(prop-2-enyl)-4-hydroxy-cyclopentanone Ethylene Acetal (5)

--A solution of ketone (3) (1g, 3.9 mmol) in ethanol (5 ml) was added dropwise at 0°C to a stirred suspension of $NaBH_4$ (0.6 g,15 mmol) in ethanol (20 ml., 95% solution). The resulting solution was stirred at this temperature for 1 h, then the excess of the reagent was destroyed with 1% HCl. The mixture was extracted with ether (3 x 30 ml). The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give quantitatively the crude acetal (5) as an oil whose purity was estimated by t.l.c. and ^{13}C n.m.r. analysis to be 100%.

m/z 256 (M^+), 238 (M^+-H_2O).

ν_{max} (film) 3 500 and 1 735s cm^{-1}

δ_H (90 MHz; $CDCl_3$) 6.0-4.9 (m 3 H), 4.2 (q 2 H), 3.9 (m 5 H), 2.8 (bs 1 H OH), 2.7-2 (complex pattern 6 H), 1.3 (t 3 H).

2,3-trans-3,4-trans-2-Ethoxycarbonyl-3-(prop-2-enyl)-4-p-toluen-sulfonyloxy cyclopentanone Ethylene Acetal (6).

--To a solution of hydroxy ketone (5) (0.6g, 2.3 mmol) in dry methylene dichloride (10 ml) was added at 0°C triethyl amine (1 ml, 3.5 mmol), p-toluenesulfonyl chloride (0.5g, 2.6 mmol), 4-dimethylaminopyridyne (DMAP) (0.030g). The mixture was stirred overnight at room temperature. After filtration, the reaction mixture was quenched with cold dil. HCl and extracted with methylene dichloride. The organic layers were washed several times with water, dried (Na_2SO_4), the solvent was removed in vacuo and the residue was

chromatographed at medium pressure (Cyclohexane/ethyl acetate 1/1) to give the tosylate (6) (0.9g 95%).
m/z 410 (M^+), 369, 365.
ν_{max} (film) 1 730s, 1 600, 1 370, 1 180, 1 090 cm^{-1}.
δ_H (90 MHz, $CDCl_3$) 7.85 (d 2 H), 7.35 (d 2 H), 5.45 (m 1 H), 4.85 (m 2 H), 4.2 (q 2 H), 3.9 (m 5 H), 2.8-1.65 (m 6 H), 2.4 (s 3 H), 1.2 (t 3 H).

2,3-trans-3,4-cis-2-Ethoxycarbonyl-3-(prop-2-enyl)-4-nitroxy-cyclopentanone Ethylene Acetal (7).

--A solution of tosylate (6) (0.5g, 1.2 mmol) and tetrabutylammonium nitrate (1.1g 3.6 mmol) in pentane was heated in sealed tube at 120°C for 5 h. The pentane solution was separated from oily-residue and the solvent removed in vacuo to give essentially pure (7) (0.35g 97%).
m/z 301 (M^+), 260, 256, 255.
ν_{max} (film) 1 730s, 1 630, 1 280 cm^{-1}.
δ_H (90MHz $CDCl_3$) 5.75 (m 1 H), 5.4 (bs 1 H), 5.15 (m 2 H), 4.2 (q 2 H), 3.9 (m 4 H), 2.9 (m 2 H), 2.3 (m 4 H), 1.2 (t 3 H).

2,3-trans-3,4-cis-2-Ethoxycarbonyl-3-(prop-2-enyl)-4-hydroxy cyclopentanone Ethylene Acetal (4) (From reduction of nitric ester).

--A solution of nitric ester (7) (0.35g 1.16 mmol) in CH_3COOH (5 ml) was treated with Zn powder in small portions, at room temperature, until no more starting material was detected by t.l.c. The reaction mixture was filtered, diluted with ether and the organic layers were washed several times with aq. (5%) $NaHCO_3$, brine, and dried (Na_2SO_4). The solvent was stripped off and the residue chromatographed at medium pressure (cyclohexane/ethyl acetate 1/1) to give (4) (0.22g 74%) identical in all respects to the product obtained from reduction of ketone (3) with K-Selectride[3c].
m/z 256 (M^+), 238 (M^+-H_2O)
ν_{max} (film) 3 500 and 1 735 cm^{-1}.
δ_H (90 MHz C_6D_6) 5.8 (m 1 H), 5.15 (m 2 H), 4.2 (m 1 H), 4.1 (q 2 H), 3.9 (m 4 H), 3-1.5 (complex pattern 7 H), 1.3 (t 3 H).

2,3-trans-3,4-cis-2-Ethoxycarbonyl-3-(prop-2-enyl)-4-t-butyldimethylsilyloxy cyclopentanone Ethylene Acetal (8).

--To a solution of alcohol (4) (5g, 19.5 mmol) in dry dimethylformamide (10 ml) t-butyl-dimethylsilyl chloride (3.45g, 23.6 mmol) and freshly crystallized imidazole (3.5g 51 mmol) were added. The mixture was stirred overnight at room temperature, poured into ice-water and extracted with ethylacetate. The extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo to give (8) (7.03g, 97%) with a good degree of purity for further elaboration.
m/z 370 (M^+), 325, 313
ν_{max} (film) 1 750, 1 650, 1 250, 1 100, 1 040 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 6.0-4.7 (m 3 H), 4.05 (q 2 H), 3.8 (m 5 H), 3.1-1.9 (m 6 H), 1.3 (t 3 H), 0.9 (s 9 H), 0.08 (s 6 H).

2,3-trans-3,4-cis-2-(Hydroxy-methyl)-3-(prop-2-enyl)-4-t-butyldimethylsilyloxy cyclopentanone Ethylene Acetal (9).

--$LiAlH_4$ (0.759g 20 mmol) was added in small portions to a solution of ester (8) (7g, 18.9 mmol) in anhydrous ethyl ether (60 ml) at 0°C. After stirring for 1 h, the mixture was treated with saturated aqueous solution of NH_4Cl and extracted with ether (3 x 150 ml). Usual work-up gave (9) (5.6g, 90.3%) homogeneous on t.l.c. (silica gel, Hexane/Ethyl acetate 1/1).
m/z 328 (M^+), 271.
ν_{max} (film) 3 530, 1 650 and 1 250 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 6.0-4.8 (m 3 H), 4.15 (m 1 H), 3.85 (bs 4 H), 3.7 (d 2 H), 2.65 (bs 1 H OH), 2.4-1.8 (m 6 H), 0.88 (s 9 H), 0.05 (s 6 H).

2,3-trans-3,4-cis-2-(Methyl-acetyloxy)-3-(prop-2-enyl)-4-t-butyldimethylsilyloxy-cyclopentanone Ethylene Acetal (10).

--A mixture of alcohol (9) (5.4g, 16.4 mmol), pyridine (5 ml), acetic anhydride (5 ml), and DMAP (0.2g) is allowed to stand for 1 h at 0°C. The solution is partitioned between ethylacetate and cold HCl (30 ml 1 N), the organic phase is washed with saturated $NaHCO_3$,

dried over $MgSO_4$ and the solvent removed in vacuo. Was obtained (10) as an oil in 98% yield (6g).
m/z 370 (M^+), 313, 253
ν_{max} (film) 1 750, 1 650 and 1 240 cm^{-1}
δ_H (90 MHz $CDCl_3$) 6.0-4.7 (m 3 H), 4.25 (d 2 H), 4.15 (d 2 H), 3.8 (bs 4 H), 2.5-1.6 (m 6 H), 2 (s 3 H), 0.88 (s 9 H), 0.05 (s 6 H).

2,3-trans-3,4-cis-2-(Methyl-acetyloxy)-3-(methyl-formyl)-4-t-butyldimethylsililoxy-cyclopentanone Ethylene Acetal (11).

--A solution of (10) (6g 16.1 mmol) in methylene dichloride (50 ml) was cooled to -78°C. Ozone was passed through the solution at the rate of 0.5 ml/min until deep blue solution. While still at -78°C the system was flushed with nitrogen until colourless solution, the temperature was then allowed to rise to 0°C and acetic acid (10 ml) was added, followed by Zn powder in small portions at room temperature monitoring by t.l.c. (SiO_2, Hexane/Ethyl-acetate 6/4) until the reduction of ozonide was complete. The resulting mixture was filtered, the pH adjusted at 7 with $NaHCO_3$ (5%), washed several times with water. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give the oily aldehyde (5.3g 88.5%) homogeneous by t.l.c. and ^{13}C n.m.r., which was employed as such in successive step.
m/z 372 (M^+), 315, 313
ν_{max} (film) 2 700, 1 740, 1 725, 1 250, 1 040 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 9.8 (s 1 H CHO), 4.2 (m 1 H), 4.15 (d 2 H), 3.9 (s 4 H), 2.7-2.2 (m 6 H), 2.05 (s 3 H), 0.9 (s 9 H), 0.05 (s 3 H), 0.025 (s 3 H).

2,3-trans-3,4-cis-2-(Hydroxy-methyl)-3-(6-methoxycarbonyl-hex-2(Z)-enyl)-4-t-butyldimethylsilyloxy-cyclopentanone Ethylene Acetal (14).

--A mixture of 50% sodium hydride-dispersion-in-oil (4.2g) and dimethylsulfoxide (50 ml freshly distilled over calcium hydride) was stirred under argon at 75°C until gas evolution ceased (1 h).
To the resulting solution (33.6 ml, 67 mmol, 2 M in sodium methylsulfinylmethide) cooled to room temperature, (4-carboxybutyl)-triphenyl-phosphonium bromide (15.6g, 35 mmol) in DMSO (40 ml) was added dropwise. After the deep red liquid had been stirred for a further 20 min, a solution of the aldehyde (11) (5.3g, 14 mmol) in DMSO (40 ml) was added. The temperature was raised to 50°C, and stirring continued for 1 h. The mixture was poured into ice-water and extracted with ethyl acetate. The cooled aqueous layer was acidified with dil. HCl and extracted with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with water, dried ($MgSO_4$) and concentrated. The resulting crude product (5g) was dissolved in methanol (100 ml) and treated with K_2CO_3 (3g) at reflux for 1 h. The methanol was stripped off and the mixture was poured into ice-water, acidified with dil. HCl, extracted with ethyl acetate, washed with brine, dried and concentrated. To the oil-residue ethereal diazomethane was added and the solution stirred at 0°C for 1 h. To this solution were added few drops of acetic acid in order to destroy the excess of reagent and the solvent was removed in vacuo. The final product was purified by chromatography at medium pressure on silica gel eluting with ethyl acetate/hexane 1/1 to yield the alcohol (14) as colourless oil (2.6g, 43% from 11).
m/z 428 (M^+), 410, 397, 371.
ν_{max} 3 530, 1 735, 1 250, 1 080, 1 040 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 5.3 (m 2 H), 4.02 (m 1 H), 3.75 (m 7 H), 3.5 (s 3 H), 2.4(bs 1 H OH), 2.2-1.3 (m 11 H), 0.8 (s 9 H), 0.05 (s 6 H).

2,3-trans-3,4-cis-2-Formyl-3-/6-methoxycarbonyl-hex-2(Z)-enyl/-4-t-butyldimethylsilyloxy-cyclopentanone Ethylene Acetal (15).

--To a solution of chromium trioxide (0.87g)-pyridine (1.5 ml)-complex in anhydrous methylene dichloride (20 ml), was added at 0°C with stirring under argon, a solution of alcohol (14) (0.5g 1.2 mmol) in methylene dichloride (10 ml). After 20 min the mixture was filtered on dry diatomaceous earth (Celite 20g), washed with ice-cooled HCl (1 N) and the solvent removed in vacuo to give the aldehyde (15) (0.45g 90%).
m/z 426 (M^+), 395, 369.
ν_{max} (film) 2 710, 1 735, 1 720, 1 250, 1 100 and 1 040 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 9.7 (d 1 H), 5.4 (m 2 H), 4.25 (m 1 H), 3.9 (m 4 H), 3.65 (s 3 H), 2.9-1.5 (m 12 H), 0.8 (s 9H), 0.05 (s 6 H).

Methyl-(8,9-cis-9,12-trans)-9-t-butyldimethylsilyloxy-11,15-dioxo-prosta-5(Z),13(E)-dienoate-11-

ethylene Acetal (16).

--To a stirred suspension of sodium hydride (50% dispersion-in-oil, 46 mg) in anhydrous tetrahydrofuran (5 ml), at 0°C was added a solution of dimethyl-(2-oxoheptyl)-phosphonate (0.222g, 1 mmol) in the same solvent (5 ml). After stirring at 0°C for 30 min a solution of the aldehyde (15) (0.42g, 1 mmol) in THF (5 ml) was added. The temperature was allowed to rise 20°C and stirring was continued for 4 h. The reaction was quenched by addition of ice-cooled HCl (0.1 N 5 ml). The resulting mixture was extracted with ethyl acetate (3 x 30 ml), and the combined extracts were washed with brine, dried (Na_2SO_4) and evaporated to give an oil which was chromatographed on medium pressure (SiO_2 Hexane/Ethyl acetate 60/30) to yield (16) (0.36g, 69%)
m/z 522 (M^+), 507, 491, 465.
ν_{max} (film) 1 735, 1 715, 1 665, 1 625, 1 250, 1 040 cm^{-1}.
δ_H (90 MHz $CDCl_3$) 6.76 (dd J=16 Hz and J=8.5 Hz 1 H), 6.25 (d J=16 Hz 1 H), 5.35 (m 2 H J cis), 4.25 (m 1 H), 3.8 (bs 4 H), 3.5 (s 3 H), 2.7-1 (m 23 H), 0.9 (s 9 H), 0.055 (s 6 H).

Methyl(8,9-cis-9,12-trans)-9-t-butyldimethylsilyloxy-11-oxo-15α -hydroxy-prosta-5(Z),13(E)-dienoate-11-ethylene Acetal (18) and Methyl(8,9-cis-9,12-trans)-9-t-butyldimethylsilyloxy-11-oxo-15β-hydroxy-prosta-5(Z),13(E)-dienoate-11-ethylene Acetal (17).

--To a solution of (16) (0.65g, 1.24 mmol) in methanol (5 ml) cooled to -10°C, was added a solution of sodium borohydride (100mg) in ice-cooled methanol (3 ml). After 1 h an aqueous solution of satured sodium hydrogen phosphate (10 ml) was added and the mixture was extracted with ethyl acetate. The extracts were dried ($MgSO_4$) and the solvent was removed to yield a colourless oil residue. Medium pressure chromatography (hexane/ethyl acetate 70/30) of this oil yield a 1/1 mixture (0.25g each) of (17) and (18) for a total yield of 77%.
(data identical for both compounds):
m/z 524 (M^+), 506, 493, 467, 449.
ν_{max} (film) 3 500, 1 750, 1 250, 1 040 cm^{-1}.
Less polar compound (17)
δ_H (90MHz $CDCl_3$) 5.63 (dd J=7Hz and J=16Hz 1 H), 5.45 (m 3 H), 4.16 (m 2 H), 3.83 (m 4 H), 3.66 (s 3 H), 2.66 (m 1 H), 2.5-1.06 (m 23 H), 0.9 (s 9 H), 0.055 (s 6 H).
More polar compound (18)
δ_H 5.63 (dd J=7Hz and J=16Hz 1 H), 5.45 (m 3 H), 4.16 (m 2 H), 3.83 (m 4 H), 3.66 (s 3 H), 2.66 (m 1 H), 2.5-1.06 (m 23 H), 0.9 (s 9 H), 0.055 (s 6 H).

(±)PGD_2 methyl ester (20).

--The most polar silyl ether (18) (0.1g 0.19 mmol) was dissolved in a mixture of 40% hydrofluoric acid-acetonitrile (1-3) (3 ml), the solution was stirred at room temperature for 3 h and then poured into 5% aqueos sodium hydrogen carbonate (5 ml) and rapidly extract with methylene dichloride (3 x 30 ml). The combined extracts were washed in turn with water and brine, dried ($MgSO_4$) and evaporated at 5°C to give a brown oil which was chromatographed on preparative t.l.c. (SiO_2, ether) to give (20) (0.05g 72%)
m/z 366 (M^+)
ν_{max} 3 450, 1 735 cm^{-1}
δ_H (300MHz Bruker CXP 300)5.63 (dd J=7 and 16 Hz, becomes a d upon irradiation at 4.09, J=16 Hz, H(C-15)), 5.45-5.58 (m 2 H (C-5,C-6), 5.43 (dd J=16 and 8.5 Hz, becomes d upon irradiation at 2.87 J=16 Hz 1 H(C-13), 4.47 (bm, becomes a d upon irradiation at 2.45 J=4Hz, 1 H (C-9)), 4.09 (bq J=7 Hz 1 H(C-15)), 3.66 (s 3 H), 2.87 (dd, J=12 and 8.5Hz, becomes a d upon irradiation at 5.43, J=12Hz, and becomes a d upon irradiation at 1.95, J=8.5, 1 H(C-12)), 2.45 (m 2 H (C-10)), 1.95 (bs 1 H (C-8)), 2.8-0.9 (m 21 H). (These values are perfectly in accord with the values reported in reference 2d).

(±)-15-epi-PGD_2 methyl ester (19)

--This product was produced from the less polar silyl ether (17) using the same method as for (20). Chromatography with ether on preparative t.l.c. (SiO_2) gave (±)epi-PGD_2 methyl ester in 60% yield.

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Table--^{13}C N.m.r. chemical shifts and assignements for cyclopentanoids derivative[a,b]

	Compounds										
	4	5	8	9	10	11	14	15	16	17	18
C(n)											
1							173.3	173.1	173.1	173.1	173.1
2							25.1	25.0	27.0	26.9	27.0
3							c 26.0	c 26.4	c 25.5	c 25.7	c 25.6
4							27.0	26.9	24.9	24.9	25.2
5			115.7	115.5	115.7		129.7	128.6	129.1	129.4	129.4
6			137.3	137.9	137.6	200.3	129.7	130.6	129.8	128.0	128.5
7			33.3	32.6	32.7	43.3	33.4	33.3	33.3	33.1	33.3
8	46.8	48.7	47.1	44.8	47.2	41.8	45.6	45.8	50.4	50.9	50.6
9	71.0	73.5	71.6	71.3	71.1	71.0	71.5	71.9	71.5	71.0	71.0
10	47.1	45.7	47.9	47.1	47.2	47.2	47.1	47.8	48.3	48.3	48.2
11	117.5	116.5	117.0	117.7	116.1	115.8	117.6	117.5	117.7	117.6	117.5
12	57.8	58.2	57.8	51.3	48.8	48.6	51.6	63.0	55.1	55.0	54.9
13	171.2	171.7	170.8	59.3	63.0	63.1	60.0	200.1	144.3	138.1	137.5
14									132.9	130.0	129.8
15									198.3	72.9	72.4
16									40.14	37.9	37.9
17									31.8	32.3	32.3
18									c 24.2	c 25.1	c 25.0
19									22.8	23.1	23.0
20									14.1	14.3	14.2

Chemical shifts in p.p.m. downfield from Me_4Si. Spectra were taken in C_6D_6 at 20.00 MHz in the fourier mode with a Varian FT 80 spectrometer.
b) Prostane numbering. c) Assignements may be reversed.

References and notes.

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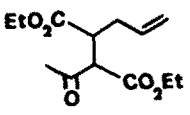
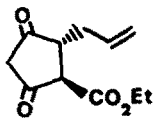
SCHEME I



(1)



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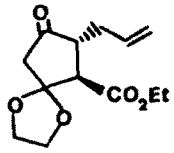

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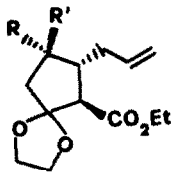
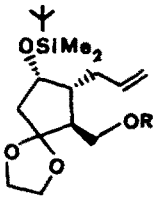
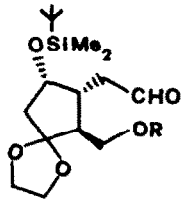


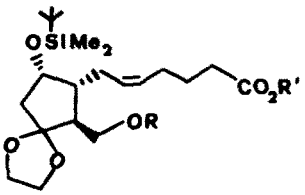
(4): R = OH; R' = H
(5): R = H; R' = OH
(6): R = H; R' = OTs
(7): R = ONO_2; R' = H
(8): R = $OSiMe_2$; R' = H



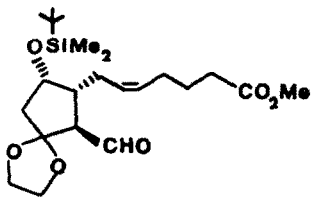
(9) : R = H
(10) : R = $COCH_3$



(11): R = $COCH_3$



(12): R = $COCH_3$; R'= H
(13): R = H; R'= H
(14): R = H; R'= Me



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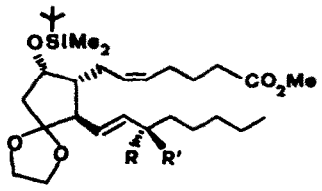
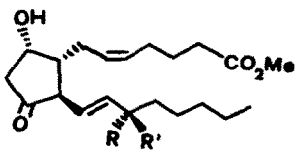


(16): R = R' = O
(17): R = H; R' = OH
(18): R = OH; R' = H



(19): R = H; R' = OH
(20): R = OH R' = H