Prostaglandins. Part 4.[1] Synthesis of (±)-11-Deoxyprostaglandins from 2-(ω-Hydroxyheptyl)cyclopent-2-enones

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Conjugate nitrile addition to 2-(7-hydroxyheptyl)cyclopent-2-enone (IIIa) and subsequent elaboration *via* the aldehydes [(VIa), (Xa)] affords a convenient direct route to (±)-11-deoxyprostaglandins of the E_1 and F_1 series. Syntheses of (±)-10-methyl- and (±)-α-nor-11-deoxyprostaglandins are also described.

TERMINALLY substituted 2-alkylcyclopent-2-enones have proved valuable intermediates for the synthesis of prostaglandins (PGs), since they readily afford the prostanoic acid skeleton by conjugate addition reactions. We have developed a route to 11-deoxyprostaglandins based upon nitrile addition to 2-(7-hydroxyheptyl)cyclopent-2-enone (IIIa) with subsequent elaboration *via* the aldehydes [(VIa), (Xa)] and Wittig coupling.[1,2] We

[1] Part 3, M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *Tetrahedron Letters*, 1974, 585.

[2] M. P. L. Caton, E. C. J. Coffee, and G. L. Watkins, *Tetrahedron Letters*, 1972, 773.

here describe full details of this work and its adaptation to the synthesis of 11-deoxyprostaglandins E_1, $F_{1\alpha}$, $F_{1\beta}$ and certain derivatives and analogues.

The value of this approach to 11-deoxyprostaglandins was enhanced by our finding that the enone (IIIa) can be prepared by isomerisation of the corresponding hydroxyalkylidenecyclopentanone (IIa), which is readily available from the reaction of cyclopentanone morpholine enamine and 7-hydroxyheptanal (Ia). Hydroxy was chosen as the terminal substituent on the grounds that this group does not require protection during the nitrile-to-aldehyde stages, and because it can be oxidised conveniently to the required carboxylic acid later in the reaction sequence.

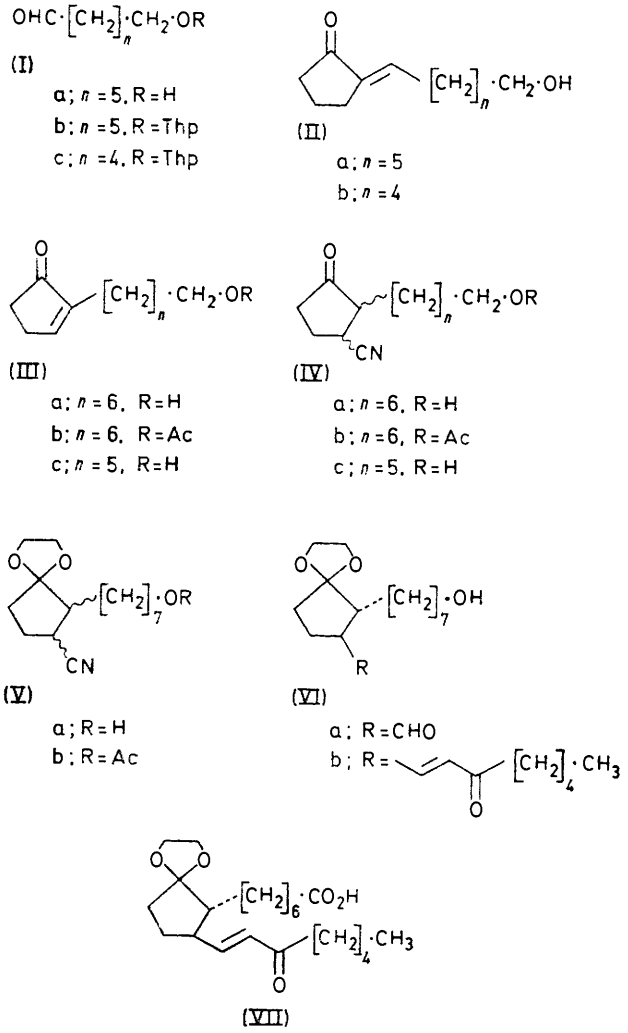
7-Hydroxyheptanal (Ia) can be made in high yield by cleavage of commercially available aleuritic acid (9,10,16-trihydroxypalmitic acid) with periodate, or, less satisfactorily, from 6-hydroxyhexanonitrile by treatment with di-isobutylaluminium hydride. The latter reaction was more easily performed on the tetrahydropyranyl (Thp) ether; this minimised the formation of insoluble intermediates. Both the hydroxy-aldehyde (Ia) and its Thp ether (Ib) afforded the enone (IIIa) in overall yields of 50—60%, it being unnecessary to isolate the intermediate exocyclic enone (IIa). Isomerisation of the double bond [(IIa) ⟶ (IIIa)] could be effected in various acidic media, but choice of reagent and conditions such that the formation of resinous by-products was minimal, was critical. Satisfactory results were obtained by heating with concentrated hydrochloric acid in butan-1-ol at 90 °C for 2.5 h.

The enone (IIIa) was also prepared, as its acetoxy-derivative (IIIb), by bromination of the enol acetate of 2-(7-acetoxyheptyl)cyclopentanone and then dehydrobromination with base. This procedure, however, involved several steps from commercially available material, and was inferior to the hydroxy-aldehyde route in overall yield.

The reaction of the enone (IIIa) with acetone cyanohydrin in the presence of base afforded the nitrile (IVa) as a mixture of *cis*- and *trans*-isomers. For the synthesis of (±)-11-deoxy-PGE_1 the acetal (Va) of this mixture was converted with di-isobutylaluminium hydride into the aldehyde (VIa), which was shown by g.l.c. to be essentially a single component. We have assumed that the latter has the *trans*-configuration and that this disposition was maintained throughout subsequent steps to the final products (VIII).[1,†] The acetoxy-enone (IIIb) could be utilised for the synthesis of the acetal (Va) by converting it *via* the nitrile (IVb) into the acetoxy-acetal (Vb) and then removing the acetoxy-group.

The aldehyde (VIa) underwent some decomposition on distillation and was best carried forward in the crude form. For the conversion (VIa) ⟶ (VIb) we now prefer to use the sodio-derivative of dimethyl 2-oxoheptylphosphonate rather than 2-oxoheptylidenetriphenylphosphorane, as described in our preliminary report,[1,2] since the latter gives rise to phosphorus-containing by-products which are difficult to eliminate. The resulting enone (VIb) was oxidised to the carboxylic acid (VII) with chromium trioxide and sulphuric acid in dimethylformamide at 0 °C.

The synthesis was completed by reduction with borohydride and then acidic hydrolysis. When the reduction was carried out with sodium borohydride in aqueous sodium hydroxide, a substantial amount of conjugate reduction took place giving rise to the dihydro-compounds (IXa and b) (as estimated from n.m.r. and mass spectra), but this could be largely avoided by using potassium borohydride in a citrate buffer at pH 8 as

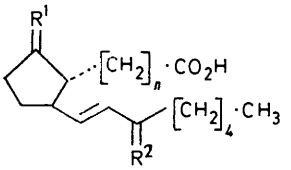


described by Miyano.[3] Purification of the final products and separation of (±)-11-deoxy-PGE_1 (VIIIa) from its C-15 epimer (VIIIb) were effected by column chromatography with ethyl acetate–toluene (1 : 4) as eluant. (±)-11-Deoxy-PGE_1 (VIIIa), the slower moving component, was recrystallised from ether–light petroleum

† Further evidence for these assignments will be presented in a forthcoming paper.

[3] M. Miyano, C. R. Dorn, and R. A. Müeller, *J. Org. Chem.*, 1972, **37**, 1810.

(b.p. 40—60°) (its m.p. agreed with literature values). The epimers (VIIIa and b) could also be separated by



(VIII)

a; R^1=O, R^2=  , n = 6

b; R^1=O, R^2=  , n = 6

c; R^1=  , R^2=  , n = 6

d; R^1= , R^2=  , n = 6

e; R^1=  , R^2=  , n = 6

f; R^1=  , R^2= , n = 6

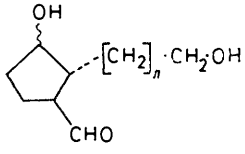
g; R^1 = R^2 = O, n = 6

h; R^1 = R^2 = O, n = 5

(IX)

a; R = 

b; R = 



(X)

a; n = 6

b; n = 5

preparative t.l.c. [ethyl acetate–cyclohexane–formic acid (40 : 40 : 1); this system was also useful for an analytical t.l.c. check on the purity of the final products, although it does not distinguish between the olefin (VIIIb) and the dihydro-compounds (IXa and b)].

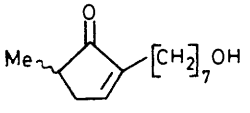
The dihydro-compounds (IXa and b) [4] could be prepared, if required, by catalytic reduction of the olefins (VIIIa and b) over 5% palladium–charcoal. We have been unable to distinguish the C-15 epimers (IXa and b) from each other by chromatography; separation must therefore be carried out before the hydrogenation stage if single epimers are required.

11-Deoxyprostaglandins of the F_1 series were obtained by borohydride reduction of the E_1 compounds. Reduction of (±)-11-deoxy-PGE_1 (VIIIa) with potassium borohydride gave a mixture of (±)-11-deoxy-$PGF_{1\alpha}$ * (VIIIc) and (±)-11-deoxy-$PGF_{1\beta}$ * (VIIId); similarly (±)-15-*epi*-11-deoxy-PGE_1 (VIIIb) afforded the epimers (VIIIe) * and (VIIIf).* The $F_{1\alpha}$ compounds (VIIIc and e) could be prepared stereospecifically by carrying out these reductions with lithium tri-s-butylborohydride (L-Selectride).[5]

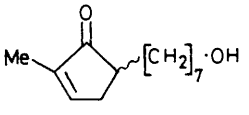
An alternative route to the $F_{1\alpha}$ compounds was available from reduction by 'Selectride' of the dioxo-acid (VIIIg), which afforded a mixture of the C-15 epimers (VIIIc and e). Since the dioxo-acid (VIIIg) can be made directly from the nitrile (IVa) by reduction with di-isobutylaluminium hydride, Wittig elaboration of the resulting aldehyde (Xa), and then oxidation, this procedure affords a simple seven-step overall route to these F_α compounds, which avoids the use of protecting groups.

(±)-α-Nor-11-deoxyprostaglandins [*e.g.* (VIIIh)] were synthesised from the aldehyde (Ic), which was prepared by oxidation of the mono-Thp ether of hexane-1,6-diol with pyridinium chlorochromate.

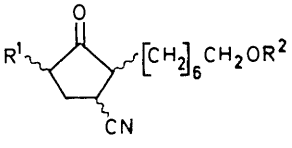
An attempt to prepare 10-methyl analogues (XV) of 11-deoxyprostaglandins by first constructing the enone (XI) was complicated by the fact that the latter compound, under the acidic reaction conditions, was partially isomerised to the enone (XII). However, the 10-methyl



(XI)



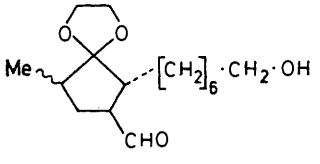
(XII)



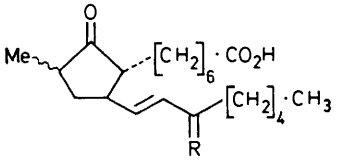
(XIII)

a; R^1=EtO·CO·CO, R^2=Thp

b; R^1=Me, R^2=H



(XIV)



(XV)

a; R = 

b; R = 

[4] J. F. Bagli and T. Bogri, *J. Org. Chem.*, 1972, **37**, 2132.

[5] C. A. Brown, *J. Amer. Chem. Soc.*, 1973, **95**, 4100.

* M.p.s agreed with literature values.

derivatives could be prepared unambiguously from the Thp ether of the hydroxy-nitrile (IVa), which with diethyl oxalate and sodium methoxide in benzene afforded the oxo-ester (XIIIa). The latter on treatment with methyl iodide in acetone and then hydrolysis with perchloric acid in ethanol afforded the nitrile (XIIIb) as a mixture of diastereoisomers. Completion of the synthesis *via* the aldehyde (XIV) then gave (±)-10-methyl-11-deoxy-PGE$_1$ (XVa) and its C-15 epimer (XVb).

EXPERIMENTAL

7-Hydroxyheptanal (Ia).—Aleuritic acid (753 g) was added with vigorous stirring to a solution of sodium hydroxide (99 g) in water (3 l). The resulting turbid solution was treated with chloroform (3 l) and then sodium periodate (634.5 g) was added in portions at 35—40 °C during 10 min. The mixture was stirred for another 15 min with cooling to 20 °C, then filtered, and the filter cake was washed with chloroform (300 ml). The aqueous layer was extracted with chloroform (3 × 300 ml) and the combined chloroform washings and extracts were stirred for 1.25 h with a mixture of saturated aqueous sodium hydrogen carbonate (1.2 l) and sodium carbonate (0.9 l). The chloroform layer was evaporated *in vacuo* below 40 °C to give 7-hydroxyheptanal as a viscous oil which slowly crystallised. A second crop was obtained by further extraction with chloroform (3 × 300 ml) of the carbonate washing; total yield 271 g (89%); m.p. 65—67° (lit.,[6] 71°) (Found: C, 64.2; H, 10.6. Calc. for $C_7H_{14}O_2$: C, 64.6; H, 10.8%).

7-(Tetrahydropyran-2-yloxy)heptanal (Ib).—Dihydropyran (21 g) was added dropwise with stirring to 6-hydroxyhexanonitrile [7] (19.1 g) and concentrated hydrochloric acid (0.5 ml) at 40 °C. The temperature was allowed to rise to 65 °C, and maintained at that level for 2 h, and then at 80 °C for a further 20 min. The cold mixture was extracted with benzene and the organic layer washed successively with saturated aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and distilled to give the Thp ether (20.9 g, 66%), b.p. 116—119° at 0.1 mmHg, $\nu_{max.}$ 1 040, 1 080, 1 120, 1 140, and 2 230 cm^{-1}.

Di-isobutylaluminium hydride (19.35 g) in dry benzene (50 ml) was added dropwise to a stirred solution of the Thp ether (20.6 g) in dry ether (200 ml) at 15—20 °C. Stirring was continued (at 15—20 °C) for 20 min and the mixture was added to ice-cold 2N-sulphuric acid (300 ml) and stirred for 45 min. The mixture was then heated at 30 °C for 0.5 h, saturated with sodium chloride, and extracted with ether, and the extracts were washed with aqueous sodium hydrogen carbonate and brine, dried (Na_2SO_4), and distilled to give the *aldehyde* (Ib) (12.75 g, 66%), b.p. 78—106° at 0.1 mmHg, $\nu_{max.}$ 1 040, 1 080, 1 120, 1 140, 1 710, and 2 700 cm^{-1} (Found: C, 67.0; H, 10.2. $C_{12}H_{22}O_3$ requires C, 67.3; H, 10.3%).

6-(Tetrahydropyran-2-yloxy)hexanal (Ic).—To a stirred suspension of pyridinium chlorochromate (60 g) and anhydrous sodium acetate (5.3 g) in dry dichloromethane (100 ml) was added 6-(tetrahydropyran-2-yloxy)hexanol [8] (50 g) in dry dichloromethane (50 ml), dropwise over 5 min. After 2 h ether (100 ml) was added and the supernatant was decanted from the black residue. The residue was thoroughly washed with ether (3 × 100 ml) and the combined organic solutions were filtered through Hyflo Supercel, washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified by column chromatography on Kieselgel 60 (500 g; Merck) (eluant ether–ethyl acetate–n-hexane, 3 : 1 : 1) to give the *aldehyde* (Ic) (26.25 g, 52.4%), $\nu_{max.}$ 1 040, 1 080, 1 120, 1 140, 1730, and 2 730 cm^{-1} (Found: C, 65.6; H, 10.4. $C_{11}H_{20}O_3$ requires C, 66.0; H, 10.1%).

2-(7-Hydroxyheptyl)cyclopent-2-enone (IIIa).—7-Hydroxyheptanal (Ia) (390 g) and the morpholine enamine of cyclopentanone (598 g) in cyclohexane (750 ml) were heated under reflux in an atmosphere of nitrogen, the water formed being continuously removed with a Dean–Stark apparatus. When separation of water was complete (4 h), the solution was treated at 30—40 °C over 15 min with a mixture of concentrated hydrochloric acid (375 ml) and water (375 ml). Toluene (375 ml) was added, the mixture was stirred for 1.5 h, and the two (upper) organic layers were separated from the (lower) aqueous layer. The latter was extracted with toluene (2 × 375 ml) and the combined organic layers were evaporated. The residue was treated with butan-1-ol (9.9 l) and concentrated hydrochloric acid (240 ml) and heated at 90 °C with stirring under nitrogen for 5 h. The cooled mixture was treated with sodium hydrogen carbonate (305 g), filtered, and distilled to give the *enone* (IIIa) (340 g, 58%), b.p. 149—155° at 0.1 mmHg; the sample for analysis had b.p. 160—162° at 0.3 mmHg (Found: C, 72.8; H, 10.7. $C_{12}H_{20}O_2$ requires C, 73.4; H, 10.3%). $\lambda_{max.}$ (EtOH) 227 nm (ε 9 800), $\nu_{max.}$ 1 630, 1 695, and 3 440 cm^{-1}.

Similarly the Thp ether (Ib) (23.2 g) gave this enone (IIIa) (10.7 g, 50%), and the Thp ether (Ic) (15 g) gave the *enone* (IIIc) (4.1 g, 30%), b.p. 118—122° at 0.08 mmHg, $\lambda_{max.}$ (EtOH) 228 nm (ε 9 030), $\nu_{max.}$ 1 630, 1 700, and 3 450 cm^{-1} (Found: C, 72.0; H, 10.0. $C_{11}H_{18}O_2$ requires C, 72.5; H, 10.0%).

2-(7-Acetoxyheptyl)cyclopentanone.— 2-(7-Bromoheptyl)-cyclopentanone (180 g),‡ potassium acetate (145 g), glacial acetic acid (6 ml), and ethanol (396 ml) were heated under reflux for 24 h. The ice-cooled mixture was filtered and evaporated and the residue was extracted with ether. The extract was washed with water, dried ($MgSO_4$), and distilled to give 2-(7-*acetoxyheptyl*)*cyclopentanone* (130 g, 79%), b.p. 125—130° at 0.05 mmHg, $\nu_{max.}$ 1 040, 1 155, 1 240, 1 370, and 1 740 cm^{-1} (Found: C, 69.3; H, 10.2. $C_{14}H_{24}O_3$ requires C, 70.0; H, 10.1%).

Enol Acetate of 2-(7-Acetoxyheptyl)cyclopentanone.—2-(7-Acetoxyheptyl)cyclopentanone (133 g), isopropenyl acetate (215 g), and toluene-*p*-sulphonic acid (2.8 g) were heated under reflux for 24 h while the acetone formed was allowed to distil off slowly. The excess of isopropenyl acetate was then removed *in vacuo*, the residue was dissolved in dichloromethane (500 ml), and the solution was washed with aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and distilled to give the *enol acetate* (144 g, 92%), b.p. 145—150° at 0.2 mmHg, $\nu_{max.}$ 1 175, 1 210, 1 235, 1 685, and 1 725 cm^{-1} (Found: C, 67.9; H, 9.4. $C_{16}H_{26}O_4$ requires C, 68.1; H, 9.3%).

‡ B.p. 130—150° at 0.02 mmHg; prepared as for the corresponding 5-bromopentyl compound by the method of R. Mayer, G. Wenschuh, and W. Töpelmann, *Chem. Ber.*, 1958, **91**, 1616.

[6] J. Colonge, L. Cottier, and G. Descotes, *Compt. rend.*, 1969, **268***C*, 1155.

[7] R. A. Smiley and C. Arnold, *J. Org. Chem.*, 1960, **25**, 257.

[8] F. Bohlmann, R. Jeute, and R. Reinecke, *Chem. Ber.*, 1969, **102**, 3283.

2-(7-*Acetoxyheptyl*)*cyclopent-2-enone* (IIIb).—To a vigorously stirred solution of the above enol acetate (193 g) in dry carbon tetrachloride (1.62 l) below −10 °C was added, dropwise, bromine (37.5 ml) in carbon tetrachloride (400 ml). The mixture was stirred, without cooling, for 1 h, washed successively with aqueous sodium disulphite and aqueous sodium carbonate, dried ($MgSO_4$), and evaporated *in vacuo* (acetone–solid CO_2). A solution of potassium carbonate (740 g) in water (1.04 l) was added to the residue and the mixture was stirred for 36 h; more potassium carbonate (740 g) was then added and the stirring continued for a further 24 h. The mixture was extracted with ether, dried (Na_2SO_4), and distilled to give the *enone* (IIIb) (91 g, 56%), b.p. 140—155° at 0.1 mmHg, $\nu_{max.}$ 1 240, 1 630, 1 695, and 1 730 cm^{-1}. A sample was purified by t.l.c. on silica gel (ether–ethyl acetate–n-hexane, 3 : 1 : 1) (Found: C, 70.6; H, 9.3. $C_{14}H_{22}O_3$ requires C, 70.6; H, 9.3%)

2-(7-*Hydroxyheptyl*)-3-*oxocyclopentanecarbonitrile* (IVa).—The enone (IIIa) (30 g), acetone cyanohydrin (15.1 g), aqueous 6% sodium carbonate (30 ml), and methanol (89 ml) were heated under reflux with stirring for 5 h. Methanol was removed *in vacuo*, water (12 ml) was added, and the mixture was extracted with ether. The extracts were dried ($MgSO_4$) and distilled to give the *nitrile* (IVa) (28 g, 82%), b.p. 175—195° at 0.05 mmHg, $\nu_{max.}$ 1 735, 2 240, and 3 450 cm^{-1}; the sample for analysis had b.p. 202—208° at 0.6—0.7 mmHg (Found: C, 69.9; H, 9.7; N, 5.9. $C_{13}H_{21}NO_2$ requires C, 69.9; H, 9.5; N, 6.3%).

Similarly the enone (IIIc) (10.5 g) afforded the nitrile (IVc) † (8.25 g, 68%), b.p. 135—178° at 0.15 mmHg, $\nu_{max.}$ 1 730, 2 230, and 3 400 cm^{-1}, and the enone (IIIb) (110 g) gave the nitrile * (IVb) (83 g, 68%), b.p. 160—195° at 0.1—0.15 mmHg, $\nu_{max.}$ 1 245, 1 730, and 2 240 cm^{-1}.

6-(7-*Hydroxyheptyl*)-1,4-*dioxaspiro*[4.4]*nonane*-7-*carbonitrile* (Va).—*Method A*. The nitrile (IVa) (20 g), ethylene glycol (5.6 g), toluene-*p*-sulphonic acid (1 g), and benzene (160 ml) were heated under reflux for 3.5 h with continuous removal of water. The cold mixture was shaken with an excess of anhydrous sodium carbonate, filtered, and distilled to give the *acetal* (Va) (19.3 g, 80.5%), b.p. 166—182° at 0.1 mmHg, $\nu_{max.}$ 950, 2 240, and 3 450 cm^{-1}; the sample for analysis had b.p. 177—179° at 0.1 mmHg (Found: C, 67.1; H, 9.2; N, 4.9. $C_{15}H_{25}NO_3$ requires C, 67.4; H, 9.4; N, 5.2%).

Method B. By method A, the oxo-nitrile (IVb) (53 g) gave the acetal (Vb) † (38.2 g, 62%), b.p. 170—186° at 0.15 mmHg, $\nu_{max.}$ 950, 1 240, 1 730, and 2 250 cm^{-1}. Compounds (Vb) (36.1 g) in methanol (200 ml) were treated with stirring at 10—20 °C with a solution of sodium borohydride (5.3 g) in aqueous 0.2N-sodium hydroxide (70 ml). Stirring was continued for a further 2 h, methanol was removed *in vacuo*, water (50 ml) was added, and the mixture was extracted with ether. The extracts were dried ($MgSO_4$) and distilled to give the acetal (Va) (29.7 g, 94%), identified by g.l.c. comparison with a sample prepared by method A.

1-{6-(7-*Hydroxyheptyl*)-1,4-*dioxaspiro*[4.4]*nonan*-7-*yl*}*oct*-1-*en*-3-*one* (VIb).—A solution of di-isobutylaluminium hydride (49 g) in dry benzene (135 ml) was added, with rapid stirring, to the acetal nitrile (Va) (40 g) in dry ether (400 ml) at 0 °C. After 15 min the mixture was added cautiously, with stirring, to aqueous 2N-acetic acid (900 ml) at 0 °C. The organic phase was separated and the aqueous phase was extracted with ether. The combined organic layers were washed with aqueous sodium hydrogen carbonate, dried (Na_2SO_4), and evaporated to give the crude aldehyde (VIa) (40 g, 89%), $\nu_{max.}$ 1 715, 2 750, and 3 450 cm^{-1}, suitable for the next stage.

Dimethyl (2-oxoheptyl)phosphonate (16.7 g; Aldrich) in dry tetrahydrofuran (50 ml) was added, dropwise, to a stirred suspension of sodium hydride (1.9 g) in tetrahydrofuran (300 ml) under nitrogen. The mixture was stirred for 16 h and then treated dropwise with the aldehyde (VIa) (20.3 g) in tetrahydrofuran (100 ml) and stirred for a further 4 h under nitrogen. The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was extracted with ether and the extract washed with water and dried ($MgSO_4$) to give the crude *enone* (VIb) (27.2 g, 99%). A sample was purified on silica gel plates (ether–ethyl acetate–n-hexane, 3 : 1 : 1); $\lambda_{max.}$ (EtOH) 230 nm (ε 15 500); $\nu_{max.}$ 950, 990, 1 045, 1 630, 1 670, and 3 470 cm^{-1} (Found: C, 71.7; H, 10.8. $C_{22}H_{38}O_4$ requires C, 72.1; H, 10.4%).

(±)-11-*Deoxy*-*PGE*$_1$ (VIIIa) *and* (±)-11-*Deoxy*-15-epi-*PGE*$_1$ (VIIIb).—Chromium trioxide (15 g; dried *in vacuo* over silica gel) was added in portions to a stirred solution of the enone (VIb) (13.7 g) in dry dimethylformamide (200 ml) at 3—10 °C. Concentrated sulphuric acid (5 ml) in dry dimethylformamide (100 ml) was added below 10 °C and the solution was stirred for 1.5 h. Ether (200 ml) and water (100 ml) were then added; the organic layer was separated and the aqueous layer was extracted with ether. The combined ether layers were washed with water and extracted into 2N-sodium carbonate (75 ml). The latter solution was washed with ether, and then covered with a layer of ether and acidified to pH 4 with concentrated hydrochloric acid. The ethereal layer was separated, the aqueous layer was extracted with ether, and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to give the crude enone acid (VII) (8.9 g), $\nu_{max.}$ 945, 985, 1 630, 1 665, and 1 710 cm^{-1}. A 2% aqueous solution of sodium citrate (750 ml) was added to the foregoing product (8.9 g) in methanol (75 ml) at −5 °C. Potassium borohydride (18.9 g) was then added in portions with stirring, pH 8 being maintained by addition, when required, of aqueous 10% citric acid. The solution was stirred for another 1.5 h, enough acetone was added to destroy the excess of borohydride, the pH was adjusted to 4 with citric acid, and the mixture was extracted with ether and evaporated. The residue was stirred at 55 °C with N-hydrochoric acid for 4 h and extracted with ether. The work-up was completed by extraction into aqueous 10% sodium carbonate followed by acidification with hydrochloric acid, extraction with ether, and drying ($MgSO_4$) to give the products (VIIIa and b) (7.6 g), of which a sample (4 g) was chromatographed on a silica column (Kieselgel 60; Merck) (ethyl acetate–toluene, 1 : 4) to give (±)-15-*epi*-11-deoxy-PGE_1 (1.35 g) (VIIIb) [9] (faster-moving component) and (±)-11-deoxy-PGE_1 (VIIIa) [9] (0.9 g) as oils. The latter crystallised from ether–light petroleum (b.p. 40—60°) to give white needles (0.6 g), m.p. 85—86° (lit.,[9] 82.5—85°). The *epi*-compound crystallised only with difficulty; a sample was recrystallised (3 ×) from ether–light petroleum (b.p. 40—60°); m.p. 50—51° (lit.,[9] 53—56°).

9,15-*Dioxoprost*-13-*enoic Acid* (VIIIg).—(*A*) Di-isobutylaluminium hydride (40 g) in dry benzene (350 ml) was added with rapid stirring to the nitrile (IVa) (20 g) in dry

* Not obtained analytically pure.

[9] F. S. Alvarez and D. Wren, *Tetrahedron Letters*, 1973, 569.

ether (350 ml) at 5—15 °C. The solution was stirred for 1 h at room temperature and added to aqueous 2N-acetic acid (400 ml), and the work-up was completed as in the preparation of the aldehyde (VIa) to give the crude aldehyde (Xa) (18.3 g, 88%), $\nu_{max.}$ 1 710, 2 720, and 3 400 cm^{-1}. The aldehyde (18.3 g) and 2-oxoheptylidenetriphenylphosphorane [2] (32 g) in dry tetrahydrofuran (165 ml) was heated under reflux for 17 h. The solution was evaporated *in vacuo* and the residue was agitated with light petroleum (b.p. 40—60 °C) until the triphenylphosphine oxide had crystallised out. The mixture was filtered and evaporated to give the crude enone (27 g), $\nu_{max.}$ 980, 1 620, 1 665, and 3 400 cm^{-1}.

Jones reagent [10] (8N; 13.5 ml) was added dropwise to a stirred solution of the enone (10 g) in acetone (66 ml) at 15—25 °C at a rate such that the initial red colour had changed to green before the next addition. The mixture was diluted with water and extracted with ether (2 ×), and the combined extracts were washed with 2N-sulphuric acid. Work-up was completed by extraction with base as for (VIIIa and b) to give the *dioxo-acid* (VIIIg) (4.7 g). A sample was subjected to preparative t.l.c. on silica gel (benzene–dioxan–acetic acid, 65 : 15 : 1) (Found: C, 70.9; H, 9.5. $C_{20}H_{32}O_4$ requires C, 71.4; H, 9.6%), $\lambda_{max.}$ (EtOH) 228 nm (ε 12 100), $\nu_{max.}$ 990, 1 630, 1 670, 1 700, and 1 735 cm^{-1}, δ ($CDCl_3$) 9.6 (s, CO_2H), 6.8 (2d, *J* 16 and 7.5 Hz, C*H*=CH·C=O), 6.17 (d, *J* 16 Hz, CH=C*H*·C=O), and 0.9 (t, *J* 5 Hz, $CH_2{\cdot}CH_3$).

(*B*) The crude acid (VII) [from (VIb) (3.66 g)] on stirring with N-hydrochloric acid (50 ml) at 55 °C for 2 h and work-up gave the dioxo-acid (VIIIg) (2.56 g). As for (*A*) above, the nitrile (IVc) (8.8 g) gave the aldehyde (Xb) (8.6 g), $\nu_{max.}$ 1 710, 2 700, and 3 400 cm^{-1}, and then the enone, $\nu_{max.}$ 1 620 and 1 660 cm^{-1}, and the *dioxo-acid* (VIIIh) (4.62 g) (Found: C, 70.4; H, 9.3. $C_{19}H_{30}O_4$ requires C, 70.8; H, 9.4%), $\lambda_{max.}$ (EtOH) 228 nm (ε 13 200), $\nu_{max.}$ 1 625, 1 670, 1 700, and 1 730 cm^{-1}.

(±)-11-*Deoxy-PGF*$_{1\alpha}$ *and Epimers* (VIIIc—f).—(*a*) 11-Deoxy-PGE_1 (VIIIa) (0.34 g) reduced with potassium borohydride (0.81 g) in aqueous 2% sodium citrate (50 ml), under the conditions used for the enone acid (VII), gave a mixture of the epimers (VIIIc and d) (0.34 g). Separation by t.l.c. on silica gel (ethyl acetate–cyclohexane–formic acid, 40 : 40 : 1) and then recrystallisations from ether–light petroleum (b.p. 40—60 °C) gave (±)-11-deoxy-$PGF_{1\alpha}$ (VIIIc) [9] (faster-moving band), m.p. 95—96° (lit.,[9] 97—98.5°), and (±)-11-deoxy-$PGF_{1\beta}$ (VIIId),[9] m.p. 67—68° (lit.,[9] 69—70.5°).

Similarly (±)-15-*epi*-11-deoxy-PGE_1 (VIIIb) (0.51 g) gave the epimer mixture (VIIIe and f) (0.52 g), which afforded (±)-15-*epi*-11-deoxy-$PGF_{1\alpha}$ (VIIIe),[9] m.p. 102—104° (lit.,[9] 102—103.5°), and (±)-15-*epi*-11-deoxy-$PGF_{1\beta}$ (VIIIf),[9] m.p. 58—60° (lit.,[9] 59—60.5°).

(*b*) (±)-11-Deoxy-PGE_1 (VIIIa) (0.34 g) was added to a 1M-solution of ' L-Selectride ' in tetrahydrofuran (2 ml) at −78 °C and the mixture stirred at this temperature for 0.5 h and then at room temperature for 2.5 h. Aqueous 3N-sodium hydroxide (1.5 ml) and 30% hydrogen peroxide (1 ml) were added at 0 °C; the mixture was stirred for 0.5 h, washed with ether, acidified to pH 1 with 2N-hydrochloric acid, and extracted with ether. The extract was dried ($MgSO_4$) and the crude product was recrystallised (3 ×) as in (*a*), to give (±)-11-deoxy-$PGF_{1\alpha}$ (VIIIc) [9] (0.13 g), m.p. 95—97°. Similarly (±)-15-*epi*-11-deoxy-PGE_1 (VIIIb) (0.34 g) gave (±)-15-*epi*-11-deoxy-$PGF_{1\alpha}$ (VIIIe) [9] (0.17 g), m.p. 102—104°.

(*c*) Under the reaction conditions described in (*b*), the dioxo-acid (VIIIg) (0.84 g) gave the epimer mixture (VIIIc and e) (0.85 g); separation of a sample (0.5 g) as in (*a*) afforded (±)-11-deoxy-$PGF_{1\alpha}$ (VIIIc) [9] (60 mg), m.p. 94—96°, and the 15-epimer (VIIIe) [9] (90 mg), m.p. 104—105°.

(±)-13,14-*Dihydro*-11-*deoxy-PGE*$_1$ (IXa).—(±)-11-Deoxy-PGE_1 (VIIIa) (0.1 g) in ethanol (25 ml) was hydrogenated at 70 lb in^{-2} over 5% palladium–charcoal and chromatographed as in (*a*) above to give the dihydro-compound (IXa) [4] (40 mg) as an oil, $\nu_{max.}$ 1 710, 1 740, and 3 460 cm^{-1}. Similarly the 15-epimer (VIIIb) (0.1 g) gave the dihydro-compound (IXb) [4] (30 mg).

2-(7-*Hydroxyheptyl*)-5-*methyl*-3-*oxocyclopentanecarbonitrile* (XIIIb).—Dihydropyran (73 g) was added dropwise with stirring at 40 °C to the nitrile (IVa) (10 g) and concentrated hydrochloric acid (4 drops). The temperature was allowed to rise to 65 °C and held at that level for 1 h. Benzene (50 ml) was added and the cooled solution was washed with aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to give the crude Thp ether (15 g), $\nu_{max.}$ 1 040, 1 080, 1 120, 1 140, 1 740, and 2 230 cm^{-1}. To an ice-cold solution of the latter (15 g) and diethyl oxalate (15.9 g) in dry benzene (110 ml) was added sodium methoxide (5.9 g), and the mixture was set aside at room temperature for 24 h. Ice–water was added and the organic layer was separated. The aqueous layer was washed with benzene and then added to aqueous 30% sodium dihydrogen phosphate (150 ml) at 0 °C. The organic layers were extracted with ice-cold aqueous 4% sodium hydroxide and the alkaline extracts were added to the sodium dihydrogen phosphate solution which was then stirred at 0 °C for 15 min and extracted with ether. The combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give the crude ethoxalyl compound (XIIIa) (11.2 g), $\nu_{max.}$ 1 605, 1 670, and 1 720 cm^{-1}. A solution of the latter, anhydrous potassium carbonate (22 g), and methyl iodide (67 ml) in acetone (450 ml) was stirred and heated under reflux for 22 h. The cold mixture was filtered, the solvent was removed *in vacuo*, and the residue was treated with water and extracted with ether. The combined extracts were washed successively with 2N-sodium hydroxide and water, and then evaporated. Aqueous 60% perchloric acid (6 drops) was added to the residue (8.4 g) in ethanol (35 ml) and the solution was set aside for 24 h. Chloroform was added and the solution was washed with aqueous 2N-sodium carbonate, and then with brine, and dried (Na_2SO_4). Distillation at 140—200 °C and 0.15 mmHg gave a diastereoisomeric mixture of *nitriles* (XIIIb) (3.5 g), $\nu_{max.}$ 1 455, 1 465, 1 730, 2 230, and 3 450 cm^{-1} (Found: C, 70.2; H, 10.0; N, 5.4. $C_{14}H_{23}NO_2$ requires C, 70.8; H, 9.8; N, 5.9%).

(±)-11-*Deoxy*-10-*methyl-PGE*$_1$ *and* (±)-11-*Deoxy*-10-*methyl*-15-epi-*PGE*$_1$ (XVa and b).—By the method used to convert the nitrile (IVa) into the aldehyde (VIa), the nitrile (XIIIb) (3.5 g) afforded the crude acetal aldehyde (XIV) (2.4 g, 57%), $\nu_{max.}$ 955, 1 040, 1 710, 2 700, and 3 400 cm^{-1}. Wittig reaction of the latter (2.4 g) with 2-oxoheptylidenetriphenylphosphorane [2] (3.8 g) in tetrahydrofuran (25 ml), as for the preparation of the enone (VIIIg), and then oxidation and reduction with borohydride as for

[10] R. G. Curtis, Sir Ian Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 1953, 457.

conversion of the enone (VII) into the acids (VIIIa and b) and t.l.c. (ethyl acetate–cyclohexane–formic acid, 40 : 40 : 1) gave a mixture of (±)-11-*deoxy*-10-*methyl*-PGE_1 (XVa) and the 15-*epimer* (XVb) (Found: C, 71.7; H, 10.7. $C_{21}H_{35}O_4$ requires C, 71.8; H, 10.0%).

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