# Prostaglandins Part 7.[1] Synthesis of (±)-11-Deoxy-10-hydroxy- and (±)-11-Deoxy-10-oxoprostaglandins

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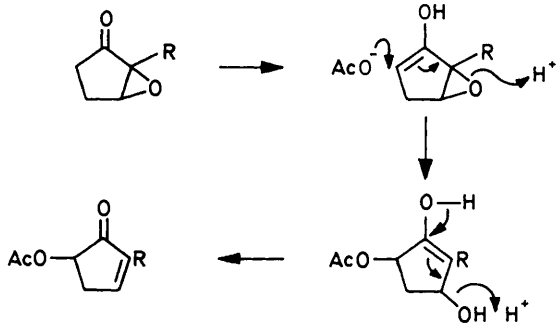
The epoxides of 2-alkylcyclopent-2-enones (I) react with acetic acid to give 5-acetoxy-2-alkylcyclopent-2-enones (II) which afford (±)-11-deoxy-10-hydroxyprostaglandins [(V) and (IX)] *via* conjugate-addition reactions. The 11-deoxy-10-hydroxyprostaglandin (IXa) readily undergoes base-catalysed autoxidation to the 11-deoxy-10-oxoprostaglandin (XIII).

Many routes to prostaglandins are based upon the synthesis of 2-alkylcyclopent-2-enone intermediates and their elaboration *via* conjugate-addition reactions. Application of our approach to 5-acetoxy-2-alkylcyclopent-2-enones (II) by acetic acid treatment of the epoxides of 2-alkylcyclopent-2-enones (I)[2] (Scheme) has enabled us to extend this procedure to the synthesis of (±)-11-deoxy-10-hydroxyprostaglandins.[3] We here describe full details of this work and its adaptation to the synthesis of (±)-11-deoxy-10-hydroxy- and (±)-11-deoxy-10-oxo-prostaglandin methyl esters (IX) and (XIII) and also of the prostenoic acid derivative (V).

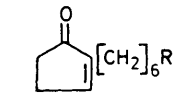
We planned initially to model the synthesis of 10-hydroxyprostaglandins on our earlier routes to 11-deoxyprostaglandins from 2-(7-hydroxyheptyl)cyclopent-2-enone (Ia).[4] Reaction of the epoxide of the enone (Ia) with acetic acid under reflux afforded the diacetoxyenone (IIa), the 5-acetoxycyclopentenone formation being accompanied by acetylation of the primary alcohol. The enone (IIa) with acetone cyanohydrin in the presence of base underwent simultaneous nitrile addition and hydrolysis of the ring acetoxy-group to give a diastereoisomeric mixture of nitriles (IIIa). We have previously shown[4] that nitrile addition to the enone (Ia) affords both *cis*- and *trans*-isomers. With nitrile (IIIa), because of the additional chiral centre at C-4 in the cyclopentane ring, a total of four diastereoisomeric products was expected. However, difficulties in separation of the isomers led us to continue the synthesis with the mixture. The tetrahydropyranyl (THP) ether (IIIb) of the nitrile mixture (IIIa), on treatment with di-isobutylaluminium hydride, afforded the dihydroxy-aldehyde (IV) which underwent Wittig elaboration with (2-oxoheptylidene)triphenylphosphorane.[5] Jones oxidation, followed by hydrolysis of the derived THP-ether-ketones with aqueous acetic acid, afforded a product, the spectral and analytical data of which were in accord with the expected 10-hydroxy-9,15-dioxoprostenoic acid (V). By analogy with our earlier work we have assumed that the *cis-trans* mixture present at the nitrile stages underwent isomerisation to give an essentially all-*trans* product. Duplication of the signals for the vinylic protons in the $^1$H n.m.r. spectrum of the product (V) indicated the presence of two components and it seemed likely that this was attributable to the presence of 10α- and 10β-diastereoisomers (Va and b). A partial separation of these diastereoisomers was achieved by preparative t.l.c. (thin-layer chromatography) [ethyl acetate–cyclohexane–formic acid (40 : 40 : 1) as eluant] to give a single isomer having the expected doublet and double doublet signals for the vinylic protons in its $^1$H n.m.r. spectrum, together with a second fraction at a higher $R_F$ value, containing both isomers in which duplication of these signals occurred.

Although this approach could in principle be used to prepare a wide variety of 10-hydroxyprostaglandins, lack of stereoselectivity rendered it unsuitable for the synthesis of 11-deoxy-10-hydroxyprostaglandins which was a primary target of this work. A more direct route to the latter compounds would result from conjugate addition of one of the well known 'ate' complexes, *e.g.* the copper–lithium reagent (VIIa),[8] to a methyl 7-(5-oxocyclopent-1-enyl)heptanoate intermediate, as used in several syntheses of natural and 11-deoxyprostaglandins. The enone-carboxylic acid (Ib),[6] prepared here by oxidation of the 7-hydroxyheptylcyclopentenone (Ia) with Jones' reagent,[7] was converted *via* the epoxide which, on treatment with acetic acid, gave the acetoxy-enone (IIb). Conjugate addition of the reagent (VIIa) to the enone (IIb) was tried without success. The acetoxy-group was therefore replaced by a suitable acid-labile grouping—tetrahydropyran-2-yloxy (THPO)—which could be hydrolysed at the end of the synthesis to the 10-hydroxy-group under mild conditions. The required THP-ether (IId) was therefore prepared by hydrolysis of the acetoxy-enone (IIe) to the free alcohol (IIc) by careful treatment with sodium carbonate in aqueous methanol,[2,3] followed by reaction with dihydropyran.

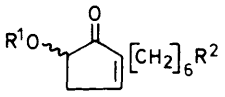


**Scheme**

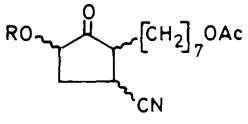
The THP-ether (IId) underwent reaction with the cuprate (VIIa) to give the product (VIII) which, on hydrolysis with acetic acid in aqueous tetrahydrofuran (THF), afforded a mixture of (±)-11-deoxy-10-hydroxy-PGE$_1$ methyl esters (IX). This was chromatographed [Kieselgel H (ethyl acetate–cyclohexane (1 : 2) as eluant] to give two isomeric products with similar spectral data. Since cuprate additions to 2-alkylcyclopentenones have previously been shown to give exclusively *trans* products,[8] it might be expected that the addition here would have given rise to four diastereoisomeric products as a consequence of the chiral centres at C-15, (C-8, C-12) and C-10. Since only 2 products were obtained it seemed probable that the conjugate addition had been directed by the tetrahydropyranyloxy-group to give exclusive attack from the least hindered side of the molecule. This contrasts with the non-stereoselective nitrile addition to the acetoxy-enone (IIa) but might be expected as a consequence of



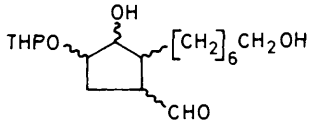
(I) a; R = $CH_2OH$
b; R = $CO_2H$



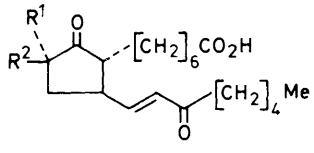
(II) a; $R^1$ = Ac, $R^2$ = $CH_2OAc$
b; $R^1$ = Ac, $R^2$ = $CO_2H$
c; $R^1$ = H, $R^2$ = $CO_2Me$
d; $R^1$ = THP, $R^2$ = $CO_2Me$
e; $R^1$ = Ac, $R^2$ = $CO_2Me$



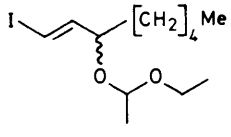
(III) a; R = H
b; R = THP



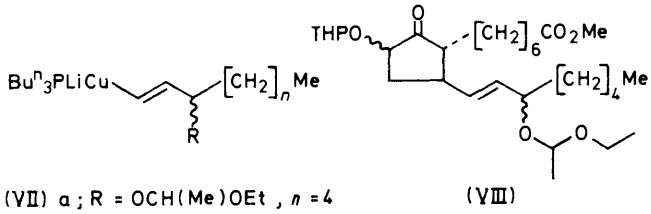
(IV)



(V) a; $R^1$ = OH, $R^2$ = H
b; $R^1$ = H, $R^2$ = OH

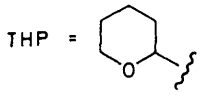


(VI)

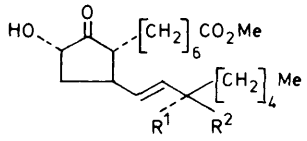


(VII) a; R = OCH(Me)OEt, $n$ = 4
b; R = H, $n$ = 3

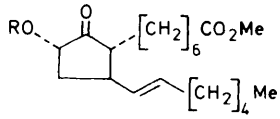
(VIII)



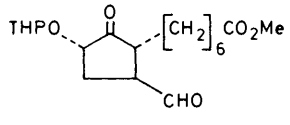
THP =



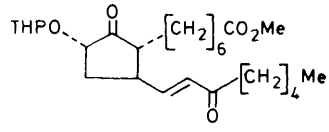
(IX) a; $R^1$ = OH, $R^2$ = H
b; $R^1$ = H, $R^2$ = OH



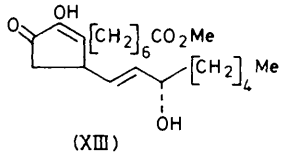
(X) a; R = THP
b; R = H



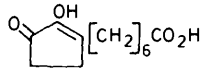
(XI)



(XII)



(XIII)



(XIV)

the bulky nature of the tetrahydropyranyloxy-grouping and the cuprate reagent. The likelihood that such steric interaction would occur was evident from the examination of stereo-models. Thus the reaction would give rise to only the two 10α-racemic products (IXa and b). It is assumed on the basis of comparative t.l.c. mobilities with those of other prostaglandins that the slower moving product, which was crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C), was the (15*S*-isomer (IXa). The disposition of groups around the cyclopentane ring was confirmed by $^1$H n.m.r. spectroscopy. Irradiation of the methine (C*H*OH) signals during homonuclear-decoupling experiments caused the collapse of the signals at δ 1.95 (due to the ring $CH_2$) to a doublet, confirming that the hydroxy-group, and not the ketone, was in the 10-position, thus excluding the possibility that an acyloin rearrangement had occurred during the reaction work-up. Assignment of the C*H*·CH=CH proton (12-H) at δ 2.67 was similarly based upon irradiation of the vinylic protons.

The 11,15-dideoxy-ω-nor-derivative (Xb) was similarly prepared using the cuprate (VIIb) derived from 1-iodohept-1-ene. This reaction afforded only a single racemic product, presumed to be the 10α-hydroxy-derivative (Xb), providing further evidence of the stereoselective nature of the reaction.

Further work was carried out to adapt this approach to a broader, more general synthesis of other analogues of the 10-hydroxyprostaglandins. Since the cuprate reagents are not always readily available for synthesis of modified analogues, it was considered desirable to make available the aldehyde (XI) which could be elaborated to a variety of analogues *via* the normal Wittig condensations. The aldehyde (XI) was synthesised by osmium tetraoxide-catalysed cleavage of the double bond in compound (Xa) with sodium periodate. Wittig condensation of the aldehyde (XI) with (2-oxoheptylidene)triphenylphosphorane gave the dioxo-derivative (XII). The latter compound did not show the duplication of the signals for the vinylic protons in the $^1$H n.m.r. spectrum observed in the similar product (V) prepared *via* the nitrile conjugate addition, providing further evidence that the cuprate conjugate addition had afforded only one of the two C-10 diasteroisomers.

Synthesis of the aldehydes of type (IV) *via* the corresponding nitromethyl compound was also considered. However, attempts to prepare the latter compound by conjugate addition of nitromethane to the enone (IIb) in the presence of sodium methoxide in methanol using the conditions employed by us in the 11-deoxyprostaglandin series [9] gave rise, as indicated by i.r. data on the crude products, to substantial amounts of the 7-(2-hydroxy-3-oxocyclopent-1-enyl)heptanoic acid (XIV). We subsequently demonstrated in a blank experiment that this transformation readily takes place on treatment of the enone (IIb) with sodium methoxide to give the 2-hydroxycyclopent-2-enone (XIV) as the sole isolated product and we have reported elsewhere the same reaction with 5-acetoxy-2-octylcyclopent-2-enone.[2] Although further preliminary experiments indicated that formation of compound (XIV) might be eliminated by employing a large excess of nitromethane, this approach was not further pursued.

In the course of the study it became apparent that the 10-hydroxyprostaglandins are unstable to base. Subsequent work showed that this was a consequence of base-catalysed autoxidation to the 9,10-dioxoprostaglandins.[1] This reaction took place very slowly when the 10-hydroxy-compound (IXa) was allowed to stand at room temperature in ethanolic aqueous sodium hydroxide, but when oxygen was passed into the reaction mixture the oxidation was complete after two hours.

Using this procedure the novel 9,10-dioxoprostanoid (XIII) was isolated and characterised. The $^1$H n.m.r. spectrum of compound (XIII) was consistent with its assigned structure; in particular the complex signal at δ 3.30 has a chemical shift characteristic of a hydrogen (12-H) located between two double bonds.

## Experimental

$^1$H N.m.r. spectra were measured in $CDCl_3$ solution unless otherwise noted on Varian A-60D or CFT 20 spectrometers. I.r. spectra were measured on thin films (liquids) or KBr discs (solids) on a Unicam SP 1000 spectrophotometer. U.v. spectra were measured in ethanol solution on a Cary 17 spectrophotometer. Light petroleum refers to that fraction boiling in the range 40—60 °C unless otherwise stated.

*7-(5-Oxocyclopent-1-enyl)heptanoic Acid* (1b).—A solution of Jones' reagent [7] (8N; 365 ml) was added dropwise to a cooled, stirred solution of 2-(7-hydroxyheptyl)cyclopent-2-enone [4] (Ia) (130 g, 0.66 mol) in acetone (825 ml) whilst maintaining the solution temperature between 5—15 °C and ensuring that an orange colour persisted at the end of the addition. The resulting mixture was stirred for a further 0.5 h, then propan-2-ol was added until a green colour persisted. Water (600 ml) was added and the mixture was thoroughly extracted with diethyl ether, the combined extracts were washed with water and were then stirred for 2 h with saturated aqueous sodium carbonate. The ethereal phase was re-extracted with saturated aqueous sodium carbonate and the total combined sodium carbonate extracts were acidified to pH 4 with concentrated hydrochloric acid. The resulting solution was extracted with diethyl ether, and the combined extracts were washed (water), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the crude acid (Ib) (104 g, 75%) which was crystallised from diethyl ether–light petroleum and had m.p. 41—43 °C (lit.,[6] 40—42 °C); $\nu_{max.}$ 3 100, 1 740, 1 710, and 1 630 cm$^{-1}$; $\lambda_{max.}$ 229 nm (ε 10 900); δ 1.1—1.9 (8 H, m, $[CH_2]_4$), 2.0—2.8 (8 H, m, 4 × $CH_2$), 7.3—7.55 (1 H, m, C=CH), and 11.3 (1 H, s, $CO_2H$).

*7-(4-Acetoxy-5-oxocyclopent-1-enyl)heptanoic Acid* (IIb).—A solution of compound (Ib) (104 g, 0.495 mol) in methanol (2 l) was treated at *ca.* 10 °C with 4M aqueous sodium hydroxide (*ca.* 100 ml) until a brown colour persisted. 30% Hydrogen peroxide (205 ml) was then added dropwise, maintaining the temperature of the mixture at *ca.* 10 °C, followed by the addition of more 4M sodium hydroxide (total volume added: 180 ml). The mixture was allowed to warm to room temperature and was left for 18 h. The mixture was then evaporated to dryness under reduced pressure (temperature <40 °C), water (650 ml) was added to the residue, the solution was washed with chloroform, acidified to pH 4 with dilute acetic acid, and extracted with chloroform. The combined extracts were washed (water), dried ($Na_2SO_4$), and evaporated to dryness under reduced pressure to give a crude epoxide (95 g, 85%), $\nu_{max.}$ 3 200br, 1 740, and 1 710 cm$^{-1}$, which was used without further purification.

A solution of the crude epoxide (95 g, 0.42 mol) in glacial acetic acid (1 l) was heated under reflux for 7 h and was then cooled and evaporated under reduced pressure. Toluene (100 ml) was added to the residue and the mixture was evaporated under reduced pressure, this step being repeated until all traces of acetic acid were removed. The residue was dissolved in diethyl ether (300 ml), the insoluble solid (*ca.* 1 g) was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure to give the *acetoxy-enone* (IIb) (92.5 g, 82%), m.p. 66—68 °C (from water) (Found: C, 62.9; H, 7.8. $C_{14}H_{20}O_5$ requires C, 62.7; H, 7.5%); $\nu_{max.}$ 3 000, 1 720, 1 700, 1 620, and 1 240 cm$^{-1}$; $\lambda_{max.}$ 230 nm (ε 9 000); δ 2.10 (3 H, s, AcO), 2.45 (1 H, m, C*H*·CHOAc *trans* to OAc), 3.0 (1 H, m, C*H*·CHOAc *cis* to OAc), 5.10 (1 H, dd, *J* 6.5 and 3 Hz, C*H*OAc), and 7.18 (1 H, m, C=CH).

*Methyl 7-(4-Acetoxy-5-oxocyclopent-1-enyl)heptanoate* (IIe).—A solution of the acid (IIb) (31.7 g, 0.118 mol) in acetone (150 ml) was added dropwise to a stirred mixture of dimethyl sulphate (16.4 g, 0.13 mol), anhydrous potassium carbonate (22.1 g, 0.13 mol), and acetone (250 ml). The resulting mixture was heated under reflux for 4 h and was then cooled. Glacial acetic acid (2 ml) was added and the mixture was boiled for a further 0.5 h. The mixture was cooled, filtered, and the filtrate was evaporated under reduced pressure. The residue was dissolved in diethyl ether and the extract was washed in turn with saturated aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give the *ester* (IIe) as an oil (26.8 g, 80%) (Found: C, 64.0; H, 8.2. $C_{15}H_{22}O_5$ requires C, 63.8; H, 7.9%); $\nu_{max.}$ 1 745, 1 720, 1 630, and 1 240 cm$^{-1}$; δ 2.10 (3 H, s, OAc), 2.48 (1 H, m, C*H*·CHOAC *trans* to OAc), 3.05 (1 H, m, C*H*·CHOAc *cis* to OAc), 3.64 (3 H, s, OMe), 5.11 (1 H, dd, *J* 6.5 and 3 Hz, C*H*OAc), and 7.30 (1 H, m, C=CH).

*Methyl 7-(4-Hydroxy-5-oxocyclopent-1-enyl)heptanoate* (IIc).—A solution of the diester (IIe) (30.0 g) in methanol (600 ml) was treated with a solution of sodium carbonate (1.2 g) and water (6 ml) for 20 h at room temperature. The mixture was evaporated under reduced pressure (temperature <25 °C), water (180 ml) was added to the residue, and the mixture was extracted with diethyl ether. The combined ethereal extracts were washed (saturated aqueous sodium chloride), dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give a pale-orange oil which crystallised on keeping. The crystals were washed with diethyl ether–light petroleum to give the crude compound (IIc) (13.6 g, 54%). Analytically pure *hydroxy-enone* was obtained by recrystallisation from diethyl ether–light petroleum; m.p. 62—63 °C (Found: C, 65.0; H, 8.5. $C_{13}H_{20}O_4$ requires C, 65.0; H, 8.4%); $\nu_{max.}$ 3 400, 1 740, 1 700, and 1 630 cm$^{-1}$; $\lambda_{max.}$ 230 nm (ε 8 500); δ 2.45 (1 H, m, C*H*·CHOH *trans* to OH), 3.05 (1 H, *m*, C*H*·CHOH *cis* to OH), 3.68 (3 H, s, OMe), 4.25 (1 H, dd, *J* 6.5 and 3 Hz, C*H*OH), and 7.2 (1 H, m, C=CH).

*Methyl 7-[5-Oxo-4-(tetrahydropyran-2-yloxy)cyclopent-1-enyl]heptanoate* (IId).—A solution of toluene-*p*-sulphonic acid (20 mg) in dry dichloromethane (5 ml) was added to an ice-cooled, stirred solution of freshly distilled dihydropyran (9.6 g, 0.113 mol) and the hydroxy-enone (IIc) (13.56 g, 0.056 mol) in dry dichloromethane (100 ml). Stirring was continued at *ca.* 20 °C for 1.5 h, triethylamine (0.5 ml) was then added, the mixture was filtered, and the filtrate was evaporated to dryness under reduced pressure to give the crude *tetrahydropyranyl ether* (IId) (22.4 g). A pure sample was obtained by column chromatography (Kieselgel H) [ethyl acetate–cyclohexane (1 : 2) as eluant] (Found: C, 66.5; H, 8.6. $C_{18}H_{28}O_5$ requires C, 66.6; H, 8.7%); $\nu_{max.}$ 1 750, 1 720, and 1 630 cm$^{-1}$; $\lambda_{max.}$ 230 nm (ε 7 300).

*(±)-11-Deoxy-10α-hydroxy-PGE$_1$ Methyl Ester* (IXa) *and (±)-11-Deoxy-10α-hydroxy-15-epi-PGE$_1$ Methyl Ester* (IXb).—1.3M t-Butyl-lithium solution in pentane (8.8 ml, 11.4 mmol) was added rapidly *via* a syringe to a stirred solution of the vinyl iodide (VI) [8] (1.85 g, 5.6 mmol) in dry diethyl ether (40 ml) under argon at −78 °C. The resulting solution was stirred at −78 °C for 2 h. Meanwhile, freshly distilled tri-n-butylphosphine (1.23 ml, 5.14 mmol) was added *via* a syringe to a stirred solution of tri-n-butylphosphine–copper(I) iodide

complex [8] (1.94 g, 5.2 mmol) in diethyl ether (15 ml) at room temperature under nitrogen. This solution was transferred *via* a syringe to the solution of the vinyl-lithium derivative at −78 °C. The resulting yellow solution of the complex (VIIa) was stirred at −78 °C for 50 min, a solution of the tetrahydropyranyloxy-enone (IId) (1.30 g, 4 mmol) in diethyl ether (50 ml) was added *via* a syringe, and the mixture was stirred at −78 °C for a further 25 min and was then warmed to *ca.* −20 °C and stirred at this temperature for 1 h. Aqueous ammonium sulphate (20%; 50 ml) was added and the mixture was poured into a mixture of diethyl ether (100 ml) and 20% aqueous ammonium sulphate (100 ml). The resulting mixture was extracted with diethyl ether, and the extract was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue (5.26 g) was stirred with a mixture of acetic acid (52 ml), water (28 ml) and THF (8 ml) at 30—35 °C for 20 h. The resulting mixture was evaporated to dryness under reduced pressure below 40 °C and toluene (30 ml) was added to and evaporated from the residue under reduced pressure to remove last traces of acetic acid, this being repeated until all acetic acid was removed. The crude product (4.80 g) was chromatographed on Kieselgel 60 (Merck) [ethyl acetate–cyclohexane (1 : 2) as eluant] to give (±)-11-*deoxy*-10α-*hydroxy-PGE*$_1$ *methyl ester* (IXa) (143 mg) (slower moving component) which was crystallised from ethyl acetate–light petroleum (b.p. 60—80 °C), m.p. 114—117 °C (Found: C, 68.9; H, 10.0. $C_{21}H_{36}O_5$ requires C, 68.5, H, 9.9%); $\nu_{max.}$ 3 300 and 1 750 $cm^{-1}$; δ ($CD_3OD$) 1.8—2.2 (total 3 H, dd, *J* 8 and 6 Hz, ring $CH_2$, and m, CHOH·CO·C*H*), 2.30 (2 H, t, *J* 7 Hz, $CH_2CO_2Me$), 2.67 (1 H, m, ring C*H*·CH=CH), 3.66 (3 H, s, OMe), 3.9—4.2 (2 H, m, 2 × C*H*OH), and 5.5—5.7 (2 H, m, C=C*H*); *m/z* 368 ($M^+$), 350 ($M - H_2O$)$^+$, 336 ($M$ − MeOH)$^+$, 332 (350 − $H_2O$)$^+$, 319 (350 − OMe)$^+$, 297 ($M - C_5H_{11}$)$^+$, 279 (297 − $H_2O$), 265 (297 − MeOH)$^+$, and 247 (265 − $H_2O$)$^+$.

The impure, faster moving component (430 mg) was further chromatographed on Kieselgel H [dichloromethane–acetone (7 : 3) as eluant] to give the 15-epi-*compound* (IXb) (95 mg) as an oil with similar spectral properties to those of the isomer (IXa).

(±)-11,15-*Dideoxy*-10α-*hydroxy*-ω-*norPGE*$_1$ *Methyl Ester* (Xb).—A 1.3M solution of t-butyl-lithium in pentane (6.0 ml, 7.8 mmol) was added rapidly *via* a syringe to a solution of 1-iodohept-1-ene (0.72 g, 3.22 mmol) in diethyl ether (50 ml) under argon at −78 °C. After 2.5 h a solution of tri-n-butylphosphine (0.7 ml, 2.92 mmol) and tri-n-butylphosphine–copper(I) iodide complex* (1.1 g, 2.92 mmol) in diethyl ether (30 ml) was added *via* a syringe and the resulting yellow mixture of the complex (VIIb) was stirred at −78 °C for 1.5 h. A solution of the enone (IId) (0.8 g, 2.4 mmol) in diethyl ether (20 ml) was then added *via* a syringe, the mixture was stirred at −78 °C for 1 h and was then allowed to warm to *ca.* −20 °C and was stirred at this temperature for 1 h. The reaction was quenched and the mixture was extracted as described for compound (IX) to give the crude product (Xa) (2.53 g) which was stirred with acetic acid–water–THF (65 : 35 : 10) for 3 h at 40 °C and was then chromatographed on Kieselgel [ethyl acetate–cyclohexane (1 : 2) as eluant] to give (±)-11,15-*dideoxy*-10α-*hydroxy*-ω-*norPGE*$_1$ *methyl ester* (Xb) (0.12 g); $\nu_{max.}$ 3 450, 1 745, 1 735, and 930 $cm^{-1}$; δ 1.8—2.6 (total 7 H, m, $CH_2CO_2Me$, ring $CH_2$, $CH_2CH$=C, and CHOH·CO·C*H*), 2.85 (1 H, m, ring C*H*·CH=CH), 3.66 (3 H, s, OMe), 4.17 (1 H, t, *J* 7 Hz, C*H*OH), and 5.3—5.6 (2 H, m, CH=CH); *m/z* 338 ($M^+$), 320 ($M - H_2O$)$^+$, 307 ($M$ − OMe)$^+$, and 289 (320 − OMe)$^+$.

* Prepared as for (VIIa).

(±)-11,15-*Dideoxy*-10α-(*tetrahydropyran*-2-*yloxy*)-ω-*nor-PGE*$_1$ *Methyl Ester* (Xa).—Using the same procedure as for preparation of compound (Xb) but without the acetic acid hydrolysis step, the title compound (Xa) was prepared from the enone (IId) (4.0 g) as a crude product (13.2 g). This was chromatographed in two portions on Kieselgel 60 [ethyl acetate–cyclohexane (1 : 4) as eluant] to give the slightly impure product (Xa) (3.2 g); $\nu_{max.}$ 1 750, 1 740, 1 200, 1 020, and 970 $cm^{-1}$, which was used without further purification or full characterisation.

*Methyl* 7-[5-*Formyl*-2-*oxo*-3-(*tetrahydropyran*-2-*yloxy*)-*cyclopentyl*]*heptanoate* (XI).—Osmium tetraoxide (0.1 g) was added to a solution of the 15-deoxynorPGE$_1$ derivative (Xa) (1.0 g, 0.0028 mol) in a mixture of dioxan (10 ml) and water 4 ml) under nitrogen. The resulting black mixture was stirred for 1 h and sodium periodate (2 g) was then added in several portions. The mixture was stirred at room temperature for 20 h and was then extracted with diethyl ether. The extracts were washed in turn with aqueous sodium carbonate and with brine, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give an oil (1.24 g), 0.7 g of which was chromatographed on Kieselgel 60 [ethyl acetate–cyclohexane (2 : 3) as eluant] to give the *aldehyde* (XI) (0.20 g); $\nu_{max.}$ 2 700, 1 740, 1 730, and 1 020 $cm^{-1}$; δ 1.8—3.1 (total 6 H, m, $CH_2CO_2Me$, ring $CH_2$, and O=C·C*H*·C*H*·CHO), 3.3—3.7 (2 H, m, $CH_2O$), 3.66 (3 H, s, OMe), 4.18 (1 H, t, *J* 7 Hz, O·CH·C=O), 4.5—5.0 (1 H, m, OCHO), and 10.0 (1 H, d, *J* 1.5 Hz, CH=O); *m/z* 354 ($M^+$), 323 ($M$ − OMe)$^+$, 305 (323 − $H_2O$)$^+$, 270 ($M$ − THP − H)$^+$, and 253 ($M$ − THPO)$^+$

(±)-11,15-*Dideoxy*-15-*oxo*-10α-(*tetrahydropyran*-2-*yloxy*)-*PGE*$_1$ *Methyl Ester* (XII).—A mixture of the aldehyde (XI) (354 mg, 1 mmol) and (2-oxoheptylidene)triphenylphosphorane [5] (375 mg, 1 mmol) was heated under reflux in dry THF (10 ml) for 9 h under nitrogen. The mixture was then cooled and evaporated to dryness under reduced pressure. The residue was dissolved in diethyl ether and triphenylphosphine oxide was removed by trituration with light petroleum to leave, on evaporation of the solvents, an oil (474 mg) which was chromatographed on Kieselgel H [50 g; ethyl acetate–cyclohexane (2 : 3) as eluant] to give the title compound (XII) (110 mg); $\nu_{max.}$ 1 745, 1 680, 1 630, and 1 020 $cm^{-1}$; $\lambda_{max.}$ 226 (ε 12 100); δ 1.8—2.7 (total 7 H, m, C=CHCOC$H_2$, $CH_2CO_2$-Me, C*H*CHO, and ring $CH_2$), 2.8 (1 H, m, C*H*CH=CH), 3.3—3.7 (2 H, m, $CH_2O$), 3.68 (3 H, s, OMe), 4.15 (1 H, m, OC*H*·C=O), 4.6—5.1 (1 H, m, $CH_2O$-C*H*O), 6.19 (1 H, d, *J* 16 Hz, C=C*H*C=O), and 6.83 (1 H, dd, *J* 16 and 8 Hz, C*H*=CHC=O).

(±)-11-*Deoxy*-10-*oxoPGE*$_1$ *Methyl Ester* (XIII).—Oxygen was bubbled through a solution of compound (IXa) (50 mg) in methanol (10 ml) containing 1M aqueous sodium hydroxide (1 drop). The mixture was then poured into brine and was thoroughly extracted with diethyl ether. The extract was washed in turn with brine and then with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to give an oil (34 mg) which was chromatographed on Kieselgel [30 g; ethyl acetate–cyclohexane (1 : 1) as eluant] to give the 9,10-*dioxoprostanoid* (XIII) (9.4 mg); $\nu_{max.}$ 3 450, 1 735, 1 695, and 1 620 $cm^{-1}$; $\lambda_{max.}$ 262 nm (ε 12 300); δ 1.9—2.9 (total 6 H: 2.15, dd, *J* 19 and 2 Hz, 11-Hβ, 2.30, t, *J* 7 Hz, $CH_2CO_2Me$, 2.0—2.5, C=C$CH_2$, and 2.64, dd, *J* 19 and 6 Hz, 11-Hα), 3.30 (1 H, ddd, *J* 8, 6, and 2 Hz, C=CCHC=C), 3.67 (3 H, s, OMe), 4.10 (1 H, q, *J* 6 Hz, C*H*OH), 5.33 (1 H, dd, *J* 15 and 8 Hz, C*H*=CH·CHOH), and 5.67 (1 H, dd, *J* 15 and 6 Hz, CH=C*H*·CHOH); *m/z* 366 ($M^+$), 348 ($M - H_2O$)$^+$, 316 (348 − MeOH)$^+$, 295 ($M - C_5H_{11}$)$^+$, and 288 (316 − CO)$^+$.

*5-Acetoxy-2-(7-acetoxyheptyl)cyclopent-2-enone* * (IIa).—Using the method described for the preparation of compound (IIb), the enone (Ia) (30 g) afforded the corresponding epoxide (25.5 g); $\nu_{max.}$ 3 450 and 1 740 $cm^{-1}$. The latter compound (25 g), on being heated under reflux in glacial acetic acid (500 ml) for 10 h, followed by removal of the acetic acid under reduced pressure, gave the crude product (IIa) (33 g), a batch of which (4 g) was purified by chromatography on a silica column (Mallinckrodt CC-4) [toluene–ethyl acetate (4 : 1) as eluant] to give the *diacetoxy-enone* (IIa) (2.2 g) (Found: C, 64.8; H, 8.2. $C_{16}H_{24}O_5$ requires C, 64.8; H, 8.2%); $\nu_{max.}$ 1 725, 1 705, 1 620, and 1 230 $cm^{-1}$; $\lambda_{max.}$ 232 nm (ε 9 200).

*2-(7-Acetoxyheptyl)-3-oxo-4-(tetrahydropyran-2-yloxy)-cyclopentanecarbonitrile* † (IIIb).—To a solution of the enone (IIa) (33.5 g) in methanol (125 ml) was added a mixture of acetone cyanohydrin (12.75 g) and sodium carbonate (1 g) in water (13.7 ml). The mixture was heated under reflux for 4.5 h. Methanol was removed under reduced pressure, water (150 ml) added to the residue, and the mixture was extracted with diethyl ether. The extracts were dried ($MgSO_4$) and evaporated to give the crude nitrile (IIIa) (35.3 g); $\nu_{max.}$ 3 425, 2 250, 1 730, and 1 250 $cm^{-1}$.

Dihydropyran (8.4 g) was added portionwise to a stirred mixture of the nitrile (IIIa) (14.05 g) and concentrated hydrochloric acid (5 drops) at 40 °C. The temperature was allowed to rise to 56 °C during the addition, further hydrochloric acid (2 drops) being introduced towards the end of the addition. The mixture was then stirred at 55 °C for 1.5 h and was then cooled; the mixture was then extracted with diethyl ether and the extract was washed in turn with 1N sodium hydroxide and with water and was then dried ($MgSO_4$). Evaporation to dryness under reduced pressure gave the crude THP-ether (IIIb) (18.1 g); $\nu_{max.}$ 2 240, 1 735, and 1 245 $cm^{-1}$. This was used in the next stage without further purification.

*10-Hydroxy-9,15-dioxoprost-13-enoic Acid* (Va and b).—A solution of di-isobutylaluminium hydride (14.2 g) in dry benzene (40 ml) was added to a rapidly stirred solution of the nitrile (IIIb) (7.3 g) in dry diethyl ether (125 ml) at below 10 °C. After 15 min the mixture was slowly added to stirred 2N acetic acid (100 ml) at below 15 °C. After 10 min the mixture was filtered, the filtrate was extracted with diethyl ether, and the filter cake was washed with diethyl ether. The ethereal solutions were combined, washed with water, and dried ($MgSO_4$) to give after work-up, the THP-aldehyde (IV) (4.4 g), $\nu_{max.}$ 3 450, 2 725, and 1 715 $cm^{-1}$.

A mixture of the latter compound (4.2 g) in dry THF (60 ml) and (2-oxoheptylidene)triphenylphosphorane [5] (4.85 g) was heated under reflux under nitrogen for 20 h. The mixture was then evaporated to dryness under reduced pressure and the residue (9.3 g), in stirred dry dimethylformamide (DMF) (80 ml), was treated portionwise with chromium trioxide (12 g) at below 15 °C. Concentrated sulphuric acid (4.2 ml) in dry DMF (90 ml) was then added slowly at below 15 °C and the mixture was stirred at below 15 °C for 1.5 h. Diethyl ether (100 ml) and water (50 ml) were then added in turn, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined ethereal layers were washed with water and were then evaporated to dryness under reduced pressure and the residue was extracted into 2N sodium carbonate (40 ml). The aqueous extract was washed with diethyl ether and was then acidified to pH 4 with concentrated hydrochloric acid and extracted with diethyl ether. The ethereal extract was dried ($MgSO_4$) to give, after work-up, the THP-ether of compound (V) (2.7 g), $\nu_{max.}$ 1 730, 1 700, 1 670, 1 625, and 980 $cm^{-1}$.

The latter compound (1.5 g), glacial acetic acid (40 ml), and water (20 ml) were heated together at 40—42 °C for 5 h, water (50 ml) was then added, and the solution was extracted with diethyl ether. The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue was treated with benzene and the mixture was evaporated under reduced pressure to remove residual acetic acid. The residual product (1.24 g) was subjected to preparative t.l.c. on silica [ethyl acetate–cyclohexane–formic acid (40 : 40 : 1) as eluant to give *10-hydroxy-9,15-dioxoprost-13-enoic acid* (V) (0.43 g) as a mixture of diastereoisomers. This mixture was again subjected to t.l.c. under the same conditions and the single, broad band obtained was arbitrarily divided into two approximately equal portions. The slower moving portion afforded a single diastereoisomer (Va or Vb) (Found: C, 67.9; H, 9.5. $C_{20}H_{32}O_5$ requires C, 68.1; H, 9.2%); $\nu_{max.}$ 3 400, 1 735, 1 700, 1 670, 1 625, and 985 $cm^{-1}$; $\lambda_{max.}$ 225 nm (ε 13 300); δ 4.13 (1 H, dd, *J* 12 and 8 Hz, C*H*OH), 6.20 (1 H, d, *J* 16 Hz, CH=C*H*CO), and 6.78 (1 H, dd, *J* 16 and 7 Hz, C*H*=CHCO).

The faster moving portion gave a mixture of diastereoisomers (Va and Vb) (Found: C, 67.7; H, 9.4. $C_{20}H_{32}O_5$ requires C, 68.1; H, 9.2%); $\nu_{max.}$ 3 400, 1 735, 1 700, 1 670, 1 625, and 985 $cm^{-1}$; $\lambda_{max.}$ 224 nm (ε 11 500); δ 6.18 and 6.16 (total 1 H, 2 × d, *J* 16 Hz, CH=C*H*CO), and 6.70 and 6.75 (total 1 H, 2 × dd, *J* 16 and 7 Hz, C*H*=CHCO).

*7-(2-Hydroxy-3-oxocyclopent-1-enyl)heptanoic Acid* (XIV).—A stirred solution of the acetoxycyclopentenone (IIb) (0.5 g) in dry methanol (5 ml) was treated with a solution of sodium methoxide in methanol [from sodium (0.18 g) in methanol (3 ml)]. The mixture was stirred for 2 h, then set aside overnight and evaporated to dryness under reduced pressure. Water and diethyl ether were then added and the aqueous layer was separated and acidified to pH 1 with concentrated hydrochloric acid and was then extracted with diethyl ether. The extract was washed with water, dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The solid residue was refluxed in diethyl ether (charcoal) and the solution was then concentrated and treated with light petroleum to afford, as a pale-cream solid, the *title acid* (XIV) (0.18 g, 40%), m.p. 100—102 °C (Found: C, 63.6; H, 8.4. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%); $\nu_{max.}$ 3 200, 1 700, and 1 630 $cm^{-1}$; $\lambda_{max.}$ 262 nm (ε 10 700).

* Alternative name: *5-Hydroxy-2-(7-hydroxyheptyl)cyclopent-2-enone diacetate.*

† Alternative name: *7-[5-Cyano-2-oxo-3-(tetrahydropyran-2-yloxy)-cyclopentyl]heptyl acetate.*

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