Synthesis of the Major Urinary Metabolite of Prostaglandin D_2

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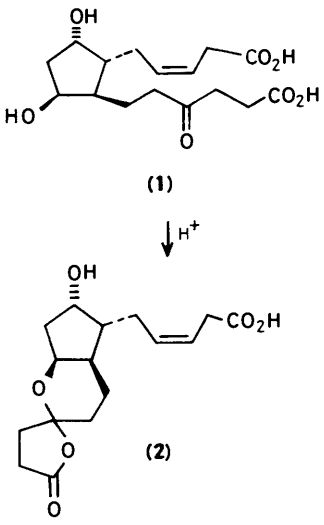
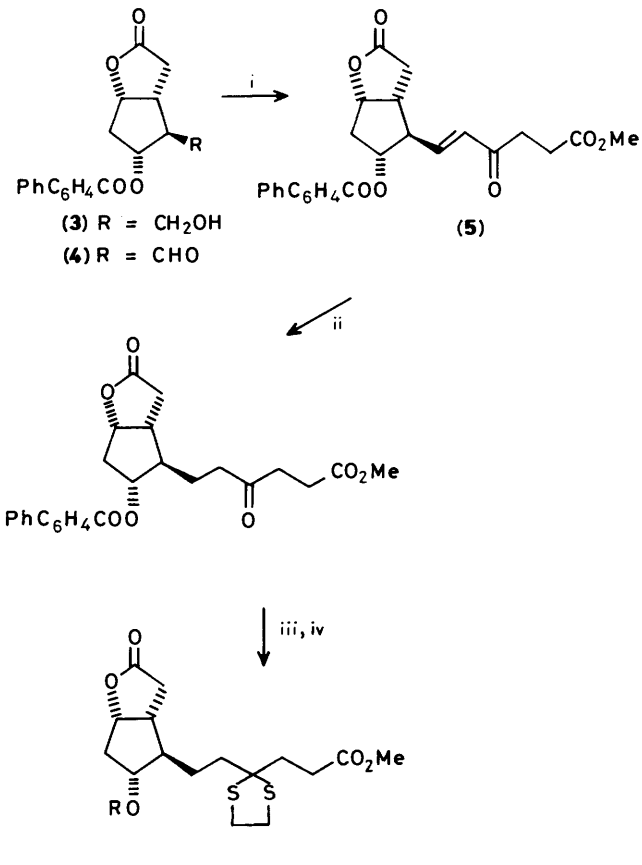
Starting from the Corey lactone (**3**), the total synthesis of a specific urinary metabolite of prostaglandin D_2, *viz.*, (*Z*)-9α,11β-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid (**1**) and its 5*E*-isomer is described. The synthetic material was isolated in a tricyclic form as the corresponding hemiacetal lactone (**2**). The g.c.m.s. characteristics of the methyl ester, trimethylsilyl ether derivative of this compound were identical with those previously described for the same derivative of the 11β-tetranor metabolite of PGD_2.

Prostaglandin D_2 (PGD_2), the principal cyclo-oxygenase product of rat and human mast cells,[1] has recently become the focus of considerable interest due to its potent ability to inhibit platelet aggregation, its antitumour activity, and other unique physiological properties.[2] In addition, it has been shown that patients with systematic mastocytosis, a disorder characterized by increased proliferation of tissue mast cells, produce abnormally large amounts of PGD_2. It has been proposed that the released PGD_2 is an important mediator of vasodilatory episodes associated with disease.[3] When PGD_2 is infused intravenously into primates it is extensively metabolised to a series of tetranor (C-16) derivatives predominantly having PGF ring structures.[4–6] It was suggested that reduction of the 11-oxo function of PGD_2 occurred by a specific 11-keto reductase to provide an 11β-hydroxy group. This was followed by subsequent oxidative metabolism and excretion of the corresponding tetranor metabolites. One of the most abundant urinary metabolites of PGD_2 in human subjects, was identified as[6] 9,11-dihydroxy-15-oxo-2,3,18,19-tetranorprost-5-ene-1,20-dioic acid (**1**). It was isolated in tricyclic form (**2**) (Scheme 1) and its structure elucidated on the basis of the mass spectrum of its methyl ester, trimethylsilyl (TMS) ether derivative. It was of interest to synthesize the 11β-tetranor metabolite for two reasons: first, to provide unequivocal proof of structure; second, to provide sufficient material for the development of a stable isotope dilution assay for this major urinary metabolite of PGD_2. The assay would be specific for PGD_2 by virtue of the fact that PGD_2 is the only known precursor of the 11β-metabolite. The availability of the assay will allow the role of PGD_2 in a number of human disease states to be assessed. Direct analysis of PGD_2 *in vivo* in most clinical situations is precluded because of its metabolic instability and resulting low plasma concentrations.



Scheme 1.

The initial target for the synthesis was the 11α-hydroxy lactone (**8**) (Scheme 2), which was obtained from the readily



Scheme 2. *Reagents:* i, $Ph_3P{=}CH_2CO(CH_2)_2CO_2Me$, THF; ii, H_2, Pd–C; iii, $HSCH_2CH_2SH$, zinc triflate, CH_2Cl_2; iv, Bu^{t}OK, MeOH–$MeCO_2Me$

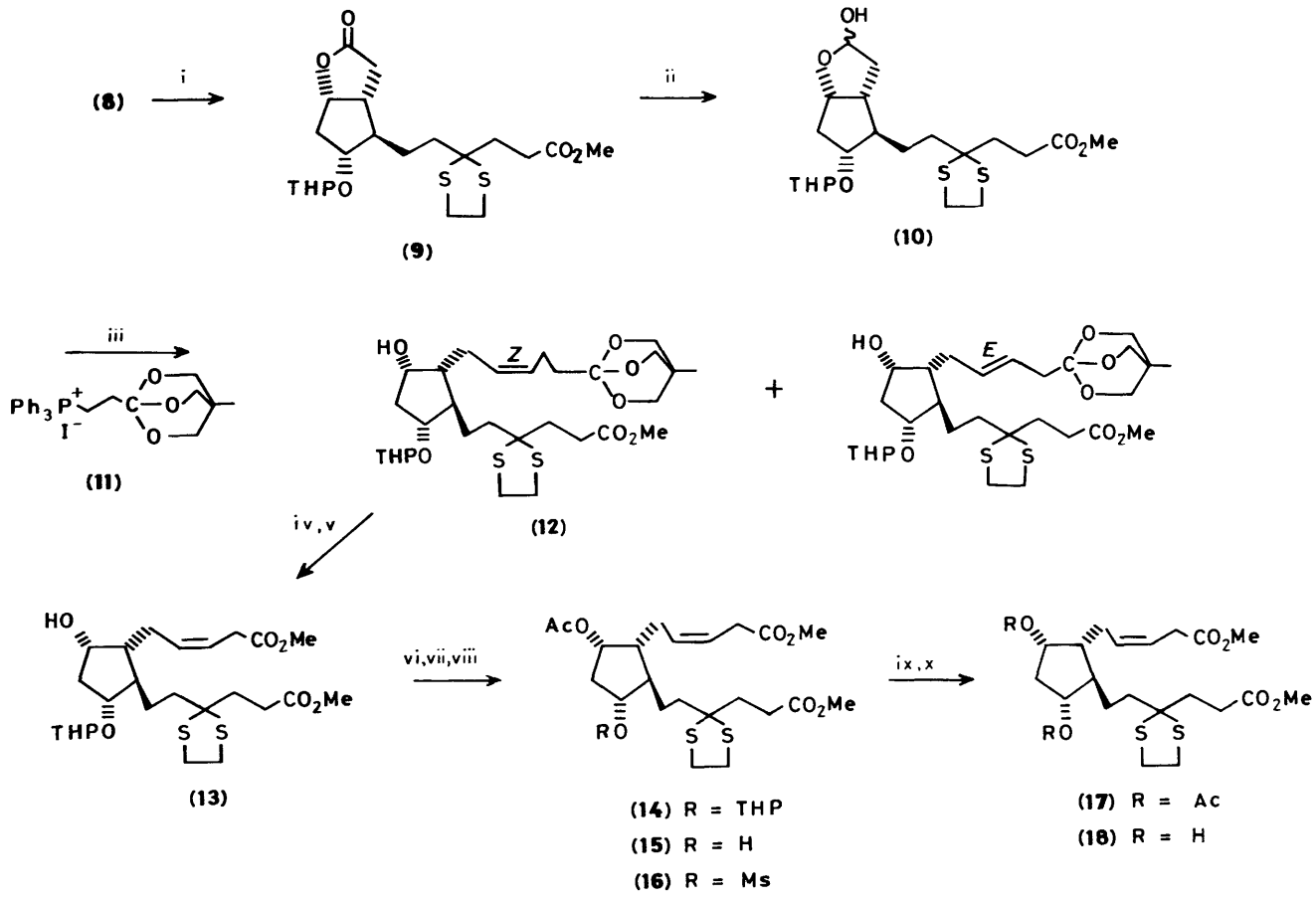
available Corey lactone (**3**) in 75% overall yield as shown. Moffatt oxidation[7] of the Corey lactone (**3**) to an aldehyde (**4**), followed by condensation with methyl 5-(triphenylphosphoranylidene)levulinate[8] led to the enone (**5**). Hydrogenation with 10% palladium on charcoal, protection[9] of the resulting ketone (**6**) with ethane-1,2-dithiol, and saponification of the *p*-phenylbenzote (**7**) with Bu^{t}OK gave the required intermediate (**8**).

Reduction of the lactone (**8**) as the tetrahydropyranyl (THP) ether (**9**) (Scheme 3) proceeded smoothly with di-isobutylaluminium hydride (DIBAL) in tetrahydrofuran (THF) at −78 °C to give the lactol (**10**). The use of more elevated temperatures or different aprotic solvents resulted in reduction of the terminal carboxy group to the corresponding alcohol. Three carbon homologation of the lactol (**10**) using traditional Wittig procedures proved to be very troublesome. The generation of phosphorane ylides in which the anion was β to an ester carboxy group led to the formation of intractable products.

It became apparent that successful homologation could only be carried out if the carboxy moiety was masked during the Wittig step as described by Corey and Shimoji.[10] The ylide derived from triphenyl(2-trioxabicyclo[2.2.2]octanylethyl)-phosphonium iodide (**11**) prepared using dimsyl sodium[10] failed to react with the lactol (**10**). Therefore, the homologation reaction was investigated in more detail using a number of model systems.[11] The use of lithium bis(trimethylsilyl)amide (LiHMDS) as the base resulted in predominant formation of *E*-isomers. The addition of hexamethylphosphoric triamide (HMPT) to the THF solvent and reduction of the temperature to −40 °C dramatically increased the amount of *Z*-isomer that was formed so that the *Z*/*E* ratio became 4:1.

In the light of the foregoing observations, the ylide was generated by reaction of the phosphorane (**11**) with LiHMDS in THF–HMPT (4:1) at 0 °C. Reaction with (**10**) was allowed to proceed for 30 min at −40 °C followed by a further 3 h at 0 °C. The procedure led to an optimal yield of homologated product (50%), in which the *Z*-β,γ-unsaturated ortho ester (**12**) predominated over the *E*-isomer in a ratio of 4:1. The geometric isomers were separated on a silica column using hexane–acetone (9:1) containing 1% triethylamine as eluant. As was observed with model compounds[11] the *Z*-homologated product eluted ahead of the *E*-isomer. The ^{1}H n.m.r. spectrum of the pure *Z*-ortho ester differed in several distinct ways from that of the *E*-isomer. The chemical shift of the 9β-H was observed 0.1 p.p.m. to higher field and the signal from the olefinic protons was broader and more complex. In addition, the chemical shift of the methylene hydrogens α to the ortho ester was 0.25 p.p.m. downfield in the *Z*-ortho ester compared with the corresponding *E*-isomer. These characteristics were also evident in the homologated products of model lactols.[11]

The pure *Z*-ortho ester (**12**) was cleaved by exposure to sodium hydrogensulphate in dimethoxyethane (DME)–water (1:1, pH 3.0) at 0 °C for 20 min. The resulting ester was saponified with 0.2M lithium hydroxide at 23 °C for 1 h to afford, after acidification and extractive isolation, the crude diacid. Esterification with 2.2 equiv. of tetramethylammonium hydroxide and methyl iodide in dimethylformamide (DMF) at 0 °C for 20 min yielded the dimethyl ester (**13**).



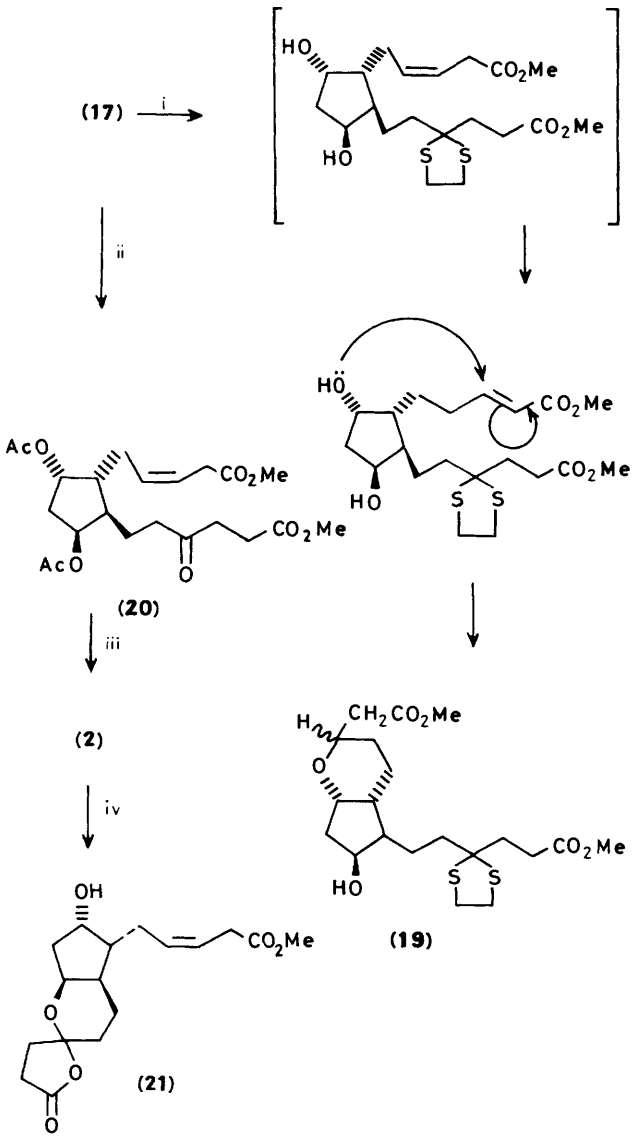
Scheme 3. *Reagents and conditions:* i, DHP, *p*-TsOH, CH_2Cl_2; ii, DIBAL, THF, −78 °C; iii, LiHMDS, THF–HMPA; iv, DME–H_2O (1:1), $NaHSO_4$, LiOH; v, Me_4NOH, MeI, CH_2Cl_2; vi, MeCOCl–pyridine, CH_2Cl_2; vii, AG50-X8 resin, MeOH; viii, MsCl, TEA, CH_2Cl_2; ix, CsOAc, 18-crown-6, toluene; x, LiOH, CH_2N_2

The next phase of synthesis was to invert the configuration at the 11-hydroxy group. The 9α-hydroxy group was protected as the acetate (**14**) and the THP protecting group removed with acidic resin AG50-X8 in methanol to give the alcohol (**15**). The configuration at 11-hydroxy group was inverted by reaction of crude mesylate (**16**) with caesium acetate and 18-crown-6 ether in toluene[12] at reflux for 10 h (Scheme 3). The 11β-acetate (**17**) was obtained in 70% yield with no evidence of any elimination products. Other reagents for inverting the 11-hydroxy function such as diethyl azodicarboxylate caused elimination reactions to predominate.

Removal of the acetyl group with potassium carbonate in methanol did not give the required dihydroxy derivative (**18**). The major product isolated showed no olefinic protons in the ^{1}H n.m.r. spectrum. It appeared that under basic conditions, the double bond moved into conjugation with the ester carbonyl group. This was followed by 1,4-addition to the enone by the 9α-hydroxy group to give the cyclic ether (**19**) (Scheme 4). However, saponification with aqueous base (LiOH, 0.2M) prevented this undesirable reaction. Subsequent acidification, extractive isolation, and esterification with diazomethane yielded the dimethyl dihydroxy diester (**18**) in 80% yield.

Oxidative deacetalization in the presence of the β,γ-unsaturated methyl ester under a variety of conditions failed to give the required product. A systematic examination of published procedures revealed that ceric ammonium nitrate[13] (CAN) in MeCN–H_2O (4:1) smoothly converted the thioacetal (**17**) into the corresponding ketone (**20**) (Scheme 4). Saponification of the dimethyl diester (**20**) with LiOH (0.2M) for 1 h followed by acidification afforded the PGD_2 metabolite (**2**). The 11-hydroxy group and ω-side chain attached at C-12 are oriented in the same β-configuration. Presumably, this facilitates the formation of a carbocyclic hemiacetal between C-11 and C-15. Subsequent lactonization of the terminal carboxy group results in the formation of the hemiacetal lactone derivative (**2**).

The electron impact (e.i.) mass spectrum of the methyl ester TMS ether of synthetic (**2**) was identical with that reported[6] for the tetranor urinary metabolite of PGD_2. The structure of (**2**) was confirmed by the ^{1}H n.m.r. spectrum of its methyl ester (**21**). It was possible to separate the two diastereoisomers of (**2**) by high resolution gas chromatography of the corresponding pentafluorobenzyl (PFB) ester, TMS ether derivative using negative ion chemical ionization mass spectrometry (n.i.c.i.m.s.). From the chromatogram it was observed that the first eluting diastereoisomer was present in slight excess over the second eluting diastereoisomer. The synthetic PGD_2 metabolite (**2**) has been used for the preparation of ^{18}O labelled standard by treatment with 5 cycles of Li^{18}OH. This compound will now be used for developing a g.c.m.s. assay for the urinary metabolite. The endogenous production of PGD_2 in humans and the pathophysiological role of PGD_2 in various human diseases will be assessed. Details of this work will be reported separately.



Scheme 4. *Reagents:* i, K_2CO_3–methanol; ii, CAN, MeCN–H_2O (4:1); iii, LiOH, DME–H_2O; iv, CH_2N_2–ether

Experimental

M.p.s were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. The ^{1}H n.m.r. spectra were recorded in $CDCl_3$ on a Bruker AM 400 or an IBM NR 300 instrument. Chemical shifts (δ_H p.p.m.) are reported relative to Me_4Si as an internal standard. Routine mass spectra and accurate mass measurements were obtained on a VG 70/250 double focusing magnetic sector instrument operating in the e.i. mode. Gas chromatography/mass spectrometry (g.c.m.s.) was carried out on a Nermag R1010C quadrupole instrument interfaced to a Varian Vista gas chromatograph. Injections were made in the splitless mode on a SPB 5 fused silica capillary column (0.32 mm internal diameter, 0.25 μm coating thickness, Supelco, Bellefonte, PA). Under standard g.c. conditions, the column was temperature programmed from 100 °C to 320 °C at 15 °C min^{-1} with helium as carrier gas at a flow rate of 1 ml min^{-1}. Methane was used as the reagent gas for n.i.c.i.m.s. at an analyser pressure of 6.4×10^{-6} Torr.

Flash chromatography was carried out on S/P silica gel 60 Å. T.l.c. was performed on Analtech silica gel GF uniplates. Organic extracts were dried with $MgSO_4$. The standard work-up procedure involved dilution of the reaction mixture with saturated aqueous sodium chloride and extraction with ethyl acetate. The organic extract was washed with water and dried. After concentration under reduced pressure, the residue was purified on a silica gel column. THF was distilled from sodium benzophenone ketyl immediately prior to use. HMPT and dimethyl sulphoxide (DMSO) were vacuum distilled from calcium hydride and stored over 3 Å molecular sieves. Dry dichloromethane was obtained by distillation from P_2O_5. All other solvents were reagent grade and were used directly. Reactions were carried out under a dry nitrogen atmosphere.

Methyl 3-[2-(2-{c-7-(*Biphenyl-4-ylcarbonyloxy*)-3-*oxo*-cis-*bicyclo*[3.3.0]*octan*-t-6-*yl*}*ethyl*)-1,3-*dithiolan*-2-*yl*]*propionate** (**7**).—Dicyclohexylcarbodi-imide (1.8 g, 8.7 mmol) was added to a stirred solution of the Corey lactone (**3**) (1 g, 2.84 mmol) in benzene–DMSO (16.5 ml, 15:1.5). After 5 min dichloroacetic acid (180 μl, 2.2 mmol) was added and the whole reaction mixture was stirred for 20 min, giving a thick white solution. Oxalic acid (762 mg, 2.84 mmol) in methanol (1.8 ml) was added dropwise and stirring was continued for 10 min. The reaction mixture was diluted with brine and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water, dried, and concentrated to give the aldehyde (**4**).

The crude aldehyde (**4**) in THF (20 ml) was stirred with methyl 5-(triphenylphoranylidine)levulinate[10] (1.8 g, 3.7 mmol) at room temperature for 3 h. Standard work-up and elution with 30% ethyl acetate in hexane gave the enone (**5**) (1.1 g, 80%), m.p. 108—110 °C (ether); δ_H 8.03 (2 H, d, *J* 8.3 Hz, ArH), 7.42—7.62 (7 H, m, ArH), 6.73 (1 H, dd, *J* 7.5 Hz and 15.8 Hz, olefin), 6.25 (1 H, d, *J* 15.8 Hz, olefin), 5.34 (1 H, m, 5-H), 5.12 (1 H, m, 3-H), 3.66 (3 H, s, CO_2Me), and 2.32—2.92 (10 H, m); *m/z* 462 (M^+), 233 ($M^+ - PhC_6H_4CO_2 - MeOH$), 205 ($M^+ - PhC_6H_4CO_2 - MeCO_2H$), 198, 191, 177, and 188 (Found: M^+, 462.1744. $C_{27}H_{26}O_7$ requires *M*, 462.1714).

Palladium–carbon (220 mg, 10%) in ethyl acetate (10 ml) was charged with H_2 gas for 15 min. The enone (**5**) (1.1 g, 2.38 mmol) in ethyl acetate (10 ml) was added and the hydrogenation was continued at room temperature until the uptake of hydrogen ceased (4 h, 54 ml). The catalyst was removed by filtration, washed with ethyl acetate (10 ml), and the combined organic extracts were concentrated to give the ketone (**6**). This was crystallized from ether as prismatic needles (990 mg, 90%), m.p. 115—116 °C; δ_H 8.02 (2 H, d, *J* 8.3 Hz, ArH), 7.42—7.62 (7 H, m, ArH), 5.32 (1 H, m), 5.12 (1 H, m), 3.67 (3 H, s, CO_2Me), and 1.64—2.90 (14 H, m) (Found: M^+, 464.1827. $C_{27}H_{28}O_7$ requires *M*, 464.1834).

The ketone (**6**) (900 mg, 1.94 mmol) in CH_2Cl_2 (50 ml) was stirred with ethane-1,2-dithiol (695 μl, 8.3 mmol) and zinc triflate (1.65 g, 4.6 mmol) at room temperature for 2 h. The reaction was diluted with brine, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 ml). The combined organic extracts were washed with water, dried, and concentrated to give a crude product. Purification on a silica gel column using ethyl acetate–hexane (1:4, v/v) afforded the pure thioacetal (**7**) (860 mg, 82%), m.p. 93—95 °C; δ_H 8.02 (2 H, d, *J* 8.2 Hz, ArH), 7.42—7.62 (7 H, m, ArH), 5.34 (1 H, m), 5.10 (1 H, m), 3.66 (3 H, s, CO_2Me), 3.25 (4 H, s, SCH_2CH_2S), and 1.62—2.88 (14 H, m); *m/z* 540 (M^+), 453 ($M^+ - CH_2CH_2CO_2Me$), 342 ($M^+ - PhC_6H_4CO_2H$), and 191 (base peak) (Found: M^+, 540.1645. $C_{29}H_{32}O_6S_2$ requires *M*, 540.1650).

Methyl 3-{2-[2-(3-*Oxo*-c-7-*tetrahydropyranyloxy*-cis-*bicyclo*[3.3.0]*octan*-t-6-*yl*)*ethyl*]-1,3-*dithiolan*-2-*yl*}*propionate** (**9**).—Bu^{t}OK (535 mg, 4.77 mmol) was added to a stirred solution of compound (**7**) (860 mg, 1.59 mmol) in methanol–methyl acetate (40 ml, 1:1) and the reaction mixture was stirred at room temperature for 2 h. Standard work-up and elution with ethyl acetate in hexane gave the pure hydroxy lactone (**8**) (510 mg, 88%); δ_H 4.98 (1 H, m, 3-H), 4.02 (1 H, m, 5-H), 3.66 (3 H, s, CO_2Me), 3.25 (4 H, s, SCH_2CH_2S), 1.48—2.88 (14 H, m) (Found: M^+, 360.1049. $C_{16}H_{24}O_5S_2$ requires *M*, 360.1054).

The alcohol (**8**) (510 mg, 1.40 mmol) in CH_2Cl_2 (10 ml) was stirred with dihydropyran (380 μl, 4.2 mmol) and a catalytic amount of toluene-*p*-sulphonic acid (20 mg, 0.12 mmol) at room temperature for 1 h. Standard work-up and elution with ethyl acetate–hexane (1:4, v/v) provided the pure THP ether (**9**) (510 mg, 70%); δ_H 5.02 (1 H, m), 4.62 (1 H, m, OCH of THP), 4.14 (1 H, m), 3.88 (1 H, m), 3.68 (3 H, s, CO_2Me), 3.49 (1 H, m, OCH_2 of THP), 3.24 (4 H, s, SCH_2CH_2S), and 1.42—2.72 (20 H, m); *m/z* 444 (M^+), 360 ($M^+ + H - THP$), 357 ($M^+ - CH_2CH_2CO_2Me$), 343 ($M^+ - OTHP$), and 311 ($M^+ - THPOH - OMe$) (Found: M^+, 444.1642. $C_{21}H_{32}O_6S_2$ requires *M*, 444.1639).

Methyl 3-(2-{2-[c-3-*Hydroxy*-c-2-(4-*methoxycarbonylbut*-2-*enyl*)-c-5-*tetrahydropyranyloxycyclopentan*-t-1-*yl*]*ethyl*}-*dithiolan*-2-*yl*)*propionate** (**13**).—DIBAL (600 μl, 0.6 mmol; 1M in THF) was added dropwise to a stirred solution of THP ether (**9**) (222 mg, 0.5 mmol) in THF (2 ml) at −78 °C and the mixture was stirred at that temperature for 30 min. The reaction was quenched by the addition of methanol (0.1 ml) and ethyl acetate (40 ml). After stirring at room temperature for 10 min the organic layer was separated. The aqueous layer was further extracted with more ethyl acetate (15 ml) and the combined organic extracts were washed with brine and dried. Concentration of the solvent under reduced pressure afforded the lactol (**10**) (202 mg, 92%) which was used directly for the next step; δ_H 5.64 (1 H, m), 4.92 (1 H, m), 4.62 (1 H, m, OCH of THP), 4.12 (1 H, m), 3.90 (1 H m), 3.67 (3 H, s, CO_2Me), 3.48 (1 H, m, OCH_2 of THP), 3.24 (4 H, s, SCH_2CH_2S), and 1.52—2.64 (20 H, m) (Found: $[M^+ - H_2O]^+$, 428.1693. $C_{21}H_{32}O_5S_2$ requires 428.1691).

Lithium bis(trimethylsilyl)amide (900 μl, 0.9 mmol, 1.0M in THF) was added to a stirred suspension of ortho ester phosphonium iodide[10] (**11**) (520 mg, 0.9 mmol) in THF–HMPA (2.5 ml, 4:1) at 0 °C. The reaction mixture was stirred for 30 min at the same temperature to generate the ylide. The reaction flask was cooled to −40 °C and the lactol (**10**) (150 mg, 0.3 mmol) in THF (2 ml) was added with stirring. Over the next 30 min the temperature was raised slowly to 0 °C. Stirring was continued for a further 2 h at 0 °C, the reaction was quenched by the addition of saturated aqueous NH_4Cl, and extraction was carried out with ethyl acetate. Concentration of the dried solvent afforded the crude 5*Z*-ortho ester (**12**) and its *E*-isomer which were separated on a silica gel column using ethyl acetate in hexane (1:9, v/v) containing 1% triethylamine. The compound that eluted first from the column was the desired 5*Z*-ortho ester (**12**) (75 mg); δ_H 5.51 (2 H, m, olefin), 4.63 (1 H, m, OCH of THP), 4.06 (1 H, m, 9-H), 3.96 (1 H, m, 11-H), 3.88 (7 H, s, OCH_2 of ortho ester and OCH_2 of THP), 3.68 (3 H, s, CO_2Me), 3.46 (1 H, m, OCH_2 of THP), 3.23 (4 H, s, SCH_2CH_2S), 2.92 (2 H, m, CH_2 α to ortho ester), 1.42—2.52 (20 H, m), and 0.78 (3 H, s, Me of ortho ester); *m/z* 586 (M^+), 502 ($M^+ + H - THP$), 501 ($M^+ - THP$), 485 ($M^+ - OTHP$), and 484 ($M^+ - THPOH$) (Found: M^+, 586.2618. $C_{29}H_{46}O_8S_2$ requires *M*, 586.2634).

The later eluting compound was the 5*E*-isomer of ortho ester (**12**) (19 mg); δ_H 5.52 (2 H, sharp m, olefin), 4.65 (1 H, m, OCH of THP), 4.12 (1 H, m, 9-H), 3.96 (1 H, m, 11-H), 3.90 (7 H, s, OCH_2 of ortho ester and OCH_2 of THP), 3.68 (3 H, s, CO_2Me), 3.45 (1 H, m, OCH_2 of THP), 3.25 (4 H, s), 2.67 (2 H, m, CH_2 α to ortho ester), 1.44—2.52 (20 H, m), and 0.78 (3 H, s, Me of ortho ester) (Found: M^+, 586.2635. $C_{29}H_{46}O_8S_2$ requires *M*, 586.2634).

The 5*Z*-ortho ester (**12**) (58 mg, 0.1 mmol) was dissolved in equal volumes of water (pH 3, adjusted with $NaHSO_4$) and DME (3 ml) and stirred at 0 °C for 20 min. Aqueous LiOH (300 μl, 2M) was added and the solution stirred at room temperature for a further 1 h. The aqueous layer was acidified with 1M HCl to pH 4.0 and extracted three times with ethyl acetate (10 ml). The combined organic extracts were washed with brine, dried, and concentrated to afford the crude dicarboxylic acid which was

* Compounds named and numbered systematically. Prostaglandin numbering is retained in the text.

immediately stirred in DMF (2 ml) with tetramethylammonium hydroxide (100 μl, 0.2 mmol) and methyl iodide (60 μl, 1.2 mmol) at 0 °C for 20 min. Standard work-up and elution with acetone in ethyl acetate (1:9, v/v) gave the dimethyl 9α-hydroxy-11β–THP diester (**13**) (36 mg, 72%); δ_H 5.58 (2 H, br m, olefin), 4.58 (1 H, m, OCH or THP), 4.05 (1 H, m, 9-H), 3.92 (1 H, m, 11-H), 3.86 (1 H, m, THP), 3.68 (6 H, s, 2 × CO_2Me), 3.48 (1 H, m, OCH_2 of THP), 3.24 (4 H, s, SCH_2CH_2S), 3.15 (2 H, m, CH_2CO_2Me), and 1.42—2.62 (20 H, m); *m/z* 516 (M^+), 485 (M^+ − OMe), 432 (M^+ + H − THP), 431 (M^+ − THP), 415 (M^+ − OTHP), 414 (M^+ − THPOH), and 396 (M^+ − THPOH − H_2O) (Found: M^+, 516.2208. $C_{25}H_{40}O_7S_2$ requires *M*, 516.2202).

Methyl 3-(2-{2-[c-3,t-5-*Diacetoxy*-c-2-(4-*methoxycarbonyt-but-2-enyl*)*cyclopentan*-1-*yl*]*ethyl*}*dithiolan*-2-*yl*)*propionate* * (**17**).—Pyridine (25 μl, 0.3 mmol) and acetyl chloride (15 μl, 0.15 mmol) were added to a solution of the alcohol (**13**) (26 mg, 0.05 mmol) in CH_2Cl_2 (1 ml) at 0 °C and the reaction mixture was stirred for 30 min. Standard work-up and elution with acetone in hexane (1:9, v/v) afforded the dimethyl 9α-acetoxy-11α-THP diester (**14**) as an oil (22 mg, 80%); δ_H 5.56 (2 H, m, olefin), 5.01 (1 H, m, 9-H), 4.58 (1 H, m, OCH of THP), 3.86 (2 H, m, 11-H and THP), 3.68 (6 H, s, 2 × CO_2Me), 3.46 (1 H, s, THP), 3.24 (4 H, s, SCH_2CH_2S), 3.06 (2 H, m, CH_2CO_2Me), 2.04 (3 H, s, OCOMe), and 1.42—2.60 (20 H, m); *m/z* 527 (M^+ − OMe), 474 (M^+ + H − THP), 413 (M^+ − THP − $MeCO_2H$), 397 (M^+ − OTHP − $MeCO_2H$), and 396 (M^+ − THPOH − $MeCO_2H$) (Found: $[M - OMe]^+$, 527.2127. $C_{26}H_{39}O_7S_2$ requires 527.2137).

The THP ether (**14**) (20 mg) in methanol (2 ml) was stirred with cation exchange resin AG50-X8 (100 mg; H^+ form, Bio-Rad Laboratories, Richmond, CA) at 23 °C for 6 h. The resin was removed by filtration and washed with methanol (5 ml). Concentration of the methanol solution and purification on a silica gel column using acetone in hexane (1:4, v/v) afforded the pure dimethyl 9α-acetoxy-11α-hydroxy diester (**15**) (15 mg, 88%); δ_H 5.54 (2 H, m, olefin), 5.08 (1 H, m, 9-H), 3.92 (1 H, m, 11-H), 3.68 (6 H, s, 2 × CO_2Me), 3.24 (4 H, s, SCH_2CH_2S), 3.08 (2 H, s, CH_2CO_2Me), 2.04 (3 H, s, OCOMe), and 1.48—2.60 (14 H, m); *m/z* 474 (M^+), 456 (M^+ − H_2O), 443 (M^+ − OCH_3), 396 (M^+ − $MeCO_2H$ − H_2O), 381, 327, 303, and 191 (Found: M^+, 474.1758. $C_{22}H_{34}O_7S_2$ requires *M*, 474.1770).

Triethylamine (18 μl, 0.15 mmol) and methanesulphonyl chloride (12 μl, 0.15 mmol) were added to a stirred solution of the alcohol (**15**) (12 mg, 0.025 mmol) in CH_2Cl_2 (1 ml) at −20 °C and the reaction mixture was stirred for 30 min at that temperature. The reaction mixture was diluted with saturated brine (5 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The organic extract was washed with water, dried, and evaporated to give the crude mesylate (**16**) which was used without further purification.

The crude mesylate (**16**) in toluene (2 ml) was heated under reflux with 18-crown-6 ether (6 mg, 0.02 mmol) and caesium acetate (15 mg, 0.08 mmol) at 115 °C for 8 h. Toluene was removed under reduced pressure and the residue dissolved in ethyl acetate. The ethyl acetate was washed sequentially with water and brine then dried and concentrated. Purification on a silica gel column by elution with acetone in hexane (1:9, v/v) yielded dimethyl 9α,11β-diacetoxy diester (**17**) (8 mg, 65%); δ_H 5.56 (2 H, m, olefin), 5.28 (1 H, m, 11-H), 5.18 (1 H, m, 9-H), 3.64 (6 H, s, 2 × CO_2Me), 3.22 (4 H, s, SCH_2CH_2S), 3.08 (2 H, s, CH_2CO_2Me), 2.08 (3 H, s, OCOMe), 1.98 (3 H, s, OCOMe), and 1.48—2.58 (14 H, m); *m/z* 516 (M^+), 485 (M^+ − OMe), 484 (M^+ − MeOH), 457 (M^+ − OCOMe), 456 (M^+ − $MeCO_2H$), 429 (M^+ − $CH_2CH_2CO_2Me$), and 396 (M^+ − 2 × $MeCO_2H$) (Found: M^+, 516.1853. $C_{24}H_{36}O_8S_2$ requires *M*, 516.1852).

Base-catalysed Cyclization of Compound (**17**).—Anhydrous powdered K_2CO_3 (2.7 mg, 0.02 mmol) was added to a stirred solution of the dimethyl diester (**17**) (10.3 mg, 0.02 mmol) in anhydrous methanol (1 ml) and the mixture was stirred at room temperature for 2 h. The reaction mixture was neutralized with 1M HCl and stirred for a further 10 min in an ice bath. After dilution with ethyl acetate (5 ml) the resulting solution was washed with aqueous $NaHCO_3$ followed by brine. The organic layer was dried and evaporated and the residue chromatographed on a silica gel column using acetone–hexane (1:4, v/v) to give the 9-deoxy-5,9α-epoxy derivative (**19**) (6.5 mg, 75%) as a mixture of enantiomers; δ_H 4.28 (1 H, m), 4.18 (2 H, m), 3.68 (3 H, s, CO_2Me), 3.66 (3 H, s, CO_2Me), 3.22 (4 H, s, SCH_2CH_2S), and 1.60—2.81 (18 H, m); *m/z* 432 (M^+), 401 (M^+ − OMe), 345 (M^+ − $CH_2CH_2CO_2Me$), and 327 (M − $CH_2CH_2CO_2Me$ − H_2O) (Found: M^+, 432.1628. $C_{20}H_{32}O_6S_2$ requires *M*, 432.1640).

(*Z*)-9α-11β-*Dihydroxy*-15-*oxo*-2,3,18,19-*tetranorprost*-5-*ene*-1,20-*dioic Acid* (**1**).—Ceric ammonium nitrate (45 mg, 0.08 mmol) was added to a stirred solution of the thioacetal (**17**) (10.2 mg, 0.02 mmol) in MeCN–H_2O (1.2 ml, 4:1) and the mixture was stirred at room temperature for 1 h. Standard work-up and elution with acetone–hexane (1:4, v/v) gave the pure 9α,11β-diacetoxy ketone (**20**) (6 mg, 70%); δ_H 5.56 (2 H, m), 5.24 (1 H, m, 11-H), 5.18 (1 H, m, 9-H), 3.64 (6 H, s, 2 × CO_2Me), 3.08 (2 H, m, CH_2CO_2Me), 2.04 (3 H, s, OCOMe), 1.98 (3 H, s, OCOMe), 1.80—2.64 (14 H, m); *m/z* 380 (M^+ − $MeCO_2H$), 320 (M^+ − 2 × $MeCO_2H$), 311 (M^+ − $CH_2COCH_2CH_2$ − CO_2Me), 289 (M^+ − 2 × $MeCO_2H$ − OMe), and 288 (M^+ − 2 × $MeCO_2H$ − MeOH) (Found: $[M - MeCO_2H]^+$, 380.1835. $C_{20}H_{28}O_7$ requires 380.1835).

The 9α,11β-diacetoxy ketone (**20**) (10 mg, 0.02 mmol) was dissolved in a mixture of DME–H_2O (2 ml, 1:1) and aqueous LiOH (0.2 ml, 2M). The mixture was stirred at room temperature for 1 h. Acidification with 1M HCl (final pH 3.0) was followed by extraction into ethyl acetate (3 × 5 ml). The organic layer was dried and concentrated to give the γ-lactone (**2**). This was then methylated by adding ethereal diazomethane. Purification on a small column using acetone–hexane (1:9, v/v) gave the methyl ester (**21**) (5 mg); δ_H 5.56 (2 H, m, olefin), 4.32 (2 H, m, 9- and 11-H), 3.66 (3 H, s, CO_2Me), and 1.52—3.22 (16 H, m); *m/z* 324 (M^+), 396 (M^+ − H_2O), 293 (M^+ − OMe), 292 (M^+ − MeOH), and 280 (M^+ − CO_2) (Found: M^+, 324.1574. $C_{17}H_{24}O_6$ requires *M*, 324.1572). The methyl ester (**21**) could be readily converted back into the free acid (**2**) using LiOH as described above.

The methyl ester (**21**) was converted into the TMS ether (bistrimethylsilyltrifluoroacetamide) and analysed by g.c.m.s. Chromatography was carried out on a 10 m SPB 5 fused silica column using the standard conditions. The derivative eluted as a single peak with a retention time of 8.20 min. The e.i. mass spectrum of the derivative was identical with that reported previously: *m/z* 396 (M^+), 381 (M^+ − Me), 337 (M^+ − CO_2Me), 306 (M^+ − Me_3SiOH), 295 and 274 (M^+ − Me_3SiOH − MeOH). γ-Lactone acid (**2**) was converted into the PFB ester, TMS ether derivative using published procedures[14] and analysed by capillary column g.c.n.i.c.i.m.s. Under these conditions one major ion corresponding to the expected[15] $[M - PFB]$ anion was observed. High resolution capillary column chromatography on a 30 m SPB5 column using the standard conditions resolved the two diastereoisomers of (**2**). The first eluting component had a retention time of 14.30 min

* As on page 2824.

and the second 14.45 min. From the reconstructed gas chromatogram it was estimated that diastereoisomers were present in a ratio of 55:45 respectively.

Supplementary Material.—The *E*-isomers of all the reported compounds were prepared under identical reaction conditions to the corresponding *Z*-isomers. Details of their ^{1}H n.m.r. and mass and spectra are available as a supplementary publication. [SUP. NO. 56720 (2 pages)].*

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* For details of the supplementary publications scheme see Instructions for Authors (1988), *J. Chem. Soc., Perkin Trans. 1*, 1988, Issue 1.

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