Total Synthesis of PGD_1 Methyl Ester and 9-epi-PGD_1 Methyl Ester

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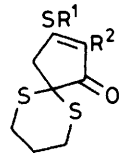
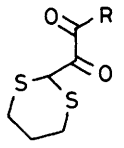
The synthesis of the title compounds (**57**) and (**53**) is described *via* the dithiane substituted enone (**17**) itself obtained in five steps from methyl dimethoxyacetate and 7-iodoheptanoic acid. Cuprate addition of the ω-side-chain to (**17**) proceeds with asymmetric induction, the desired diastereoisomers (**26**) and (**30**) predominating. Reduction of the C-9 carbonyl group stereospecifically gives the 9β-alcohol which is converted into the 9α-alcohol, and thence to the title compounds by removal of protecting groups at C-11 and C-15.

Despite the vast amount of effort which has been devoted to the synthesis of prostaglandins over recent years [1,2] there have been few approaches to the PGDs.[3,4] This is somewhat surprising in view of the effect of PGD_2 on platelet aggregation.[5] We have published in a preliminary paper our approach to PGD_1 methyl ester (**57**)[6] and now present the full account of this work. Our approach relies on the method we have developed for the synthesis of the highly substituted cyclopentane system as in (**1**).[7] Initial studies were carried out with the model systems (**2**) and (**3**) before attention was turned to the modifications required to obtain PGD_1 from (**4**).



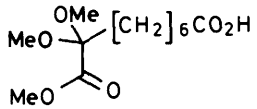
(**1**) R^1 = Me or Ph
(**2**) R^1 = Ph, R^2 = Me
(**3**) $R^1 = R^2$ = Me
(**4**) R^1 = Ph, R^2 = $[CH_2]_6CO_2H$
(**5**) R^1 = Me, R^2 = $[CH_2]_6CO_2H$



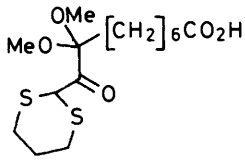
(**6**) R = Me
(**7**) R = $[CH_2]_6CO_2H$

Model Studies.—The synthesis of (**2**) and (**3**) from the diketodithiane (**6**) and vinylphosphonium salts (**11**) and (**12**) respectively has been described.[7] Reduction of the carbonyl group in (**2**) was easily effected with sodium borohydride to give the alcohol (**13**) which was immediately treated with aqueous acid in an attempt to obtain the enone (**16**). However, under a wide range of conditions, varying both the concentration and nature of the acid used, only a low yield of the enone was obtained. Another product isolated from the reaction was (**18**), presumably formed by trapping of the intermediate carbocation with liberated thiophenol. Unfortunately, attempts to remedy this situation by adding thiophenol trapping agents such as methyl vinyl ketone and benzhydrol (diphenylmethanol) were not successful. We considered that a solution to the problem might lie in using the methylthio alcohol (**14**) rather than the phenylthio derivative (**13**). The carbocation from (**14**) should be more stable than that from (**13**) due to the differing availability of the lone pair on sulphur, and might therefore give a higher yield of the desired enone. Thus we were forced to return to the starting point of the synthesis and use (**3**). Reduction of the carbonyl group in (**3**) required more vigorous conditions than had been the case for (**2**). Sodium borohydride had no effect, but the reduction was easily achieved with lithium aluminium hydride. Presumably the different ease of reduction of these compounds is a further reflection of the relative availability of the sulphur lone pair in a methylthio and a phenylthio compound. The intermediate alcohol (**14**) was not isolated but the THF (tetrahydrofuran) solution was immediately poured into hydrochloric acid–methanol.[8] The solution became warm and a smell of methanethiol was apparent. Work-up and chromatography gave the desired enone (**16**) in 66% yield together with the by-product (**19**) in 29% yield. The improved yield of enone is at least in part due to the highly volatile methanethiol being expelled from the solution. Such is not the case in the hydrolysis of (**13**) where the less volatile thiophenol remains in solution to trap the intermediate carbocation.

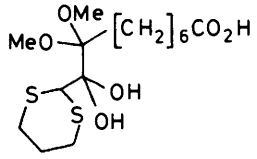
The ω-side-chain required for the PGs was now to be added



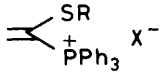
(**8**)



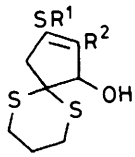
(**9**)



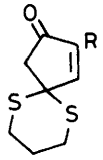
(**10**)



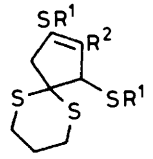
(**11**) R = Ph, X = I
(**12**) R = Me, X = Cl



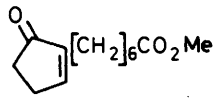
(**13**) R^1 = Ph, R^2 = Me
(**14**) $R^1 = R^2$ = Me
(**15**) R^1 = Me, R^2 = $[CH_2]_6CO_2H$



(**16**) R = Me
(**17**) R = $[CH_2]_6CO_2Me$



(18) R^1 = Ph, R^2 = Me
(19) R^1 = R^2 = Me



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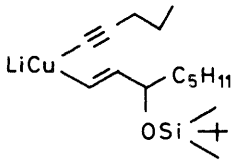

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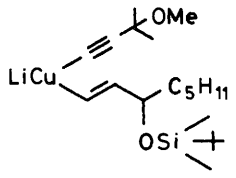

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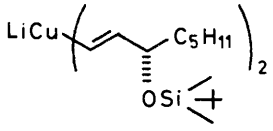
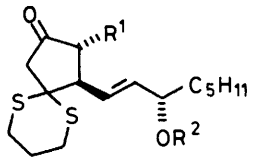


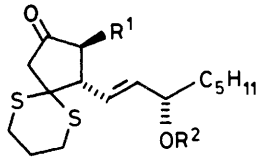
(23)

to the enone (16) using a cuprate reaction. The use of the heterocuprate reagents (21)[9] and (22)[10] resulted in no reaction and it was necessary to resort to the more reactive homocuprate (23)[11] in the presence of tributylphosphine in order to achieve the desired conversion.

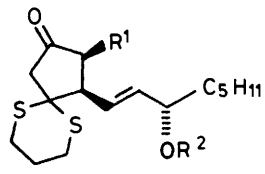
Based on similar cuprate additions in PG synthesis,[11] especially those involving the symmetrical enone (20),[12] we expected to obtain approximately equal amounts of the two diastereoisomers (24) and (28). (Reactions were carried out with both racemic and resolved homocuprate; for simplicity only the products from the reactions with resolved cuprate are shown.) However, the results obtained were surprising from two points of view. First, two products were obtained by chromatography and it was not expected that (24) and (28) should be separable. Spectral analysis showed that the two products were themselves mixtures of isomers. The spectral evidence indicated that the two products isolated were (i) a mixture of *trans*-isomers (24) and (28) and (ii) a mixture of *cis*-isomers (32) and (36). The ratio of *trans*:*cis* [*i.e.* (24) + (28):(32) + (36)] was 1.5:1. The assignment of stereochemistry in these compounds is based on ^{13}C n.m.r. studies. In structures (24), (28), (32), and (36) the chemical shifts of the methyl carbon and the vinylic carbon which is γ to that methyl vary, depending upon the relative positions of those carbons to each other in space. Carbons three bonds distant from a substituent have been shown to exhibit upfield shifts due to sterically induced polarisation of the C–H bonds,[13] and in rigid cyclic systems this effect is at a maximum when the substituent and the γ-carbon are *gauche* (γ-*gauche* effect). Thus in (24), (28), (32), and (36) the effect should be greater in the *cis*-isomers where the carbons are *gauche* than in the *trans*-isomers where the carbons are anticlinal. The Table gives the observed shifts and allows assignment of stereochemistry. It should be noted that the isolation of *cis*-isomers from similar cuprate additions in PG synthesis does not seem to have been reported previously. However, it is not clear whether this is a result of such products not being formed in related systems or simply not being separated from the reaction mixture. Unfortunately, attempts to epimerise the undesired *cis*-isomers (32) and (36) with mild base led only to extensive decomposition.



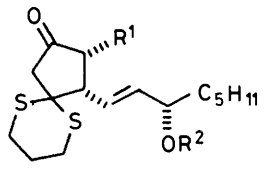
(24) R^1 = Me, R^2 = Si
(25) R^1 = Me, R^2 = H
(26) R^1 = $[CH_2]_6CO_2Me$, R^2 = Si
(27) R^1 = $[CH_2]_6CO_2Me$, R^2 = H



(28) R^1 = Me, R^2 = Si
(29) R^1 = Me, R^2 = H
(30) R^1 = $[CH_2]_6CO_2Me$, R^2 = Si
(31) R^1 = $[CH_2]_6CO_2Me$, R^2 = H



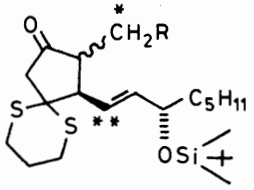
(32) R^1 = Me, R^2 = Si
(33) R^1 = Me, R^2 = H
(34) R^1 = $[CH_2]_6CO_2Me$, R^2 = Si
(35) R^1 = $[CH_2]_6CO_2Me$, R^2 = H



(36) R^1 = Me, R^2 = Si
(37) R^1 = Me, R^2 = H
(38) R^1 = $[CH_2]_6CO_2Me$, R^2 = Si
(39) R^1 = $[CH_2]_6CO_2Me$, R^2 = H

Secondly, as mentioned above, it was expected that the ratio of diastereoisomers (24):(28) would be *ca.* 1:1. However, the ^{13}C n.m.r. spectrum of the mixture suggested a ratio of between 2 and 3 to 1. This was confirmed by desilylation and separation of the alcohols (25) and (29). The chromatographically more polar isomer predominated and the ratio of products was 2.4:1. A similar result was obtained for the ratio of *cis*-isomers (33) and (37) obtained by desilylation of the mixture (32) + (36).

Table. Assignment of stereochemistry in various 6,10-dithiaspiro[4.5]-decanones.



R	Compounds	^{13}C Shifts (p.p.m) * **	Stereochemistry
H	(**24**) + (**28**)	12.9, 125.1	*trans*
H	(**32**) + (**36**)	10.7, 123.4	*cis*
$[CH_2]_5CO_2Me$	(**26**) + (**30**)	28.3, 125.7	*trans*
$[CH_2]_5CO_2Me$	(**34**) + (**38**)	25.4, 123.15	*cis*

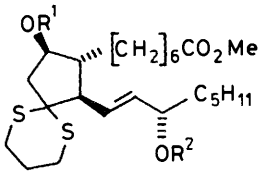
PG Synthesis.—Having established with the model studies a viable route to a suitably substituted cyclopentanone, attention was turned towards the synthesis of PGD_1. Alkylation of methyl dimethoxyacetate [7,14] with the lithium salt of 7-bromoheptanoic acid gave only poor conversion but use of the corresponding iodo derivative gave the acid ester (**8**) in 81% yield. In order to achieve this yield it was necessary to use relatively large volumes of THF to solubilise the lithium 7-iodoheptanoate, and to maintain the temperature at −30 °C. Treatment of compound (**8**) with lithiodithiane in the presence of excess of LDA (lithium di-isopropylamide) gave two compounds. The desired acid (**9**) was obtained in 55% yield together with a chromatographically more polar compound which showed an enhanced hydroxy-group peak in its i.r. spectrum. The structure assigned to this product is the hydrate (**10**), since it was found that it could be converted into (**9**) under vacuum or by azeotropic distillation with benzene. The total yield of the acid (**9**) was improved to 90% in this way. Hydrolysis of the acetal group in (**9**) was achieved with aqueous TFA (trifluoroacetic acid) giving 74% of diketo acid (**7**). Cyclisation to the desired cyclopentane system was achieved efficiently, as previously described, with vinylphosphonium salts (**11**) and (**12**), giving the cyclopentenones (**4**) and (**5**) in 79 and 76% yield respectively. Following our experience in the model series it was anticipated that the reduction–acid-catalysed rearrangement sequence would be most profitable from the methylthio derivative (**5**). However, selective reduction of the cyclopentenone carbonyl, in the presence of the carboxylic acid, proved difficult. Sodium borohydride and sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) only caused reduction under conditions which also reduced the acid (similar results were obtained with the corresponding methyl ester). On the other hand lithium tri-t-butoxyaluminium hydride and lithium borohydride in THF were without effect. However, when a small amount of methanol was added to the reaction mixture containing the latter reducing agent rapid and complete reduction took place in the desired manner to provide compound (**15**). This unstable allylic alcohol was immediately rearranged with hydrochloric acid in methanol, conditions which resulted in partial esterification of the acid. The esterification was driven to completion by the addition of conc. sulphuric acid. Thus the enone (**17**) was obtained in 59% overall yield from (**5**).

Conjugate addition of the ω-side-chain was now achieved with the homocuprate (**23**) using the conditions worked out in the model series, and the results were broadly similar. The *cis* and *trans* pairs of diastereoisomers (**26**), (**30**), (**34**), and (**38**) were obtained in 63% combined yield. The ratio of *trans* to *cis* was 2.3:1, the assignment of stereochemistry resting, as before, on ^{13}C n.m.r. data (Table). The increase in the *trans*:*cis* ratio over the model series presumably results from the increase in size of the α-side-chain in the prostanoid system. Deprotection at C-15* in the mixtures (**26**) + (**30**) and (**34**) + (**38**), and chromatographic separation, showed that the ratios (**27**):(**31**) and (**35**):(**39**) were 3.5:1. The excess of the desired diastereoisomer (**27**) over the *ent*-15-*epi*-isomer (**31**) represents an asymmetric induction of the stereochemistry at the C-12 centre by the substituent at C-15. Similar cuprate additions with the *E*-cuprate (**23**) in PG synthesis have normally resulted in only a slight deviation from a 1:1 ratio [11] although the corresponding *Z*-cuprate has been shown to produce predominantly one of the possible diastereoisomers.[15] The stereochemical outcome of our cuprate reactions must result from there being a difference in the energies of the two possible transition states, although molecular models do not make it clear why this should be so. Possibly there is some interaction between the bulky C-15 substituent and the dithiane ring. It is especially difficult to analyse this problem when the real mechanism of cuprate additions is still a subject of dispute.[16]

The next step in the synthetic plan required stereospecific reduction of the C-9 carbonyl. Use of K-selectride proceeded with total consumption of starting material but not more than 30% of product alcohol could be isolated on acidic work-up. (It was not possible to employ the more standard oxidative work-up procedure [17] because oxidation at sulphur might also have occurred.) We have observed low yields in other reductions with borane base reagents when the substrate contains a dithiane ring, and feel that some type of intractable complex may be formed. When reduction of the mixture (**26**) + (**30**) was carried out with sodium borohydride the product showed a single spot on t.l.c., corresponding to the product obtained from the K-selectride reduction. Experience suggested that the C-9 epimeric alcohol mixtures [(**40**) + (**43**)] and [(**47**) + (**49**)] would be chromatographically separable [18,19] and therefore that a stereospecific reduction had taken place. Confirmation of this was seen in the n.m.r. spectrum of the product which showed the C-9 proton at δ 3.92. The Upjohn group have shown that for 9-hydroxyprostanoids a resonance at δ 3.9 is indicative of a 9β configuration in the natural prostanoid series whereas a resonance at around δ 4.2 indicates a 9α configuration.[19] Thus the product of the reduction was (**40**) + (**43**), and further confirmation was obtained by desilylation at C-15 and separation of the product diols (**41**) and (**44**). The 400 MHz n.m.r. spectrum of the diol (**41**), in the presence of D_2O, showed the C-9 proton as an eight-line signal at δ 3.92. Further, desulphurisation of (**41**) with Raney nickel, followed by saponification, gave a product which co-chromatographed with authentic 11-deoxy$PGF_{1\beta}$. A study of molecular models does not show why the borohydride reduction is stereospecific since both faces of the molecule seem freely accessible.

In order to obtain PGD_1 it was now necessary to invert the stereochemistry at C-9. Similar inversions in PG chemistry have been achieved by S_N2 displacements on mesylates (methanesulphonates) or tosylates (toluene-*p*-sulphonates) using superoxide,[20] formate,[21] and acetate anions.[22] Thus the mixture (**40**) + (**43**) was converted into the mesylates (**42**) + (**45**) which, without purification, were treated with tetrabutylammonium acetate. The inverted acetates (**46**) + (**48**) were obtained in 65% yield together with 13% of the elimination products (**50**) + (**51**). Treatment of the acetates (**46**) + (**48**) with sodium methoxide afforded the 9α-alcohols (**47**) + (**49**) whose n.m.r. spectrum showed the C-9 proton at δ 4.18, in accordance with the Upjohn findings.[19] These alcohols were also chromatographically more

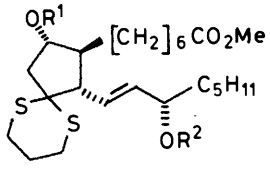
* Prostane numbering.



(40) $R^1 = H, R^2 = Si$

(41) $R^1 = R^2 = H$

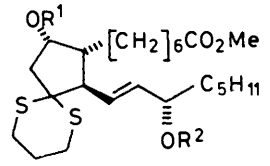
(42) $R^1 = SO_2CH_3, R^2 = Si$



(43) $R^1 = H, R^2 = Si$

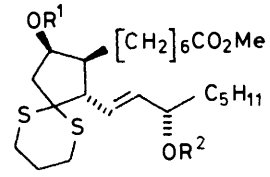
(44) $R^1 = R^2 = H$

(45) $R^1 = SO_2CH_3, R^2 = Si$



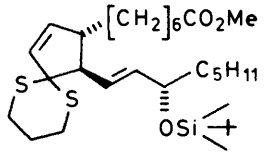
(46) $R^1 = COCH_3, R^2 = Si$

(47) $R^1 = H, R^2 = Si$

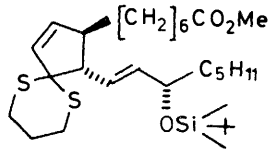


(48) $R^1 = COCH_3, R^2 = Si$

(49) $R^1 = H, R^2 = Si$



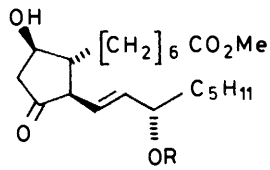
(50)



(51)

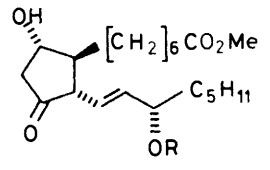
polar than the 9β-hydroxy precursors, in common with findings in most prostanoid systems.

Deprotection of the C-11 carbonyl functionality now had to be achieved, a transformation for which a wide range of methods is available. A recent method described by Olah uses trichloroisocyanuric acid–silver nitrate.[23] Application of this method to the alcohols (**40**) + (**43**) gave a 52% combined yield of the ketols (**52**) + (**54**). A similar conversion with this reagent could not be achieved from the 9α-alcohols (**46**) + (**48**), but the desired reaction was effected with boron trifluoride–mercury(II) oxide[24] which gave compounds (**56**) + (**58**) in 60% yield. Finally, deprotection at C-15 was achieved with 5% hydrofluoric acid.[25] In this way (**52**) + (**54**) gave a mixture of the chromatographically separable diols (**53**) (*i.e.* 9-*epi*-PGD_1 methyl ester) and (**55**) while similar treatment of the ketols (**56**) and (**58**) gave a 68% yield of PGD_1 methyl ester (**57**) and its *ent*-15-*epi*-isomer (**59**) in the ratio 3.5 : 1.



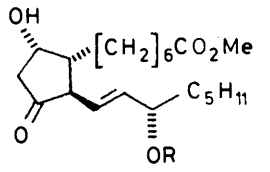
(52) $R = Si$

(53) $R = H$



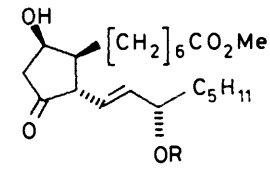
(54) $R = Si$

(55) $R = H$



(56) $R = Si$

(57) $R = H$



(58) $R = Si$

(59) $R = H$

Experimental

Materials and Techniques.—Dry THF was obtained by distillation from potassium. Dry diethyl ether was obtained by distillation from lithium aluminium hydride. Di-isopropylamine was distilled from calcium hydride. Thin-layer chromatograms were obtained using Merck '5734' plastic-backed plates and short-column chromatography was carried out using either Merck '7736' or '7734' silica gel. ^1H N.m.r. data were obtained from Perkin-Elmer R-600 FT, Varian EM390, Perkin-Elmer R34, Bruker WM 250, and Bruker WM 400 spectrometers. *J* Values are quoted in Hz. ^{13}C N.m.r. data were obtained from a Jeol CFT 160 A spectrometer. Spectra were recorded in $CDCl_3$ solution with Me_4Si as internal standard. I.r. spectra were obtained from a Pye Unicam SP 200 grating i.r. spectrophotometer as liquid films unless otherwise stated. Mass spectral data were obtained from AEI MS9 or MS30 instruments. Light petroleum refers to the fraction boiling in the range 40—60 °C.

3-Methyl-6,10-dithiaspiro[4.5]*dec-3-en-2-one* (**16**).—To a solution of the ketone (**3**)[7] (1 g, 4.05 mmol) in dry THF (25 ml) was added lithium aluminium hydride (150 mg) and the mixture was stirred for 30 min. The excess of hydride was then quenched by addition of methanol and the resulting solution was poured into a stirred mixture of methanol and conc. hydrochloric acid (2:1) (100 ml) and stirred for 15 min. The mixture was diluted with water (200 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed with 5% aqueous sodium hydrogen carbonate solution (2 × 25 ml), dried ($MgSO_4$), and evaporated to give a yellow oil which was chromatographed with ethyl acetate–light petroleum–triethylamine (10:89:1). This afforded the *enone* (**16**) (536 mg, 66%), m.p. 51—53 °C (Found: C, 54.05; H, 6.05. $C_9H_{12}OS_2$ requires C, 53.96; H, 6.04%); $\nu_{max.}$ 1 715 and 1 640 cm^{-1}; δ_H 1.84 (3 H, d, *J* 1.5, CH_3), 2.1 (2 H, m, 8-H_2), 2.92 (2 H, s, 1-H_2), 3.02 (4 H, m, 7- and 9-H_2), and 7.52 (1 H, d, *J* 1.5, 4-H) and the *by-product* (**19**) as a pale

yellow oil (240 mg, 29%) (Found: C, 47.45; H, 6.45. $C_{11}H_{18}S_4$ requires C, 47.45; H, 6.5%); $\nu_{max.}$ 1 640 cm^{-1}; δ_H 1.72 (2 H, s), 1.85 (3 H, s), 2.21 (3 H, s), 2.9 (6 H, m), and 3.72 (1 H, s).

Diastereoisomers of 4-[(1E,3S)-3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*]-3-*methyl*-6,10-*dithiaspiro*[4.5]*decan*-2-*one* (**24**) + (**28**) + (**32**) + (**36**).—To a solution of (1*E*,3*S*)-3-t-butyldimethylsilyloxy-1-iodo-oct-1-ene (3.5 ml, 10.72 mmol) in dry ether (50 ml) was added, under nitrogen, a solution of n-butyllithium in hexane (6.7 ml, 10.72 mmol) at −78 °C. The solution was stirred for 1 h at −78 °C before a solution of bis(tri-n-butylphosphine)copper(I) iodide (5.38 mmol) in dry ether (40 ml) was added dropwise during 5 min *via* a cannula. The resulting pale yellow solution was stirred for 30 min at −78 °C and then a solution of enone (**16**) (536 mg, 2.68 mmol) in ether (10 ml) was added dropwise by the cannula. The mixture was stirred at −78 °C for 1 h and poured into vigorously stirred saturated aqueous ammonium chloride (250 ml). The layers were separated and the aqueous phase was extracted with ether (2 × 50 ml). The combined organic layers were washed with 10% aqueous ammonium sulphate, adjusted to pH 9 with ammonium hydroxide (until the aqueous layer was no longer blue), and dried ($MgSO_4$). Removal of the solvent gave a pale yellow oil which was chromatographed with ethyl acetate–light petroleum (5:95) to afford recovered enone (**16**) (183 mg), the cis-*isomers* (**32**) + (**36**) as an oil (242 mg) (Found: C, 62.0; H, 9.45. $C_{23}H_{42}O_2S_2Si$ requires C, 62.39; H, 9.56%); $\nu_{max.}$ 1 750 cm^{-1}; δ_H 0.03, 0.05, and 0.1 [6 H, 3 s, $Si(CH_3)_2$], 0.8—1.0 (15 H, m and s, Bu^t and 2 × CH_3), 2.03 (2 H, m), 2.5—3.3 (8 H, m), 4.12 (1 H, dd, *J* 6 and 10), 5.2 (1 H, dd, *J* 10 and 15), and 5.68 (1 H, m); δ_C −4.7 (q), −4.3 (q), 10.7 (q), 18.2 (s), 22.6 (t), 24.8 (t), 24.9 (t), 25.8 (q), 27.4 (t), 28.1 (t), 31.8 (t), 38.5 (t), 46.4 (d), 50.5 (t, minor diastereoisomer), 50.7 (t, major diastereoisomer), 52.7 (s), 54.0 (d, major), 54.3 (d, minor), 72.8 (d, major), 72.9 (d, minor), 123.4 (d, minor), and 123.6 p.p.m. (d, major), and the trans-*isomers* (**24**) + (**28**) as a waxy solid (357 mg), m.p. 28—30 °C (Found: C, 61.8; H, 9.26%); $\nu_{max.}$ 1 750 cm^{-1}; δ_H 0.1 (6 H, s), 0.92 (12 H, m and s), 1.1 (3 H, m), 1.2—1.8 (8 H, m) 1.8—2.3 (2 H, m), 2.4—3.2 (4 H, m), 2.7 (1 H, d), 3.4 (1 H, d, *J* 16), 4.18 (1 H, dd, *J* 6 and 10), and 5.5—6.0 (2 H, m); δ_C −4.7 (q), −4.1 (q), 12.9 (q), 14.0 (q), 18.3 (s), 22.7 (t), 25.0 (t), 25.5 (t), 25.9 (q), 27.1 (t), 28.3 (t), 31.8 (t), 38.3 (t), 46.3 (d, major), 46.3 (d, minor), 54.5 (s), 54.8 (t), 59.1 (d, major), 59.4 (d, minor), 73.1 (d), 125.1 (d, minor), 125.4 (d, major), 138.1 (d, major), 138.8 (d, minor), and 214.5 p.p.m. (s). Total yield of *cis* + *trans* products: 72% based upon consumed enone (**16**).

8,8-*Dimethoxy*-8-*methoxycarbonyloctanoic Acid* (*Methyl Hydrogen* 2,2-*Dimethoxynonanedioate*) (**8**).—To THF (500 ml) containing di-isopropylamine (15.9 g, 0.1125 mol) at −78 °C under N_2 was added n-butyl-lithium in hexane (73.5 ml, 0.1125 mol). After the mixture had been stirred for 20 min a solution of methyl dimethoxyacetate[7] (9.225 ml, 75 mmol) in dry THF (20 ml) was added dropwise during 20 min. After this mixture had been stirred for 30 min at −78 °C, a solution of 7-iodoheptanoic acid (9.3 g, 36 mmol) in THF (20 ml) was added dropwise. The reaction mixture was then stirred at −30 °C for 16 h. Water (300 ml) was added and the layers were separated. The organic layer was extracted with water (2 × 100 ml) and the combined aqueous layers were acidified to pH 5 with dil. hydrochloric acid, and extracted with ether (3 × 100 ml). The aqueous layer was re-acidified to pH 5 and extracted again with ether (100 ml). The combined ether layers were washed in turn with water (2 × 100 ml) and brine (100 ml), dried ($MgSO_4$), and evaporated to give the product (**8**) as a pale yellow oil (9.96 g, 81%) (Found: C, 54.1; H, 8.15. $C_{12}H_{22}O_6$ requires C, 54.9; H, 8.4%); $\nu_{max.}$ 3 500—2 500, 1 740, and 1 705 cm^{-1}; δ_H 1.0—2.0 (10 H, m), 2.36 (2 H, t, *J* 7), 3.27 (6 H, s), 3.8 (3 H, s), and 10.58 (1 H, br s).

9-(1,3-*Dithian*-2-*yl*)-8,8-*dimethoxy*-9-*oxononanoic Acid* (**9**).—To dry THF (50 ml) under N_2 were added 1,3-dithiane (0.48 g, 4 mmol) and di-isopropylamine (1.13 mmol). The mixture was cooled to −78 °C and n-butyl-lithium in hexane (7.48 ml, 11.4 mmol) was added dropwise. After the mixture had been stirred for 30 min at −78 °C a solution of the acid (**8**) (0.83 g, 3.2 mmol) in THF (10 ml) was added dropwise, and this mixture was stirred for 5 h at −30 °C. Water (50 ml) and ether (50 ml) were added, the layers were separated, and the organic layer was extracted with water (2 × 10 ml). The combined aqueous layers were washed with ether (50 ml), acidified to pH 5, and quickly extracted with ether (2 × 50 ml). The final ether extracts were washed with water (25 ml), dried ($MgSO_4$), and evaporated to give a pale yellow oil which was dissolved in benzene (100 ml), the solution was evaporated, and the residue chromatographed with ethyl acetate–light petroleum–acetic acid (20:79:1) to give the *product* (**9**) as an oil (0.92 g, 90%) (Found: C, 50.9; H, 7.7. $C_{15}H_{26}O_5S_2$ requires C, 51.4; H, 7.45%); $\nu_{max.}$ 3 650—2 300, 1 740, and 1 710 cm^{-1}; δ_H 1.0—2.0 (10 H, m), 2.0—3.6 (6 H, m), 3.22 (6 H, s), 3.3—3.6 (2 H, m), 4.68 (1 H, s), and 10.0 (1 H, s).

9-(1,3-*Dithian*-2-*yl*)-8,9-*dioxononanoic Acid* (**7**).—The acid (**9**) (5.85 g, 16.7 mmol) was dissolved in 5% aqueous TFA (25 ml) and the solution was stirred at room temperature for 10 min. The mixture was diluted with ether (150 ml), poured into water (100 ml), and the layers were separated. The yellow organic layer was washed in turn with water (5 × 50 ml) and 1% aqueous sodium hydrogen carbonate (2 × 5 ml), dried ($MgSO_4$), and diluted with light petroleum (50 ml). The solvent volume was reduced to *ca.* 40 ml and the *product* (**7**) was obtained as a bright yellow solid (3.28 g, 74%), m.p. 96—98 °C (Found: C, 51.2; H, 6.8. $C_{13}H_{20}O_4S_2$ requires C, 51.28; H, 6.62%); $\nu_{max.}(CHBr_3)$ 1 740 and 1 710 cm^{-1}; δ_H 1.2—2.2 (10 H, m), 2.33 (2 H, t, *J* 7), 2.5 (2 H, m), 2.82 (2 H, t, *J* 7), and 9.79 (1 H, s).

7-(3-*Methylthio*-1-*oxo*-6,10-*dithiaspiro*[4.5]*dec*-2-*en*-2-*yl*)-*heptanoic Acid* (**5**).—To a solution of the diketo acid (**7**) (3.04 g, 10 mmol) in dry THF (75 ml) was added sodium hydride (0.6 g of 80% dispersion, 20 mmol). After the mixture had been stirred for 15 min the vinylphosphonium salt (3.75 g) (**12**) was added in one portion. The mixture was stirred for 45 min, diluted with water (150 ml), and the layers were separated. The organic phase was washed with water (2 × 50 ml) and the combined aqueous layers were washed with ether (4 × 50 ml). The aqueous layer was acidified with dil. hydrochloric acid and extracted with ether (4 × 50 ml). The final ether extracts were washed in turn with water (50 ml) and brine (50 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed with ethyl acetate–light petroleum–acetic acid (30:69:1) to give the *product* (**5**) as a white crystalline solid (2.68 g, 78%), m.p. 88—90 °C (Found: C, 53.2; H, 6.6. $C_{16}H_{24}O_3S_3$ requires C, 53.3; H, 6.7%); $\nu_{max.}$(KBr) 3 700—2 400, 1 710, 1 680, and 1 610 cm^{-1}; δ_H 1.48 (8 H, m), 2.0—2.8 (8 H, m), 2.4 (3 H, s), 2.8 (2 H, s), 3.93 (2 H, dt, *J* 3 and 12), and 9.75 (1 H, s).

7-(1-*Oxo*-3-*phenylthio*-6,10-*dithiaspiro*[4.5]*dec*-2-*en*-2-*yl*)-*heptanoic Acid* (**4**).—From vinylphosphonium salt (**11**) using the same method as for (**5**), the *product* (**4**) was obtained as a white crystalline solid (76%), m.p. 99.5—101.5 °C (Found: C, 59.7; H, 6.25. $C_{21}H_{26}O_3S_3$ requires C, 59.7; H, 6.2%); $\nu_{max.}$ ($CHBr_3$) 3 490—2 350, 1 700, and 1 680 cm^{-1}; δ_H 1.0—1.8 (10 H, m), 2.0—2.3 (4 H, m), 2.41 (2 H, t, *J* 7), 2.57 (2 H, s), 4.0 (2 H, m), 6.7—7.2 (5 H, m), and 10.1 (1 H, s).

Methyl 7-(3-*Oxo*-6,10-*dithiaspiro*[4.5]*dec*-1-*en*-2-*yl*)*heptanoate* (**17**).—To a solution of the acid (**5**) (490 mg, 1.36 mmol) in THF (30 ml) was added lithium borohydride (300 mg) followed by methanol (2 ml) added dropwise during 20 min. The mixture was then carefully poured into a stirred mixture of methanol–conc. hydrochloric acid (2:1) (50 ml), and stirred for 10 min, before the addition of conc. sulphuric acid (5 ml). After 10 min, water (200 ml) was added and the mixture was extracted with ether (3 × 50 ml). The combined extracts were washed in turn with water (2 × 25 ml) and brine (25 ml), dried ($MgSO_4$) and evaporated to give an oil which was chromatographed with ethyl acetate–light petroleum (15:85) to afford the desired *enone* (**17**) as a pale yellow oil (250 mg, 56%) (Found: C, 58.45; H, 7.35. $C_{16}H_{24}O_3S_2$ requires C, 58.5; H, 7.35%); $\nu_{max.}$ 1 745, 1 708, and 1 630 cm^{-1}; δ_H (400 MHz) 1.28 (4 H, m), 1.49 (2 H, m), 1.57 (2 H, m), 2.02 (2 H, m), 2.15 (2 H, dt, *J* 7.5 and 1.5), 2.26 (2 H, t, *J* 7.5), 2.84 (2 H, s), 2.9 (2 H, m), 3.02 (2 H, m), 3.60 (3 H, s), and 7.38 (1 H, s).

Diastereoisomers of Methyl 7-{1-[(1E,3S)-3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*]-3-*oxo*-6,10-*dithiaspiro*[4.5]*decan*-2-*yl*}*heptanoate* (**26**) + (**30**) + (**34**) + (**38**).—These were obtained from (**17**) using the same method as for (**24**) + (**28**) + (**32**) + (**36**). cis-*Isomers* (**34**) + (**38**) were an oil (20.1%) (Found: C, 62.9; H, 9.3. $C_{30}H_{54}O_4S_2Si$ requires C, 63.1; H, 9.53%); $\nu_{max.}$ 1 745 cm^{-1}; δ_H 0.05 (6 H, s), 0.9 (12 H, s and m), 1.1—1.9 (18 H, m), 2.07 (2 H, m), 2.33 (2 H, t, *J* 8), 2.7 (1 H, d, *J* 6), 3.0 (1 H, d, *J* 6), 2.5—3.2 (5 H, m), 3.35 (1 H, dd, *J* 7.5 and 10.5), 3.69 (3 H, s), 4.16 (1 H, m), 5.2 (1 H, dd, *J* 10.5 and 16), and 5.72 (1 H, dd, *J* 6 and 16); δ_C −4.8 (q), −4.4 (q), 14.0 (t), 18.2 (s), 22.7 (t), 24.8 (t), 24.9 (t), 25.4 (t), 25.8 (q), 27.0 (t), 27.4 (t), 28.1 (t), 29.0 (t), 29.2 (t), 31.9 (t), 34.0 (t), 38.6 (t), 50.7 (t, major), 50.6 (t, minor), 51.3 (q), 51.8 (d and s), 52.9 (d, major), 52.6 (d, minor), 72.8 (d), 123.1 (d), 138.4 (d, major), 138.1 (d, minor), 173.9 (s), and 214.0 p.p.m. (s). trans-*Isomers* (**26**) + (**30**) were a waxy oil (35%) (Found: C, 63.0; H, 9.8%); $\nu_{max.}$ 1 750 cm^{-1}; δ_H 0.08 (6 H, s), 0.9 (12 H, s and m), 1.1—1.7 (18 H, m), 2.02 (2 H, m), 2.29 (2 H, t, *J* 7), 2.4—3.1 (5 H, m), 2.65 (1 H, d, *J* 18), 3.37 (1 H, d, *J* 18), 3.66 (3 H, s), 4.19 (1 H, m), and 5.5—6.0 (2 H, m); δ_C −4.7 (q), −4.1 (q), 14.0 (q), 18.3 (s), 22.6 (t), 24.8 (2 t), 25.4 (t), 25.9 (q), 26.4 (t), 27.0 (t), 28.3 (2 t), 28.9 (t), 29.4 (t), 31.8 (t), 23.9 (t), 38.2 (t), 50.9 (d), 51.3 (q), 54.7 (s), 55.1 (t), 56.5 (d), 73.0 (d), 125.8 (d, major), 125.6 (d, minor), 138.7 (d, major), 138.0 (d, minor), 173.8 (s), and 214.2 p.p.m. (s).

Diastereoisomers of Methyl 7-{1-[(1E,3S)-3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*]-3-*hydroxy*-6,10-*dithiaspiro*[4.5]*decan*-2-*yl*}-*heptanoate* (**40**) + (**43**).—The mixture of *trans*-ketones (**26**) + (**30**) (115 mg, 0.2 mmol) was dissolved in methanol–THF (1:1) (10 ml) and the solution was cooled to −40 °C. Sodium borohydride (50 mg, 1.3 mmol) was added and the mixture was maintained at *ca.* −40 °C for 3 h. It was then poured into water (50 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed in turn with 0.1M hydrochloric acid (10 ml), water (10 ml), and brine (10 ml), dried ($MgSO_4$), and evaporated to give the *product mixture* (**40**) + (**43**) as an oil (115 mg, 100%) (Found: C, 62.8; H, 9.45. $C_{30}H_{56}O_4S_2Si$ requires C, 62.9; H, 9.85%); $\nu_{max.}$ 3 480 and 1 740 cm^{-1}; δ_H 0.1 (6 H, 3 s), 0.91 (12 H, s and t), 1.3 (12 H, m), 1.49—1.64 (6 H, m), 1.88 (1 H, m), 2.1 (2 H, m), 2.16 (1 H, m), 2.2 (1 H, m), 2.32 (3 H, m), 2.82—3.04 (4 H, m), 3.68 (3 H, s), 3.92 (1 H, m), 4.12 (1 H, m), 5.53 (1 H, ddd, *J* 2, 6.5, and 17), and 5.71 (1 H, m).

Methyl 7-{3β-*Hydroxy*-1β-[(1E,3S)-3-*hydroxyoct*-1-*enyl*]-6,10-*dithiaspiro*[4.5]*decan*-2α-*yl*}*heptanoate* (**41**).—The mixture of alcohols (**40**) + (**43**) (100 mg, 0.2 mmol) was dissolved in a mixture of 40% hydrofluoric acid–THF–acetonitrile (5:45:45) (5 ml). The solution was stirred for 30 min at room temperature, poured into 5% aqueous sodium hydrogen carbonate (20 ml) and extracted with chloroform (3 × 10 ml). The combined extracts were washed in turn with water (10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated to give an oil which was chromatographed with ethyl acetate–light petroleum (35:65) to give the minor isomer (**44**) (14 mg) and the major isomer (**41**) (51.6 mg) (total yield (78%) [*m/z* 458.2472 (M^+). $C_{24}H_{42}O_4S_2$ requires *M*, 458.2465]; $\nu_{max.}$ 3 480 and 1 745 cm^{-1}; δ_H ($CDCl_3$ + D_2O) 0.9 (3 H, t, *J* 7), 1.32 (12 H, m), 1.5—1.62 (8 H, m), 1.99 (2 H, m), 2.14 (1 H, m), 2.17 (1 H, m), 2.3 (3 H, t, *J* 7), 2.32 (1 H, d, *J* 7.5), 2.78 (2 H, m), 2.84 (1 H, dd, *J* 2 and 14), 3.07 (2 H, m), 3.68 (3 H, s), 3.92 (1 H, ddd, *J* 2, 4.5, and 9), 4.15 (1 H, dd, *J* 7 and 14), 5.58 (1 H, dd, *J* 7 and 15), and 5.78 (1 H, ddd, *J* 1, 8, and 15).

Methyl (13E,15S)-15-*t*-*Butyldimethylsilyloxy*-9β-*hydroxy*-11-*oxoprost*-13-*en*-1-*oate and its* ent-15-*Epimer* (**52**) + (**54**).—To a stirred solution of the alcohols (**40**) + (**43**) (220.5 mg, 0.385 mmol) in acetonitrile–acetone–water (45:45:10) (15 ml) was added silver nitrate (131 mg, 0.77 mmol). Upon dissolution the mixture was cooled to −5 °C and a solution of trichloroisocyanuric acid (89.5 mg, 0.385 mmol) in acetonitrile–water (9:1) (1 ml) was added all at once. After 1 min the mixture was rapidly poured into 1% aqueous sodium hydrogen carbonate, extracted with ether (3 × 20 ml), and the extracts were washed in turn with water (10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated to afford a pale green oil which was rapidly chromatographed with ethyl acetate–light petroleum (2:3) to give the *product mixture* (**52**) + (**54**) (112 mg, 60.4%) (Found: C, 66.7; H, 10.35. $C_{27}H_{50}O_5Si$ requires C, 67.1; H, 10.5%); $\nu_{max.}$ 3 500, 1 750, and 1 730sh cm^{-1}; δ_H 0.1 (6 H, s), 0.95 (9 H, s), 1.3—1.9 (21 H, m), 1.95 (2 H, m), 2.31 (2 H, t, *J* 6), 3.69 (3 H, s), 4.05—4.19 (2 H, m), and 5.6 (2 H, m).

Methyl (13E,15S)-9β,15-*Dihydroxy*-11-*oxoprost*-13-*en*-1-*oate* (**53**).—The mixture of silyl ethers (**52**) + (**54**) (35 mg) was dissolved in a mixture of 40% hydrofluoric acid–THF–acetonitrile (5:45:45) (5 ml) and the solution was stirred at room temperature for 1 h and then poured into 5% aqueous sodium hydrogen carbonate and rapidly extracted with chloroform (3 × 10 ml). The combined extracts were washed in turn with water (5 ml) and brine (5 ml), dried ($MgSO_4$), and evaporated at < 5 °C to give a brown oil which was chromatographed with ethyl acetate–light petroleum (3:2) to give the product (**53**) (13.8 mg) and the isomer (**55**) (5.2 mg) (total yield 71%). Compound (**53**) showed $\nu_{max.}$ 3 450 and 1 740 cm^{-1}; δ_H 0.9 (3 H, m), 1.36 (19 H, m), 2.34 (8 H, m), 3.69 (3 H, s), 4.15 (2 H, m), and 5.6 (2 H, m).

Diastereoisomers of Methyl 7-{1-[(1E,3S)-3-*t*-*Butyldimethylsilyloxyoct*-1-*enyl*)-3-*hydroxy*-6,10-*dithiaspiro*[4.5]*decan*-2-*yl*}-*heptanoate* (**47**) + (**49**).—To a stirred solution of the alcohols (**40**) + (**43**) (373 mg, 0.65 mmol) in dry pyridine (10 ml) was added methanesulphonyl chloride (110.5 mg, 0.97 mmol). After 30 min the mixture was poured into 0.5M hydrochloric acid (50 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed in turn with 0.5M hydrochloric acid (3 × 10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated to give a pale brown oil which was placed under high vacuum overnight to remove excess of methanesulphonyl chloride. The crude mesylate was dissolved in acetone (20 ml) and tetra-n-butylammonium acetate (500 mg) was added rapidly. The mixture was refluxed under N_2 overnight, poured into water (50 ml), and extracted with ether (3 × 20 ml). The combined extracts were washed in turn with water (20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated to give a brown oil which was chromatographed with ethyl acetate–light petroleum (7.5:92.5) to give the elimination product (**50**) + (**51**) (50 mg, 14%) [*m/z* 554.3297 (M^+). $C_{30}H_{54}O_3S_2Si$ requires *M*, 554.3311]; $\nu_{max.}$ 1 750 and 1 655 cm^{-1}; δ_H 0.09 (6 H, s), 0.9 (12 H, s),

1.1—1.7 (16 H, m), 1.9 (2 H, t), 2.6 (2 H, m), 2.85 (6 H, m), 3.65 (3 H, s), 4.15 (1 H, m), 5.6—5.95 (3 H, m), and 5.95 (1 H, d, *J* 8) and the acetates (**46**) + (**48**) (248 mg, 62%), $\nu_{max.}$ 1 750 cm^{-1}; δ_H 2.04 (3 H, s), and 5.22 (1 H, m). The acetates (**46**) + (**48**) (248 mg) were dissolved in a solution of sodium methoxide prepared from sodium (0.5 g) in methanol (10 ml) and left at room temperature for 2 h. The mixture was poured into dil. hydrochloric acid (50 ml) and extracted with ether (3 × 20 ml). The combined extracts were washed in turn with water (2 × 20 ml) and brine (20 ml), dried ($MgSO_4$), and evaporated to afford the product alcohols (**47**) + (**49**) as an oil (195 mg, 85%) [*m/z* 572.3402 (M^+). $C_{30}H_{54}O_2S_2Si$ requires *M*, 572.3417]; $\nu_{max.}$ 3 450 and 1 750 cm^{-1}; δ_H similar to the epimeric mixture (**40**) + (**43**) except 9-H* at δ 4.28 (1 H, m).

Methyl (13E,15S)-15-*t-Butyldimethylsilyloxy*-9α-*hydroxy*-11-*oxoprost*-13-*en*-1-*oate and its* ent-15-*Epimer* (**56**) + (**58**).—To a stirred suspension of red mercury(II) oxide (45 mg, 1.8 mmol) in 15% aqueous THF (8 ml) was added freshly distilled BF_3·Et_2O (25 μl, 1.8 mmol). The mixture was cooled to 0 °C and the mixture of alcohols (**47**) + (**49**) (55 mg, 0.88 mmol) in THF (2 ml) was added. The resulting solution was stirred for 30 min, diluted with ether (20 ml), washed in turn with 1% aqueous *sodium hydrogen carbonate* (5 ml), water (5 ml), and brine (5 ml), dried ($MgSO_4$), and evaporated to give a yellow oil which was rapidly chromatographed with ethyl acetate–light petroleum (3:7) to give the title compounds (**56**) + (**58**) (23 mg, 50%), $\nu_{max.}$ 3 500, 1 750, and 1 730sh cm^{-1}; δ_H 0.09 (6 H, s), 0.9 (9 H, s), 1.34 (21 H, m), 2.3 (3 H, t, *J* 7), 2.85 (3 H, m), 3.68 (3 H, s), 4.11 (1 H, m), 4.5 (1 H, m), and 5.48 (2 H, m).

PGD$_1$ Methyl Ester and ent-15-epi-*PGD$_1$ Methyl Ester* (**57**) + (**59**).—These were produced from (**56**) + (**58**) (21 mg) using the same method as for (**52**) + (**54**). Chromatography with ethyl acetate–light petroleum (55:45) gave PGD_1 methyl ester (**57**) (7 mg, 44%) [*m/z* 368.2542 (M^+). $C_{21}H_{36}O_5$ requires *M*, 368.2563]; $\nu_{max.}$ 3 500, 1 750, and 1 730sh cm^{-1}; δ_H 0.88 (3 H, t), 1.2—1.75 (18 H, m), 2.01 (3 H, m), 2.31 (2 H, t, *J* 7), 2.44 (2 H, d, *J* 3), 2.78 (1 H, dd, *J* 8 and 12), 3.68 (3 H, s), 4.09 (1 H, m), 4.55 (1 H, m), 5.41 (1 H, dd, *J* 6.5 and 16.5), 5.61 (1 H, dd, *J* 6.5 and 16.5) and *ent*-15-*epi*-PGD_1 methyl ester (**59**) (2 mg, 12.5%); $\nu_{max.}$ as for (**57**); δ_H as for (**57**) except δ 4.28 (1 H, m) instead of the signal at δ 4.55.

* Prostane numbering.

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