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SYNTHESIS OF A NOVEL PROSTAGLANDIN H_2 (PGH_2) ANALOGUE

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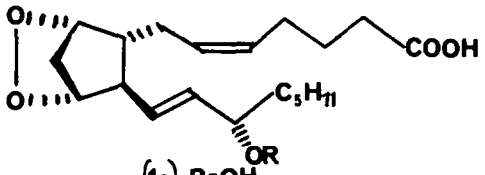
ABSTRACT: We describe a five-step synthesis of a PGH_2 analogue from (R)-glyceraldehyde acetonide via formation of 1,2(S)-O-isopropylidene-hex-3(E)-en-5-one, conjugate addition of prostanoid C_{13}-C_{20} side-chain as the cuprate with C_1-C_7 side-chain used to quench the resultant enolate, and finally acid-catalysed ketal exchange to provide the desired analogue.

It is now twelve years since the prostaglandin endoperoxides PGG_2(1a) and PGH_2(1b) were isolated and shown to be precursors of the prostaglandins.[1] They have short biological half-lives (around 5 minutes under physiological conditions), but exhibit potent biological activities including contraction of bronchial smooth muscle and irreversible aggregation of blood platelets.[2] A number of analogues have been produced,[3] and most of these are structures in which one or both of the peroxide oxygen atoms have been replaced by another heteroatom or by a methine or methylene group. Little biological data is available in the research literature, but some of the analogues, e.g. (2),[4] are claimed to have useful properties (inhibition of human platelet thromboxane synthetase in this instance).

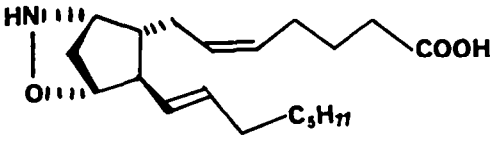
We planned to prepare analogues of general structure (3) by the convergent approach shown in the Scheme, and this route is both short and potentially flexible. Our starting compound was (R)-glyceraldehyde acetonide (4) available from 1,2:5,6-di-O-isopropylidene (D)-mannitol (5), which can be prepared by a variety of methods.[5] Initially, the method of Baer was used to prepare (5), but variable amounts of mono- and tri-isopropylidene derivatives were obtained, and the recently described method of Horton was found to give more reproducible results. Cleavage of the diacetonide was effected using sodium metaperiodate in moist THF, and the desired glyceraldehyde acetonide (4) was obtained in admixture with its hydrate (i.r. bands at 1740 and 3460 cm^{-1}).

This mixture was used immediately for Wittig reactions with a variety of stabilised ylids. With carbomethoxymethylidene triphenylphosphorane a mixture of cis- and trans- products (6a and b) were obtained in a combined yield of 80-90%, but with a preponderance of the cis-isomer (6a). The ratio of isomers varied with the hydrate content, but since the aldehyde (4) polymerised easily, drying by means of a Dean and Stark apparatus was not a practical solution to this problem.

Reaction of (4) (in admixture with hydrate) with 2-keto-propylidene triphenylphosphorane in dichloromethane at -20° provided unsaturated



(1a) R=OH
(1b) R=H



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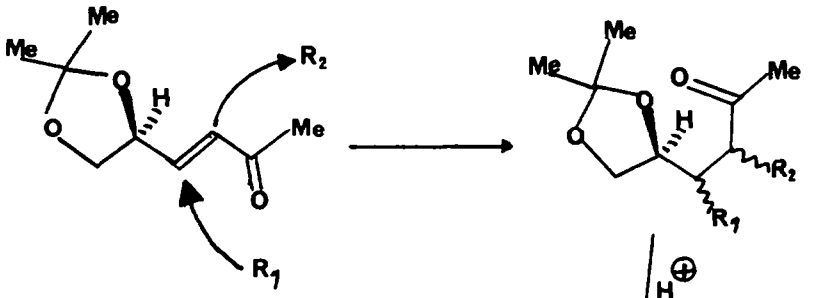
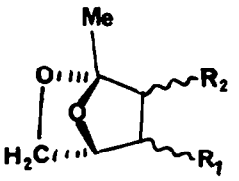
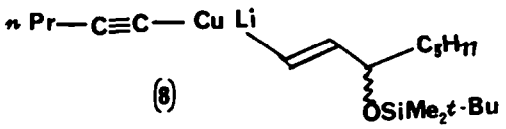


SCHEME



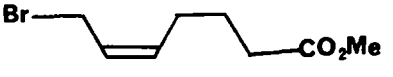
(3)

For example, R_1 may be:



(8)

For example, R_2 may be:



(10)

ketones (7a and b) in a typical combined yield of 70%, and a ratio of 1:2.5 (7a:7b). Similar yields were obtained with the ylid from dimethyl-2-ketopropylphosphonate in THF, but only the trans- product was obtained with this reagent.

The cuprate reactions were carried out using the mixed cuprate (8), prepared according to the methods of the Glaxo[6] and Syntex[7] groups. The enolate thus formed (9) was treated with a variety of electrophiles, namely methylbromoethanoate, ethylene oxide, ethylchloromethanoate,methyl-7-bromo-hept-5(Z)-enoate (10),[8] and trimethylchlorosilane. The first two reagents failed to react, and the sole product was the ketone (11) (this was also the product of quenching with water). Reaction with the other three reagents provided the desired products (12), (13) and (14) in yields of 46%, 7%, and 43%. In each case the products were mixtures of diastereoisomers, and no attempt was made to effect separation at this stage.

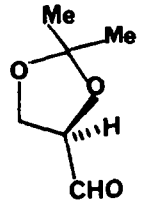
In view of the poor yield of (13) (others have also reported disappointing results when quenching cuprates with complex electrophiles[9]), alkylation of the enol silyl ether (14) was carried out using methyl -7-bromo-hept-5(Z)-enoate (10) in conjunction with methyl lithium. The general utility of this method has been proven by numerous workers,[10] and in our hands the alkylation proceeded as planned to yield (13) (as a mixture of diastereoisomers) in 51% yield. As an alternative approach to enol silyl ether (14), we have also taken cuprate product (11) and silylated this using chlorotrimethylsilane in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to produce (14) in 77% isolated yield.

The final stage in the synthesis was accomplished using pyridinium-p-toluene-sulphonate in moist acetone (55° for 24 hours) to effect deprotection at C-15, and acetal exchange, with obtention of two major products (15a,b; combined yield 50%) and a host of minor products. Flash chromatography, followed by preparative t.l.c. was required in order to effect separation, and the ^1H n.m.r. data (at 360 MHz) are presented in the Table. The near identity of the two spectra suggests that they are C-15 epimers, and the values of $J_{11,12}$ = 8.5Hz and $J_{8,12}$ = 11.5Hz for each stereoisomer accords with the bis-endo-configuration shown.[11] Little information concerning the ^1H n.m.r. spectra of endoperoxide analogues is available, but such as there is[12] supports these assignments. On the basis of t.l.c. characteristics we have assigned the 15α-(15s)-stereochemistry to (15a) since this is more polar in all systems tried.

Finally, having established that the route was viable, we were disappointed to discover that the compounds were extremely labile and required fresh purification before each spectroscopic study. In consequence, only limited biological testing was possible, and although both compounds proved to have anti-aggregatory activity on blood platelets (ADP-induced aggregation), these results must be treated with caution.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (liquid films for oils and Nujol mulls for solids); ^1H n.m.r. spectra were recorded with a Varian T-60 (60 MHz), Varian HA 100 (100 MHz) or Bruker WH 360 (360 MHz) instruments (tetramethylsilane as internal standard); and mass spectra were recorded on an A.E.I. MS12 spectrometer. Kieselgel $GF_{254+366}$ Merck) was used for analytical t.l.c., and flash chromatography was performed with Merck silica gel (230-400 mesh). Organic solvents were distilled from calcium hydride when required anhydrous, and petrol is pet. ether (40-60).



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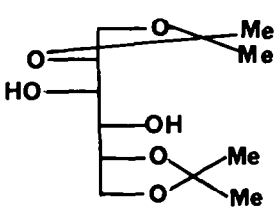
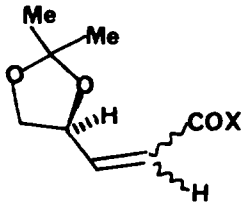
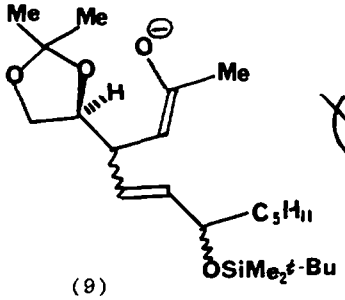


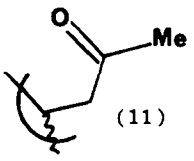
(5)



(6a,b) X=OCH_3
(7a,b) X=CH_3
(6a,7a) cis product
(6b,7b) trans product



(9)



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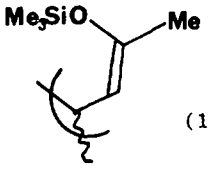
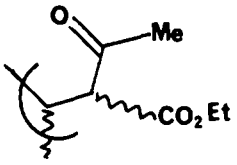
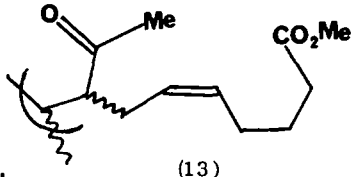


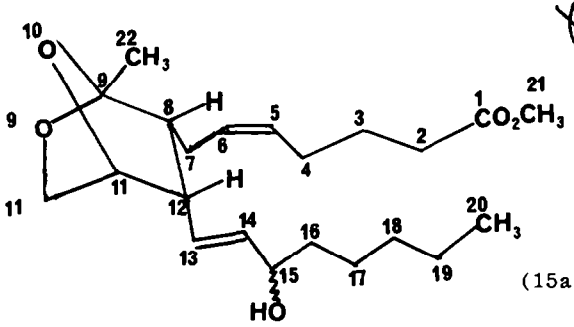
(14)



(12)



(13)



(15a,b)

1,2:5,6-Di-O-isopropylidene-D-Mannitol(5)-
A solution of D-mannitol (9.1g, 0.05 mol) in dry DMF (200 ml) containing Drierite® (0.5g) was stirred at 0°, and 2-methoxypropene (7.21g, 9.6 ml, 0.1 mol) was added followed by a catalytic amount of p-TSA (ca. 0.1g). Further aliquots of 2-methoxy propene (2x1 ml) were added over a two hour period, and then t.l.c. (MeOH:$CHCl_3$, 1:4) showed that mannitol had completely reacted. The mixture was stirred vigorously with anhydrous Na_2CO_3 (2.5g) for 1 hour, then filtered, and the crude product isolated after evaporation of the solvents (< 1 torr., 40°C). This oil was treated with boiling petrol, and the combined extracts concentrated to yield essentially pure diacetonide (5) (10g, 76%). Recrystallisation from dibutyl ether provided pure material. M.pt. 119-121° (Lit. 122°); ν_{max} 3390, 3270, 1210, 1070, 860 cm^{-1}; δ ($CDCl_3$, 60 MHz) 1.38(6H,s,2xCH_3), 1.43(6H,s,2xCH_3). 2.63(2H,d,J 7Hz, 2xOH), 3.5-4.5(8H,m,remaining H).

2,3-O-Isopropylidene-D-glyceraldehyde (4)-
1,2:5,6-Di-O-isopropylidene-D-mannitol (5) (5.868g, 0.0224 mol) in THF (75 ml) was added to a suspension of sodium periodate (5.264g, 0.0246 mol) in water (10 ml) and THF (15 ml). The mixture was shaken for 1 hour, then ether (100 ml) was added, and the mixture filtered and evaporated. The residue was dissolved in dichloromethane, dried and the solvent removed *in vacuo* to yield a colourless oil (4.941g, *ca.*85%).
ν_{max} (neat) 3460, 1740, 1380, 1220, 1070 and 840 cm^{-1}; δ($CDCl_3$,60 MHz) 1.45(3H,s,CH_3), 1.50(3H,s,CH_3), 3.9-4.6(3H,m,H-2 and H-3), 9.75(1H,d,J 1.5Hz, -CHO) ppm.

1,2-O-Isopropylidene-hex-3-en-5-one (7)
Isopropylidene-D-glyceraldehyde (4) (4.685g, *ca.* 36.0 mol) was dissolved in dichloromethane (50 ml) and 2-keto-propylidene triphenylphosphorane (12.735g, 40.0 m mol) in dichloromethane (90 ml) added. The solution was immediately placed in the deep-freeze (*ca.* -18°C). After 40 hours at that temperature the solvent was removed, the residue extracted with petrol, filtered, and the filtrate evaporated. The product was purified by flash column chromatography, using ether:petrol 1:1 as the eluant, to yield the *cis* isomer (7a) (1.177g, 19%) and the *trans* isomer (7b) (3.122g, 51%).
ν_{max} (neat) (7a) 3000, 1700, 1625, 1185, and 1060 cm^{-1}; (7b) 3000, 1685, 1635, and 1065 cm^{-1}; $\delta(CDCl_3$, 100 MHz) (7a): 1.3(3H,s,CH_3); 1.35(3H,s,CH_3); 2.15(3H,s,$COCH_3$); 3.45(1H,dd,Jgem 8Hz,$J_{1,2}$ 7Hz,H-1); 4.35(1H,dd,J_{gem} 8Hz, $J_{1,2}$ 7Hz,H-1); 5.25(1H,m,H-2); 6.15(2H,m,H-3 and H-4). (7b): 1.40(3H,s,CH_3); 1.46(3H,s,CH_3); 2.25(3H,s,$COCH_3$); 3.65(1H,dd,J_{gem} 8.0Hz,$J_{1,2}$ 7.0Hz,H-1); 4.19(1H,dd,J_{gem} 8.0Hz,$J_{1,2}$ = 6.5Hz,H-1); 4.68(1H,m,H-2); 6.31(1H,dd,$J_{3,4}$ 1.0Hz,H-4); 6.70(1H,dd,$J_{3,4}$ = 16.0Hz,$J_{2,3}$ 5.5Hz,H-3).
M/e(%) (7a): 112.0526 (20) $M^+-C_3H_6O$, $C_6H_8O_2$ requires 112.0522;
(7b): 155.0707 (28) M^+-CH_3, $C_8H_{11}O_3$ requires 155.0708.

Dimethyl-2-oxopropyl-phosphonate (2.076g, 12.5 m mol) in THF)10 ml) was added dropwise to a stirred suspension of sodium hydride (50% in oil, 0.600g, 12.5 m mol) in THF (100ml), under nitrogen. The mixture was then stirred for 1½ hours at room temperature, the reaction flask evacuated to remove the hydrogen formed and the mixture placed under nitrogen again. Isopropylidene-D-glyceraldehyde (4) (1.30g, *ca.* 10 m mol) in THF (30 ml) was then added dropwise at 0-5°C. The mixture was stirred at this temperature for 2 hours, ether (50 ml) added, the mixture filtered and the solvent removed *in vacuo* to yield a yellow oil. This oil was purified by flash column chromatography, using 35% ethyl acetate in petrol as the eluant, to give (7b) as a colourless oil (1.191g, *ca.* 70%).

3-(t-Butyldimethylsilyloxy)-oct-1-yne - t-Butyldimethylsilyl chloride (7.552g, 50.1 m mol) was dissolved in DMF (60 ml), and oct-3-ol-1-yne (7.3 ml, 50 m mol) and imidazole (5.106g, 75.0 m mol) added. The reaction was stirred at 35-40°C for 24 hours and then water (100 ml) was added. The mixture was extracted with distilled petrol (3 x 125 ml), the combined organic extracts dried and then evaporated. The crude product was purified by column chromatography on silica gel (60-120 mesh), using 2% ether in petrol as the eluant, to give a colourless oil (10.908g, 91%).
ν_{max} (neat) 3320, 2960, 2930, 2860, 1255, 1080, 835, 775 cm^{-1};
$\delta(CDCl_3$, 60MHz) 0.1(6H,2xs, $Si(CH_3)_2$); 0.9(12H,s,t-Bu,CH_3-8); 1.1-2.0(8H,m,4xCH_2); 2.35(1H,m,H-1); 4.35(1H,m,H-3).
t.l.c.: Rf = 0.59 (ether:petrol, 1:9).

3-(t-Butyldimethylsilyoxy)-1-iodo-oct-1(E)-ene
3-(t-Butyldimethylsilyoxy)-oct-1-yne (6.102g, 25.0 m mol) in THF (30 ml) was added to a stirred solution of 9-borabicyclo[3.3.1]nonane in THF (0.5M, 58 ml, 29 m mol), under nitrogen at 0°C in the dark. The reaction was stirred for 5 hours at room temperature, cooled to 0°C and then anhydrous trimethylamine-N-oxide (6.20g, 83 m mol) added portionwise. The mixture was stirred for 40 minutes at room temperature, then poured into aqueous sodium hydroxide (200 ml, 15%), and iodine (16.5g, 65 m mol) in THF (35 ml) added immediately. The mixture was stirred vigorously in the dark for 40 minutes, the layers separated, and the aqueous layer extracted with ether (2 x 75 ml). The combined organic phases were washed with aqueous sodium thiosulphate (1M, 100 ml), dried and evaporated. The crude product was purified by column chromatography on silica gel (100-200 mesh), using 2-3% ether in petrol as the eluant, to give a pale pink oil (5.032g, 55%).
νmax (neat) 2960, 2930, 2860, 1605 (weak), 1260, 1090, 945, 835, 775 cm^{-1};
$\delta(CDCl_3$, 100 MHz) 0.04(6H,s,$Si(CH_3)_2$); 0.86(12H, s ,t-Bu,CH_3-8); 1.05-1.65(10H,m,4xCH_2); 4.05(1H,broad q,H-3); 6.14(1H,dd,$J_{1,2}$= 14.5 Hz, $J_{1,3}$ ≈ 0.75 Hz, H-1); 6.50(1H,dd,$J_{1,2}$ = 14.5Hz, $J_{2,3}$= 6.0 Hz, H-2).
t.l.c. Rf = 0.36 (petrol).

Preparation of the lithium organocuprate species (8) -
n-Butyllithium (1.5M in hexane, 1 equivalent) was added slowly to a stirred solution of 3-(t-butyldimethylsilyloxy)-1-iodo-oct-1(E)-ene (1 equivalent) in dry ether (1 ml/m mol), at -78°C under nitrogen. After 1½ hours at this temperature, a solution of pent-1-ynyl copper (1 equivalent) in hexamethylphosphorus triamide (HMP) (2 equivalents) and dry ether (1.5 ml/m mol) was added slowly, and stirring continued for 1½ hours at -78°C.

7-(t-Butyldimethylsilyloxy)-4-(1',2'-O-isopropylidene)-dodeca-5(E)-en-2-one (11) - 1,2-O-Isopropylidene-hex-3(E)-en-5-one (7b) (0.681g, 4.00 m mol) in dry ether (2 ml) was added slowly to a stirred solution of the lithium organocuprate species (8) (4.0 m mol). The reaction was stirred for 3½ hours at -78°C, saturated aqueous ammonium chloride (20 ml) added, and the mixture stirred while warming to room temperature. The layers were separated and the aqueous extracted with ether (2 x 20 ml). The combined organic extracts were washed with cold hydrochloric acid (0.5M, 2 x 20 ml) and then water (20 ml). After drying and evaporation the products were separated by flash

column chromatography, using 20% ether in petrol as eluant, to give ketone (11) as a mixture of diastereoisomers (0.28g; 17%) and 3-(t-butyldimethylsiloxy)-oct-1-ene (0.34g). Spectral data for (11) are:
ν_{max} (neat) 2950, 2925, 2850, 1725, 1250, 1060, and 830 cm^{-1};
δ($CDCl_3$, 220MHz) 0.85(12H,s+t,t-Bu and CH_3-12), 1.00-1.60(14H,m, isopropylidene CH_3, CH_2-8, H-9, H-10 and H-11), 2.08 and 2.10 (3H,2xs, CH_3-1 of diastereoisomers), 2.20-3.00(3H,m,CH_2-3,H-4), 3.50-4.26 (4H,m, CH_2-2',H-1' and H-7), 5.29-5.56(2H,m,H-5 and H-6) ppm;
m/e(%) 397.2777 (2), M^+-CH_3 ($C_{22}H_{41}O_4Si$ requires 397.2774), 355.2302 (2), M^+-C_4H_9 ($C_{19}H_{35}O_4Si$ requires 355.2304).

7-(t-Butyldimethylsilyloxy)-4-(1',2'-O-isopropylidene)-2-trimethylsilyloxy-dodec-2,5(E)-diene - The lithium organocuprate species [8](6.0 m mol) was prepared as previously described. 1,2-O-Isopropylidene-hex-3(E)-en-5-one [7b] (1.021g, 6.0 m mol) in dry ether (3 ml) was then added, the mixture stirred for 3½ hours at -78°C, then trimethylsilylchloride (3.8 ml, 30 m mol) and triethylamine (4.2 ml, 30 m mol) in THF (15 ml) were added. The mixture was stirred for 1½ hours at -78°C, then water (50 ml) and petrol (30 ml) were added, and the mixture warmed to room temperature. The layers were separated and the aqueous extracted with petrol (2 x 50 ml). The combined organic phases were washed with cold hydrochloric acid (0.5M, 2 x 30 ml), dried and evaporated. The products were separated by flash column chromatography, using 6-7% ether in petrol as eluant, to give (14) as a colourless oil (1.246g, 43%).
ν_{max} (neat) 2960, 2935, 2860, 1680 (weak), 1380, 1255, 1070, 980, 845, 775 cm^{-1};
δ ($CDCl_3$, 100 MHz) 0.10(6H,s,$SiMe_2$), 0.25(9H,s,$SiMe_3$), 0.95(12H,s,t-Bu and CH_3-12), 1.15-1.70(14H, isopropylidene methyls, CH_2-8, H-9, H-10 and H-11), 1.90(3H,s,CH_3-1), 3.1-4.7(6H,m,H-3,H-1', CH_2-2', H-7 and H-4), 5.30-5.65(2H,m,H-5 and H-6);
m/e (%) 484.3409 (0.3) M^+($C_{26}H_{52}O_4Si_2$ requires 484.3404); 383.2821 (100) M^+-$C_5H_9O_2$ ($C_{21}H_{43}O_2Si_2$ requires 383.2802); t.l.c.: R_f = 0.44 (ether:petrol, 1:9).

Alternatively, ketone (11) (1.0g, 2.43 m mole), diazobicyclo[5.4.0]undec-7-ene DBU (0.568g, 0.56 ml, 3.74 m mole) and trimethylchlorosilane (0.40 g, 0.46 ml, 3.64 m mole) were dissolved in dichloromethane (20 ml), and the mixture stirred under nitrogen for 16 hours. Reaction was then half-complete, and further aliquots (0.5 ml each) of DBU and Me_3SiCl were added. After a further 24 hours reaction was complete, petrol (100 ml) was added, and the mixture treated with aq. HCl (0.5M, 5 ml), $NaHCO_3$ solution, and water. The organic extract was dried and purified by chromatography (silica, 60-120 mesh, 9:1 petrol:ether) to yield (14) (0.9g, 77%) as a colourless oil.

Methyl-12-(t-butyldimethylsilyloxy)-8-ethanoyl-9-(1',2'-O-isopropylidene)-heptadec-5(Z),10(E)-dien-oate (13) - Methyllithium (1.5M in ether, 0.73 ml, 1.1 m mol) was added slowly to a stirred solution of 7-(t-butyldimethylsilyloxy)-4-(1',2'-O-isopropylidene)-2-trimethylsilyloxy-dodec-2,5(E)-diene (14) (485 mg, 1.0 m mol) in THF (5 ml) at -78°C under nitrogen. The reaction was stirred for 1½ hours at -60→ -50°C then methyl-7-bromo-hept-5(Z)-enoate (10) (553 mg, 2.5 m mol) in HMPA (4 ml) and THF (5 ml) was added. The solution was then stirred for 2½ hours at -55→ -40°C and 3 hours at -30→ -20°C, water (20 ml) added, and the mixture separated. The aqueous phase was extracted with ether (3 x 25 ml), and the combined organic phases washed with cold aqueous hydrochloric acid (0.5M, 2 x 20 ml), dried and evaporated. The product mixture was separated by flash column chromatography, using 18-25% ether in petrol as eluant. The first compound to be eluted was the excess bromide (10) (278 mg, 1.26 m mol), followed by traces of the non-alkylated compound (11). The required product (13) was then eluted as a mixture of two diastereoisomers, (350 mg; 63%).
ν_{max} (neat) 2960, 2930, 2860, 1740, 1715, 1250, 1215, 1160, 1065, 835 cm^{-1};
δ($CDCl_3$, 220 MHz) 0.02(6H,pr of s, $Si(CH_3)_2$); 0.78(12H,s,SitBu, CH_3-17); 1.06-1.46(14H,m,CH_2-13,14,15,16 isopropylidene CH_3), 1.58(2H,m,CH_2-3); 1.90-2.18(7H,pr. of s and m, $COCH_3$, CH_2-4, CH_2-7); 2.24(2H,t,J 8Hz,CH_2-2); 2.50 and 2.68(2H,2m,H-8,H-9); 3.46-3.68(4H,s and m,OCH_3,H-1'); 3.80-4.10 (3H,m,CH_2-2',H-12); 5.10-5.64(4H,m,H-5,6,10,11).

9,11-Epoxymethano-9-methyl-10-oxa PGH_2 methyl ester (15) (6,7-Dioxa-1-methyl-2-(6'-carbomethoxy-hex-2'(Z)-ene)-3-(oct-1"(E)-en-3"-ol)-bicyclo[2.2.1]heptane).
Pyridinium-p-toluene-sulphonate (25 mg, 0.1 m mol) and methyl-12-(t-butyldimethylsilyloxy)-8-ethanoyl-9-(1',2'-O-isopropylidene)-heptadec-5(Z), 10(E)-dien-oate (13) (160 mg, 0.29 m mol) were dissolved in acetone (9.5 ml) and water (0.5 ml). The solution was refluxed for 6½ hours, then stirred at 55°C for 16 hours. The solvent was evaporated, water (20 ml) added and the mixture extracted with dichloromethane (3 x 20 ml). The organic extracts were combined, dried and evaporated. The residue was purified by flash column chromatography, using 0-5% methanol in ether as eluant, to give (15b) (27 mg, 25%) and (15a) (28 mg, 25%).

ν_{max} (in solution in CH_2Cl_2, 0.1 mm NaCl cell): (15b) - 3600 (sharp) and 3450 (broad), 2960, 2940, 2870, 1735, 1220, 1110, 1030, 975 cm^{-1}; (15a) - 3600 (sharp) and 3430 (broad), 2960, 2940, 2870, 1735, 1220, 1110, 1030, 975 cm^{-1}.
More (15a) and (15b) were synthesized by the same method, and the combined products were purified further, by preparative t.l.c., using 5% methanol in ether as eluant. The ^1H n.m.r. data is given in the TABLE.

m/e (%) (15b) 380.2560 (5) M^+ ($C_{22}H_{36}O_5$ requires 380.2563).
t.l.c. R_f = 0.42 (15b) and 0.33 (15a)
(MeOH:ether, 1:19)
R_f = 0.34 (15b) and 0.20(15a) (ethyl acetate)
R_f = 0.46(15b) and 0.39 (15a)
(MeOH:$CHCl_3$, 1:9).

TABLE (360 MHz ^1H n.m.r. data)

15(a) Signal (δ)	15(b) Signal (δ)	No. of H	Multiplicity	J(Hz)	Assignment
0.90	0.90	3	t	7	CH_3-20
1.23-1.43	1.23-1.43	9	m	-	CH_2-16,17,18, 19, OH
1.48	1.48	3	s	-	CH_3-22
1.68	1.68	2	quintet	7.5	CH_2-3
1.76	1.76	1	m	-	H-8
2.02-2.17	2.02-2.19	3	m	-	CH_2-4,H-7
2.24-2.35	2.21-2.35	3	m+t	7.5 for t	H-7,CH_2-2
2.68	2.69	1	dt	8.5,11.5	H-12
3.48	3.45	1	dd	12.0,2.5	H-11a
3.64	3.64	3	s	-	CH_3-21
3.69	3.68	1	dd	12.0,2.5	H-11a
3.82	3.80	1	dt	8.5,2.5	H-11
4.03	4.04	1	broad q	6.0	H-15
5.34	5.35	1	m	-	H-5,H-6
5.44	5.46	1	m	-	
5.46	5.48	1	dd	8.5,15.0	H-13
5.58	5.60	1	dd	6.0,15.0	H-14

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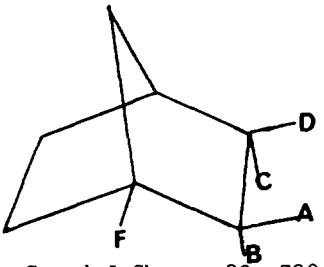

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ADDENDUM

Ethyl-6-(t-butyldimethylsilyloxy)-2-ethanoyl-3-(1',2'-O-isopropylidene)-undec-4(E)-enoate (12) - The lithium organocuprate species (8) (3.56 m mol) was prepared as previously described. 1,2-O-Isopropylidene-hex-3(E)-en-5-one (7b) (0.606 g, 3.56 m mol) in dry ether (2 ml) was then added, the mixture stirred for 2½ hours at -78°C, then ethyl chloroformate (1.0 ml, 11 m mol) in HMPA (2 ml) and THF (15 ml) was added. The mixture was stirred for 1¾ hours at -78°C, and then ethanol (1 ml) added. The reaction was worked up as usual and the products separated by flash column chromatography, using 10-15% ether in petrol as eluant, to yield (12) as a colourless oil (0.796 g), and as a mixture of diasterioisomers.

$\nu_{max.}$ 2960, 2930, 1760, 1705 (weak), 1370, 1235 (broad), 1070, 835, 775 cm^{-1};

δ ($CDCl_3$, 100 MHz): 0.01 and 0.03 (6H, 2s, $Si(CH_3)_2$); 0.90 (12H, s, SitBu, CH_3 - 11); 1.12 - 1.60 (17H, m, 3xCH_3, CH_2-7,8,9,10); 2.00 (3H, s, -$COCH_3$); 3.04 - 3.44 (1H, m, H-3); 3.52 - 3.78 (1H, m, H-1'), 3.84 - 4.38 (5H, m, H-2', H-6, -OCH_2-), 4.84 - 5.06 (1H, m, H-2), 5.40 - 5.66 (2H, m, H-4, H-5) p.p.m.; m/e (%) 469.2988 (0.4), M^+ - CH_3 ($C_{25}H_{45}O_6Si$ requires 469.2985), 427.2515 (9), M^+ - C_4H_9 ($C_{22}H_{39}O_6Si$ requires 427.2516.