Synthesis of (±)-10,10-Dimethylprostaglandin E_1 Methyl Ester and its 15-Epimer

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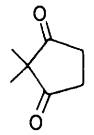
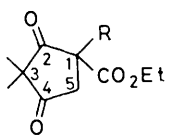
(±)-10,10-Dimethylprostaglandin E_1 methyl ester (28) and its 15-epimer (32) have been synthesised in 20 steps from the readily available 2,2-dimethylcyclopentane-1,3-dione (1). The key step in the synthesis, selective reduction of the C-2 carbonyl function of ethyl 5-(6-ethoxycarbonylhexyl)-3,3-dimethyl-2,4-dioxocyclopentanecarboxylate (9) to give the corresponding all-*trans*-hydroxycyclopentanone derivative (11), has been achieved by catalytic hydrogenation over Adams catalyst.

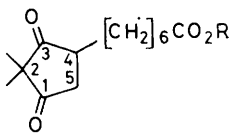
THE synthesis of analogues of the naturally occurring prostaglandins (PGs) has aroused much recent interest. Recently, syntheses of ring-methylated prostaglandins have been described, *e.g.* 8-methyl-PGC_2,[1] 12-methyl-PGA_2,[2] and 12-methyl-PGE_2.[3] These compounds have in common a 'metabolically blocked' five-membered



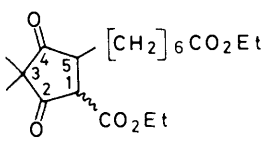
(1)



(2) R = H
(3) R = K
(4) R = $[CH_2]_6CO_2Me$
(5) R = $[CH_2]_6CO_2Et$
(6) R = $CH_2C{\equiv}C[CH_2]_3CO_2Et$



(7) R = H
(8) R = Et



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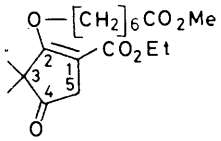


(10)

ring. In our efforts to prepare novel prostaglandins with more specific pharmacological properties, we considered the introduction of two methyl groups at C-10. We describe here details of the synthesis of (±)-10,10-dimethyl-PGE_1 and its 15-epimer.[4] It was expected that these analogues would afford more sustained biological potency because they are structurally protected against the well known ready dehydration of the β-hydroxy-ketone moiety of E-type prostaglandins, producing PGAs which are deactivated *in vivo* by transformation into the biologically inactive PGBs.

Reaction of 2,2-dimethylcyclopentane-1,3-dione[5] (1) with ethyl diethoxyphosphorylformate[6] and sodium hydride produced the β-oxo-ester (2) in 65% yield. Attempts to introduce the ethoxycarbonyl function in (1) with diethyl carbonate[7] in the presence of sodium hydride gave much lower yields. Reaction of (2) with potassium hydroxide in aqueous ethanol provided the potassium salt (3), which was alkylated with methyl 7-bromoheptanoate[8] in dimethyl sulphoxide for 16 h at ambient temperature to give a mixture of *C*- and *O*-alkylation products, (4) and (10), respectively, in the ratio 7 : 3. This ratio could be improved to 4 : 1 by performing the reaction in refluxing xylene or toluene, but the required long reaction times (2—3 days) and the insolubility of (3) made this procedure less practical. Use of the sodium salt and even the thallium(I) salt of (2) gave no improvement. The ratio of *C*- to *O*-alkylation was easily determined by the ^1H n.m.r. spectrum, displaying the signal for the C-5 protons of (10) as a sharp singlet (δ 3.26) and that of the C-5 protons of (4) as an AB system (δ 3.30 and 2.70).

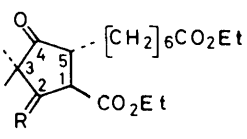
The mixture of (4) and (10), which could not be separated by simple distillation or column chromatography, was decarboxylated in boiling dilute hydrochloric acid to give the acid (7); under these conditions the enol ether (10) was both hydrolysed and decarboxylated to produce (1), which was easily recovered in the work-up procedure. Esterification of (7) with diazoethane afforded (8) in 45% overall yield from (1).

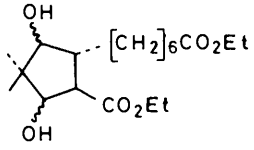
Alkylation of β-oxo-esters with the more reactive allylic or propargylic halides generally produces less *O*-alkylation products.[9] Therefore the potassium salt (3) was also treated with ethyl 7-bromohept-5-ynoate,[10] which indeed gave solely the *C*-alkylation product (6), also a key intermediate for synthesis of 10,10-dimethyl-

[1] E. J. Corey and H. S. Sachdev, *J. Amer. Chem. Soc.*, 1973, **95**, 8483.
[2] E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Letters*, 1975, 1161.
[3] P. A. Grieco, C. S. Pogonowski, M. Nishizawa, and C. L. Wang, *Tetrahedron Letters*, 1975, 2541.
[4] Preliminary communication, O. G. Plantema, H. de Koning, and H. O. Huisman, *Tetrahedron Letters*, 1975, 4595.
[5] W. G. Agosta and A. B. Smith, *J. Org. Chem.*, 1970, **35**, 3856.
[6] I. Shahak, *Tetrahedron Letters*, 1966, 2201.
[7] E. J. Corey, R. B. Mitra, and H. Uda, *J. Amer. Chem. Soc.*, 1964, **86**, 485.
[8] D. E. Ames, R. E. Bowman, and R. G. Mason, *J. Chem. Soc.*, 1950, 174.
[9] H. O. House, 'Modern Synthetic Reactions,' Benjamin, Menlo Park, California, 2nd edn., 1972, p. 536.
[10] J. Martel and E. Toromanoff, G.P. 2121361 (*Chem. Abs.*, 1972, **76**, 24712d).

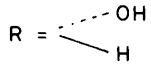
PGF_1[11a] and -PGF_2.[11b] Hydrogenation of (6) over palladium–charcoal provided the saturated compound (5), which was decarboxylated with lithium iodide in refluxing dimethylformamide,[12] affording (8) in 42% overall yield from (2). This lower yield and the lengthy preparation of the bromoheptynoate, however, are disadvantages of this procedure.

Reaction of (8) with ethyl diethoxyphosphorylformate and sodium hydride afforded the β-oxo-ester (9) in 70% yield. One important synthetic operation we had to accomplish for synthesis of PGE_1 analogues was selective reduction of the C-2 carbonyl function to generate a hydroxycyclopentanone derivative with the appropriate stereochemistry. This was best achieved * by catalytic hydrogenation over Adams catalyst in acetic acid, affording a mixture of 65% of the target compound (11) together with only traces of the isomeric hydroxycyclopentanone (12) and 35% of the cyclopentanediols (13). The mixture could easily be separated by column chromatography to furnish 60% of pure (11).

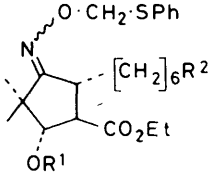




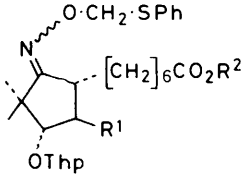
(13)

(11) R = 

(12) R = 



(14) R^1 = H, R^2 = CO_2Et
(15) R^1 = Thp, R^2 = CO_2Et
(16) R^1 = Thp, R^2 = CH_2OH
(17) R^1 = Thp, R^2 = CO_2K



(18) R^1 = CH_2·OH, R^2 = K
(19) R^1 = CH_2·OH, R^2 = Me
(20) R^1 = CH_2·OH, R^2 = Et
(21) R^1 = CHO, R^2 = Me

Introduction of the allylic alcohol side chain, the next step in the sequence, called for selectivity between the ester group on the ring and that at the end of the chain. The most attractive route seemed to be the procedure described by Finch *et al.*,[14] *i.e.* protection of the C-2 hydroxy and the C-4 carbonyl functions and subsequent reduction of the ring ester group with borohydride. Reaction of (11) with phenylthiomethoxyamine hydrochloride [14] in pyridine gave the oxime (14) as a 1 : 1 mixture of *E*- and *Z*-isomers. The hydroxy-group was subsequently protected by formation of the tetrahydropyranyl ether (15). Unfortunately, upon treatment of (15) with sodium borohydride, only the sterically less hindered ester group at the end of the chain was slowly reduced, leading to the alcohol (16) instead of the desired alcohol (20). Apparently assistance of the *trans*-tetrahydropyranyloxy-group in the reduction of the ring ester, as postulated by Finch *et al.*,[14] is not operative in our case because of steric hindrance by the two methyl groups. However, selective hydrolysis of the less hindered ester function in (15) with 1 equiv. of potassium hydroxide in aqueous ethanol, followed by reduction of the remaining ester function of the potassium salt (17) with lithium borohydride in diglyme at 100 °C and reaction of the resulting crude carboxylate salt (18) with methyl iodide in hexamethylphosphoric triamide,[15] gave the ester alcohol (19) in 30% yield from (11).

Moffatt oxidation of the alcohol (19) with 1-cyclohexyl-3-(2-morpholinoethyl)carbodi-imide methotoluene-*p*-sulphonate and treatment of the crude aldehyde (21), thus obtained, with the sodium salt of dimethyl 2-oxoheptylphosphonate [16] afforded the enone (22), characterized as the free alcohol (23). Reduction of enone (22) with zinc borohydride in 1,2-dimethoxyethane [16] produced a mixture of enols (24). Subsequent hydrolysis with acetic acid in aqueous tetrahydrofuran and chromatographic separation gave the C-15 epimers (25) [31% yield from (19)] and (29) [28% yield from (19)]. The 15α-hydroxy-configuration was assigned to the more polar epimer by analogy with the chromatographic behaviour of similar derivatives of PGE_1.[14]

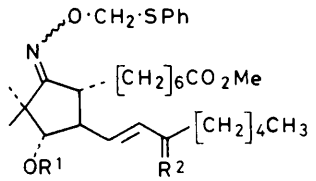
The phenylthiomethyloxime was cleaved to give the unsubstituted oxime in two steps. Treatment of (25) with a mixture of mercury(II) chloride, mercury(II) oxide, and potassium acetate in acetic acid furnished the acetoxymethyloxime (26), which was hydrolysed with potassium carbonate to afford the oxime (27) in 65% yield. The final step, removal of the oxime group, proceeded in 40% yield *via* nitrosation with sodium nitrite in aqueous acetic acid, confirming the poor results of Finch *et al.*[14] for this step. Treatment of the oxime (27) with aqueous titanium trichloride according to Timms' procedure,[17] however, afforded (±)-10,10-dimethyl-PGE_1 methyl ester (28) in quantitative yield. By the same sequence, phenylthiomethyloxime (29) was converted into (±)-10,10-dimethyl-15-*epi*-PGE_1 methyl ester (32) in 75% yield.

The relative polarities on silica gel of (28) and (32), as

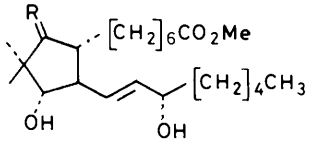
* An investigation into the reduction of (9) and the elucidation of the structure of the reduction products is described in ref. 13.

[11] O. G. Plantema, H. de Koning, and H. O. Huisman, (*a*) *Tetrahedron Letters*, 1975, 2945; (*b*) unpublished data.
[12] J. E. McMurry and G. B. Wong, *Synth. Comm.*, 1972, **2**, 389.
[13] O. G. Plantema, H. de Koning, and H. O. Huisman, *Rec. Trav. chim.*, 1977, **96**, 129.
[14] N. Finch, L. Della Vecchia, J. J. Fitt, R. Stephani, and I. Vlattas, *J. Org. Chem.*, 1973, **38**, 4412.
[15] J. E. Shaw, D. C. Kunerth, and J. J. Sherry, *Tetrahedron Letters*, 1973, 689.
[16] E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *J. Amer. Chem. Soc.*, 1969, **91**, 5675.
[17] G. H. Timms and E. Wildsmith, *Tetrahedron Letters*, 1971, 195.

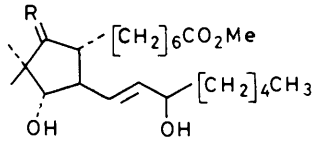
compared with those of PGE_1 methyl ester and its 15-epimer,[18] confirmed the configurational assignment at C-15. After the completion of this work, Hamon *et al.*[19] published a different sequence leading to (28) and (32), but only (28) showed very weak agonistic activity while



(22) R^1 = Thp, R^2 = O
(23) R^1 = H, R^2 = O
(24) R^1 = Thp, R^2 = OH, H



(25) R = NO·CH$_2$·SPh
(26) R = NO·CH$_2$·OAc
(27) R = N–OH
(28) R = O



(29) R = NO·CH$_2$·SPh
(30) R = NO·CH$_2$·OAc
(31) R = N–OH
(32) R = O

(32) was inactive, thus providing biological support for the assignment at C-15.

EXPERIMENTAL

I.r. spectra were taken on an Unicam SP 200 or a Perkin-Elmer 125 instrument. ^{1}H N.m.r. spectra were recorded on a Varian HA-100 and ^{13}C n.m.r. spectra on a Varian XL-100-15 FT instrument at 25.2 MHz with proton noise decoupling; chemical shifts are given in the δ scale, relative to internal tetramethylsilane. Mass spectra were obtained with an A.E.I. MS-9 instrument. Elemental analyses were performed by Mr. H. Pieters of this laboratory. R_F Values are quoted for Merck silica gel GF 254 t.l.c. plates of 0.25 mm thickness, eluted with cyclohexane–ethyl acetate (1 : 1), unless otherwise stated.

Ethyl 3,3-*Dimethyl*-2,4-*dioxocyclopentanecarboxylate* (2).—To a stirred suspension of sodium hydride (36 g, 1.5 mol) in dibutyl ether (500 ml) and ethyl diethoxyphosphorylformate (150 g, 0.71 mol) was added in portions, under nitrogen, 2,2-dimethylcyclopentane-1,3-dione (87 g, 0.69 mol). The reaction was initiated by adding a few drops of ethanol and stirring was continued at 50 °C. After 3 h, when hydrogen evolution had stopped, the mixture was cooled and poured into a mixture of dry ethanol (800 ml) and sulphuric acid (80 g). After stirring for 30 min the mixture was poured into ice–water and extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* and the residue was distilled to afford the *ester* (2) (89 g, 65%) b.p. 69—71° at 0.04 Torr, $\nu_{max.}$ ($CHCl_3$) 1 750 (C=O), 1 725 (C=O), 1 660, and 1 630 cm^{-1} (β-oxo-ester); δ($CDCl_3$) 1.16, 1.18, and 1.20 (3 × s, CH_3), 1.28 and 1.29 (2 × t, *J* 7 Hz, ester CH_3), 2.96 (dd, *J* 17.5 and 11.0 Hz, H-5 of keto form), 3.12 (s, 2 × H-5 of enol form), 3.27 (dd, *J* 17.5 and 7.5 Hz, H-5 of keto form), 3.87 (dd, *J* 11 and 7.5 Hz, H-1 of keto form), and 4.25 (m, ester CH_2); *m/e* 198 (M^+), 170, 153, and 70 (base peak) (Found: C, 60.3; H, 7.3. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.1%).

Potassium Salt of Ethyl 3,3-*Dimethyl*-2,4-*dioxocyclopentanecarboxylate* (3).—The oxo-ester (2) (5.0 g, 25.2 mmol) was added within 5 min at −5 °C to a stirred solution of potassium hydroxide (1.41 g, 25.2 mmol) in the minimum amount of ethanol–water (30 : 1). The mixture was stirred for 5 min at 0 °C and then cold ether (200 ml) was added. The precipitate was filtered off, washed with cold dry ethanol and ether, and dried *in vacuo* at 60 °C to yield the salt (3) (5.6 g, 94%), $\nu_{max.}$ (KBr) 1 730 and 1 655 cm^{-1}; δ[$(CD_3)_2SO$] 0.90 (s, 2 × CH_3), 1.14, (t, *J* 7 Hz, ester CH_3), 2.99 (s, 5-H_2), and 3.89 (q, *J* 7 Hz, ester CH_2).

Ethyl 1-(6-*Ethoxycarbonylhexyl*)-3,3-*dimethyl*-2,4-*dioxocyclopentanecarboxylate* (5).—A solution of the alkyne (6) in ethanol was hydrogenated over 10% Pd–C in a Parr apparatus at 4 atm for 2 h to furnish the ester (5) in quantitative yield, δ($CDCl_3$) 1.13 and 1.20 (2 × s, CH_3), 1.23 (t, *J* 7 Hz, ester CH_3), 2.27 (t, *J* 7 Hz, CH_2CO_2Et), 2.72 and 3.29 (2 × d, *J* 19 Hz, 5-H_2), and 4.08 and 4.15 (2 × q, *J* 7 Hz, ester CH_2).

Ethyl 1-(6-*Ethoxycarbonylhex*-2-*ynyl*)-3,3-*dimethyl*-2,4-*dioxocyclopentanecarboxylate* (6).—Ethyl 7-bromohept-5-ynoate (32 g, 0.14 mol) was added to a solution of the potassium salt (3) (28.9 g, 0.122 mol) in dry dimethyl sulphoxide (150 ml) and the mixture was stirred overnight at room temperature. Then it was poured into ice–water and extracted several times with n-hexane. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (elution with cyclohexane–ethyl acetate, 9 : 1) to give the *alkyne* (6) (35.0 g, 82%), δ($CDCl_3$) 1.18 and 1.24 (2 × s, CH_3), 1.23 and 1.24 (2 × t, *J* 7 Hz, ester CH_3), 2.33 (t, *J* 7 Hz, CH_2CO_2Et), 2.71 and 3.04 (2 × dt, *J* 16.5 and 2.5 Hz, C·CH_2·C≡C), 3.15 (s, 5-H_2), and 4.10 and 4.17 (2 × q, *J* 7 Hz, ester CH_2) (Found: C, 65.2; H, 7.5. $C_{19}H_{26}O_6$ requires C, 65.1; H, 7.5%).

4-(6-*Ethoxycarbonylhexyl*)-2,2-*dimethylcyclopentane*-1,3-*dione* (8).—(i) A solution of the potassium salt (3) (2.4 g, 10 mmol) and methyl 7-bromoheptanoate (2.8 g, 12 mmol) in dry dimethyl sulphoxide (25 ml) was stirred overnight and worked up as described above to give a mixture of compounds (4) and (10) in the ratio 7 : 3 in 90% yield; $\nu_{max.}$ ($CHCl_3$) 1 740 (C=O), 1 725 (CO_2R), and 1 710 and 1 620 cm^{-1} (C=C–CO_2Et); δ($CDCl_3$) 2.70 and 3.30 [2 × d, *J* 19 Hz, 5-H_2 in (4)], 3.26 [s, 5-H_2 in (10)], and 4.30 [t, *J* 7 Hz, CH_2·O·C=C in (10)].

The crude mixture of *C*- and *O*-alkylated products was refluxed in 3M-hydrochloric acid (50 ml) for 16 h. After cooling, water was added and the mixture was extracted with ether. The organic layer was extracted with M-potassium carbonate. Evaporation of the remaining ethereal solution gave the dione (1) (0.29 g). The potassium carbonate extract was acidified with dilute hydrochloric acid and extracted with ether. This extract was washed with

[18] T. O. Oesterling, W. Morozowich, and T. J. Roseman, *J. Pharm. Sci.*, 1972, **61**, 1861.

[19] A. Hamon, B. Lacoume, G. Pasquet, and W. R. Pilgrim, *Tetrahedron Letters*, 1976, 211, 1340.

brine, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude acid (7), which could be purified by distillation or crystallisation from ether, affording pure *acid* (7) in 50% yield from (3), b.p. 140—155° at 0.01 Torr, m.p. 45—46°, $\nu_{max.}$ ($CHCl_3$) 3 600—2 500 (CO_2H), 1 760 (C=O), and 1 720 cm^{-1} (CO_2H); δ($CDCl_3$) 1.10 and 1.13 (2 × s, CH_3), 2.25 (t, *J* 7 Hz, CH_2CO_2H), and 9.0br (s, CO_2H) (Found: C, 66.0; H, 8.7. $C_{14}H_{22}O_4$ requires C, 66.1; H, 8.7%).

A solution of the crude acid (7) in dichloromethane was treated with an excess of diazoethane in dichloromethane. After 15 min the solvent was evaporated off and the residue was distilled *in vacuo* to furnish the ethyl ester (8) [50% from (3)].

(ii) A solution of the diester (5) (7.1 g, 20 mmol) in dry dimethylformamide (50 ml) was refluxed with dry lithium iodide (6 g) until evolution of carbon dioxide had ceased. After cooling, the mixture was partitioned between water and ether and the organic layer was washed with water and dried ($MgSO_4$). Distillation afforded the ester (8) in 84% yield, b.p. 140—144° at 0.01 Torr, m.p. *ca.* 20°, $\nu_{max.}$ ($CHCl_3$) 1 755 (C=O) and 1 720 cm^{-1} (CO_2Et); δ($CDCl_3$) 1.11 and 1.14 (2 × s, CH_3), 1.25 (t, *J* 7 Hz, ester CH_3), 2.28 (t, *J* 7 Hz, CH_2CO_2Et), and 4.12 (q, *J* 7 Hz, ester CH_2).

Ethyl 5-(6-Ethoxycarbonylhexyl)-3,3-dimethyl-2,4-dioxocyclopentanecarboxylate (9).—Ethoxycarbonylation of (8) with ethyl diethoxyphosphorylformate for 16 h at 60 °C, according to the procedure described for (2), yielded the *diester* (9) (70%), b.p. 160—165° at 0.01 Torr, $\nu_{max.}$ ($CHCl_3$) 1 740 (C=O), 1 720, 1 660, and 1 620 cm^{-1} (β-oxo-ester); δ($CDCl_3$) 1.15—1.30 (m, 4 × CH_3), 2.28 (t, *J* 7 Hz, CH_2CO_2-Et), and 4.2 (m, CH_2 of 2 esters); *m/e* 354 (M^+), 309, 70, and 44 (base peak) (Found: C, 64.5; H, 8.5. $C_{19}H_{30}O_6$ requires C, 64.4; H, 8.55%).

Catalytic Hydrogenation of the Diester (9).—Hydrogenation of the diketone (9) (1.77 g, 5 mmol) over Adams catalyst in acetic acid (10 ml) was carried out in a Parr apparatus at 4 atm. After shaking for 16 h, the catalyst was removed and the solvent was evaporated off *in vacuo*. The residue was chromatographed on silica gel (elution with cyclohexane–ethyl acetate, 4 : 1) to give a mixture (50 mg) of (12) (t.l.c. R_F 0.35) and (11) (R_F 0.34), a sample of pure (11) (1.06 g, 60%), and a mixture (250 mg) of diols (13) (R_F 0.29—0.23). The mixture of (11) and (12) was treated with chlorotrimethylsilane and hexamethyldisilazane in pyridine,[20] producing the trimethylsilyl ethers, which were separated by preparative g.l.c. (SE 30; 4 m; 260 °C). Hydrolysis of the corresponding silyl ether gave pure (12).

Ethyl 5-(6-Ethoxycarbonylhexyl(2-hydroxy-3,3-dimethyl-4-oxocyclopentane carboxylate (11) showed $\nu_{max.}$ (CCl_4) 3 600—3 400 (OH, dependent on concentration) and 1 740—1 730 cm^{-1} (C=O, CO_2Et); δ($CDCl_3$) 0.94 and 1.12 (2 × s, CH_3), 2.27 (t, *J* 7 Hz, CH_2CO_2Et), 2.52 (m, H-5), 2.73 (dd, $J_{1,2}$ 9.0 Hz, $J_{1,5}$ 11.2 Hz, H-1), and 4.09 (d, $J_{1,2}$ 9 Hz, H-2) (Found: C, 63.9; H, 9.0. $C_{19}H_{32}O_6$ requires C, 64.0; H, 9.05%). The *epimer* (12) showed $\nu_{max.}$ (CCl_4) 3 500 (OH, independent of concentration), 1 740—1 730 (C=O, CO_2Et), and 1 715 cm^{-1} (CO_2Et); δ($CDCl_3$) 0.95 and 1.14 (2 × s, CH_3), 2.27 (t, *J* 7 Hz, CH_2CO_2Et), 2.83 (m, H-5), 2.99 (dd, $J_{1,2}$ 3.6, $J_{1,5}$ 11.4 Hz, H-1), and 4.14(d, $J_{1,2}$ 3.6 Hz, H-2.

The O-Phenylthiomethyloxime (14).—Phenylthiomethoxyamine hydrochloride (5.0 g, 26 mmol) was added to a solution of the ketone (11) (3.50 g, 9.83 mmol) in dry pyridine (50 ml) and the mixture was stirred for 7 days at room temperature. The solvent was removed *in vacuo* and the residue was partitioned between ether and water. The ether layer was shaken repeatedly with 0.5M-hydrochloric acid, and with water, and then dried ($MgSO_4$). Column chromatography (silica gel; cyclohexane–ethyl acetate, 9 : 1) afforded the *oxime* (14) (4.10 g, 85%), t.l.c. R_F 0.35; $\nu_{max.}$ ($CHCl_3$) 3 500 (OH), 1 720 (CO_2Et), and 1 570 cm^{-1} (Ph); δ($CDCl_3$) 2.28 and 2.31 (2 × t, *J* 7 Hz, CH_2CO_2Et), 3.9 (m, CHOH), 4.1 (m, 2 × CH_2 of ester), 5.47 and 5.49 (2 × s, OCH_2S), and 7.2—7.6 (aromatic H) (Found: C, 63.1; H, 7.9; N, 3.0; S, 6.7. $C_{26}H_{39}NO_6S$ requires C, 63.25; H, 8.0; N, 2.85; S, 6.5%).

The Tetrahydropyranyl Ether (15).—A solution of the alcohol (14) (4.0 g, 8.1 mmol), dihydropyran (6.0 g), and toluene-*p*-sulphonic acid (5 mg) in dry dichloromethane was stirred overnight at room temperature and then concentrated *in vacuo*. The residue was diluted with ether and washed with saturated aqueous sodium hydrogen carbonate and water. After drying, the solvent was removed and the residue chromatographed on silica gel (cyclohexane–ethyl acetate, 9 : 1) to give the ether (15) (4.2 g, 90%), t.l.c. R_F 0.45; $\nu_{max.}$ ($CHCl_3$) 1 720 (CO_2Et) and 1 570 cm^{-1} (Ph).

The Cyclohexylmethanol (19).—A solution of the diester (15) (650 mg, 1.12 mmol) in aqueous 80% ethanolic potassium hydroxide (10 ml; 0.125M) was stirred for 16 h at room temperature. Following removal of most of the ethanol *in vacuo*, the residue was diluted with water and extracted with ether several times. The aqueous solution was evaporated to dryness *in vacuo*, with the temperature kept below 30 °C, to give the crude potassium salt (17) (510 mg, 77%).

This was dissolved in dry diglyme (25 ml), lithium borohydride (110 mg, 5 mmol) was added, and the mixture was stirred for 24 h at 100 °C under nitrogen. Following evaporation *in vacuo*, the excess of hydride was decomposed with ice–water. The aqueous solution of the carboxylate (18), thus obtained, was stirred for 2 h with hexamethylphosphoric triamide (10 ml) and methyl iodide (4 ml). Water was then added and the mixture was extracted with ether several times. The combined extracts were washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over silica gel (cyclohexane–ethyl acetate, 3 : 1) to afford the ester alcohol (19) [225 mg, 39% from (15)], t.l.c. R_F 0.40; $\nu_{max.}$ ($CHCl_3$) 3 450 (OH), 1 720 (CO_2Me), and 1 570 cm^{-1} (Ph).

The Enone (22).—The alcohol (19) (245 mg, 0.47 mmol) was dissolved in dry dimethyl sulphoxide (3 ml) and benzene (3 ml) containing pyridine (0.07 ml) and trifluoroacetic acid (0.04 ml). Then 1-cyclohexyl-3-(2-morpholinoethyl)carbodi-imide methotoluene-*p*-sulphonate (1.0 g) was added and the mixture was stirred for 24 h at room temperature. After addition of water, the mixture was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and concentrated *in vacuo* to give the crude aldehyde (21) (225 mg, 92%), t.l.c. R_F 0.50.

Dimethyl 2-oxoheptylphosphonate (200 mg, 0.9 mmol) was added to a suspension of sodium hydride (20 mg, 0.8 mmol) in dry tetrahydrofuran (4 ml) under nitrogen. After stirring for 5 min at room temperature, the crude aldehyde (21) in tetrahydrofuran (1 ml) was added and stirring was continued for another 1 h at room temperature and then for 1 h at 40 °C. After cooling and addition of water, the mixture was extracted with ether. The extract

[20] A. E. Pierce, 'Silylation of Organic Compounds,' Pierce Chemical Company, Rockford, Illinois, 1968, p. 20.

was washed with water, dried ($MgSO_4$), and concentrated *in vacuo*. Column chromatography on silica gel (cyclohexane–ethyl acetate, 9 : 1) gave the enone (22) [230 mg, 80% from (19)], t.l.c. R_F 0.55; $\nu_{max.}$ ($CHCl_3$) 1 720 (CO_2Me), 1 690, 1 660 and 1 620 (enone), and 1 580 cm^{-1} (Ph).

Hydrolysis of the Ether (22) *to the Alcohol* (23).—A solution of the tetrahydropyranyl ether (22) (225 mg) in a mixture (5 ml) of acetic acid, water, and tetrahydrofuran (6 : 3 : 1) was stirred for 3 h at 50 °C. The solvent was evaporated off *in vacuo* and the residue was purified on a silica gel column (cyclohexane–ethyl acetate, 4 : 1) to give the *alcohol* (23) (145 mg, 75%), t.l.c. R_F 0.40 and 0.42 (*E*- and *Z*-oxime); $\nu_{max.}$ ($CHCl_3$) 3 500 (OH), 1 720 (CO_2Me), 1 690, 1 660 and 1 620 (enone), and 1 580 cm^{-1} (Ph); $\delta(CDCl_3)$ 0.89 (t, *J* 7 Hz, 19-CH_3), 2.23 and 2.27 (2 × t, *J* 7 Hz, CH_2CO_2Me), 2.52 (t, *J* 7 Hz, CH_2CO), 3.63 (s, CO_2CH_3), 5.42 and 5.47 (2 × s, OCH_2S), 6.20 and 6.23 (2 × d, *J* 15.5 Hz, 14-H), 6.68 (dd, *J* 15.5 and 7.5 Hz, 13-H), and 7.2—7.5 (m, C_6H_5) (Found: C, 67.8; H, 8.7; N, 2.7; S, 5.9. $C_{30}H_{45}NO_5S$ requires C, 67.75; H, 8.55; N, 2.65; S, 6.05%).

Reduction of the Enone (22) *to the Enols* (24).—A solution of the enone (22) (150 mg, 0.24 mmol) in dry 1,2-dimethoxyethane (2 ml) was added, under nitrogen, to a clear solution of zinc borohydride (0.8 ml; 0.5M) [prepared by stirring sodium borohydride (0.95 g) and zinc chloride (1.7 g) in dry dimethoxyethane (25 ml) for 16 h at 10 °C]. The mixture was stirred for 3 h at room temperature and then saturated aqueous sodium hydrogen tartrate was added dropwise until no further evolution of gas was observed. The solution was extracted with dichloromethane and the organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude mixture of 15-epimeric enols (24) (130 mg, 87%), t.l.c. R_F 0.40 and 0.45, which was used in the next step without further purification.

Hydrolysis of the Ether (24) *to the Diols* (25) *and* (29).—The crude mixture of enols (24) (130 mg) was hydrolysed, according to the procedure described for (23). Column chromatography on silica gel (cyclohexane–ethyl acetate, 2 : 1) afforded the diols (25) [50 mg, 39% from (22)] and (29) [45 mg, 35% from (22)]. Compound (25) showed t.l.c. R_F 0.20; $\nu_{max.}$ ($CHCl_3$) 3 500 (OH), 1 720 (CO_2Me), and 1 580 cm^{-1} (Ph); $\delta(CDCl_3)$ 0.87 (t, *J* 7 Hz, 19-CH_3), 2.22 and 2.28 (2 × t, *J* 7 Hz, CH_2CO_2Me), 3.30 and 3.34 (2 × d, *J* 9.5 Hz, 11-H), 3.63 (s, CO_2CH_3), 4.00 (m, 15-H), 5.40 and 5.44 (2 × s, OCH_2S), 5.50 (m, 13- and 14-H), and 7.1—7.5 (m, C_6H_5). Compound (29) showed t.l.c. R_F 0.25; $\nu_{max.}$ ($CHCl_3$) 3 500 (OH), 1 720 (CO_2Me), and 1 580 cm^{-1} (Ph); $\delta(CDCl_3)$ 0.87 (t, *J* 7 Hz, 19-CH_3), 2.25 (m, CH_2CO_2Me), 3.30 and 3.35 (2 × d, *J* 10 Hz, 11-H), 3.63 (s, CO_2Me), 4.08 (m, 15-H), 5.40 and 5.44 (2 × s, OCH_2S), 5.55 (m, 13- and 14-H), and 7.1—7.5 (m, C_6H_5).

The Acetoxymethyloxime (26).—The phenylthiomethyloxime (25) (50 mg) was dissolved in acetic acid (5 ml) and a solution of mercury(II) chloride (230 mg), potassium acetate (210 mg), and mercury(II) oxide (100 mg) in acetic acid (10 ml) was added. The mixture was stirred for 1 h and diluted with acetone, and then hydrogen sulphide was bubbled in until a black precipitate formed. The mixture was filtered and the filtrate was evaporated *in vacuo*. Following addition of water, the mixture was extracted with ether. The ethereal extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give the crude acetoxymethyloxime (26) (40 mg), t.l.c. R_F 0.40 (silica gel; ethyl acetate); $\delta(CDCl_3)$ 2.04 (s, CH_3CO), 3.63 (CO_2Me), and 5.60 (m, 4 H).

The Oxime (27).—The crude acetoxymethyloxime (26) (40 mg) was dissolved in methanol (5 ml) and aqueous 10% potassium carbonate (0.5 ml) was added. After stirring for 45 min, methanol was evaporated off *in vacuo* at room temperature. Water was added to the residue, which was then extracted with ether. The extract was washed with water, dried ($MgSO_4$), and evaporated *in vacuo* to give the crude oxime (27) (25 mg), t.l.c. R_F 0.28 and 0.35 (silica gel; ethyl acetate); $\delta(CDCl_3)$ 3.64 (s, CO_2CH_3), 4.10 (m, 15-H), and 5.6 (m, 13- and 14-H).

(±)-10,10-*Dimethyl-PGE*$_1$ *Methyl Ester* (28).—The crude oxime (27) (25 mg) was dissolved in dioxan (1 ml) and 50% aqueous acetic acid (1 ml). Then, under nitrogen, ammonia (0.25 g) was added, followed by titanium trichloride (0.5 ml; 10% solution in 4% hydrochloric acid). The mixture was stirred for 16 h at room temperature and then partitioned between water and ether. The organic layer was washed with aqueous sodium hydrogen carbonate, and with water, dried ($MgSO_4$) and evaporated *in vacuo* to give the crude prostaglandin analogue (28) [25 mg, 65% from (25)]. Column chromatography of the crude product through silica gel (cyclohexane–ethyl acetate, 3 : 2) afforded pure *product* (28) (19 mg, 51%), t.l.c. R_F 0.37 (silica gel; ethyl acetate); $\nu_{max.}$ ($CHCl_3$) 3 500 (OH), 1 720 (CO_2Me), and 1 600 cm^{-1} (C=C); $\delta(CDCl_3)$ 0.89 (t, *J* 7 Hz, 19-CH_3), 0.92 and 1.11 (2 × s, CH_3), 2.28 (t, *J* 7 Hz, CH_2CO_2Me), 3.59 (d, *J ca.* 8 Hz, 11-H), 3.65 (s, CO_2CH_3), 4.16 (m, 15-H), and 5.63 (m, 13- and 14-H); $\delta_C(CDCl_3)$ 17.4 and 22.6 (2 × 10-CH_3), 48.9 (C-10), 50.3 (C-12), 52.6 (C-8), 72.9 (C-15), 80.5 (C-11), 132.4 (C-13), 136.5 (C-14), and 212.8 (C-9); *m/e* 378 ($M^+ - H_2O$), 360 ($M - 2H_2O$), 325 ($M - C_5H_{11}$), 307 ($M - H_2O - C_5H_{11}$), and 279 ($M - H_2O - C_5H_{11}CO$).

(±)-10,10-*Dimethyl*-15-epi-*PGE*$_1$ *Methyl Ester* (32).—Following the procedures described above, the phenylthiomethyloxime (29) (45 mg) was converted *via* (30) (40 mg; R_F 0.50) and (31) (30 mg; R_F 0.37 and 0.43) into crude (32) [25 mg, 75% from (29)]. Column chromatography afforded the pure 15-epi-*prostaglandin analogue* (32) (14 mg, 42%), t.l.c. R_F 0.47 (silica gel; ethyl acetate); i.r., ^1H n.m.r., and mass spectral data similar to those of (28).

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