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THE SYNTHESIS OF $PGF_1\alpha$ BY RE-STRUCTURING OF CASTOR OIL

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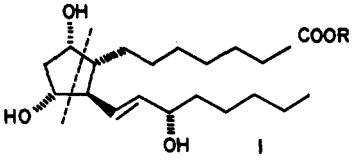
Abstract—Castor oil has been transformed—via methyl ricinoleate—to $PGF_1\alpha$ by strategy wherein 16 of the 18 carbons of the castor oil backbone are incorporated in the C-20 $PGF_1\alpha$, involving, *inter alia*, a novel procedure for the regiospecific functionalisation of terminal olefins, a novel degradation of aldehyde to lower acid and strategies useful for the generation of the highly functionalised prostanoid system, which specially illustrate the utility of MEM protecting group in diverse types of chemical transformations. Additionally, this work describes the preparation of synthons having potential utility and the synthesis of novel homo—$PGF_1\alpha$.

The C-17 unit of $PGF_1\alpha$ (1) arising from the bifurcation along the dotted line, bears a striking resemblance to



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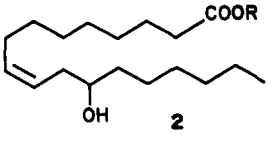

2

castor oil (2). The recognition that in several approaches to prostaglandins, the residual 3-carbon unit stems from cyclopentadiene via 4+2 adducts makes this similarity striking. The re-structuring of 2 was planned through key fragmentation products 3 and 4, the former providing the C-10 synthon 5, which via the 4+2 adduct 6 would lead to the prostanoid unit 7 and this, in turn, by reaction with phosphonate 8—generated from the minor fragmentation product 4—and reduction will give rise to $PGF_1\alpha$ (Chart 1). We report that the 2→1 change has been accomplished wherein 16 carbons of the C-18 castor oil are incorporated in the C-20 $PGF_1\alpha$. This novel transformation, we feel, *inter alia*, exemplifies the utilisation of raw materials for rare products, by intermediates, several off which are themselves potentially related to a host of prostaglandin analogs, sex pheromones and macrolides.[1] It further illustrates a novel procedure for regiospecific functionalisation of terminal olefins, a novel degradation of aldehydes to lower acids, strategies useful for the generation of the highly functionalised prostanoid system and particularly the use of the methoxyethoxymethyl (MEM) protecting group which survived all the reactions involved in the route to $PGF_1\alpha$, namely, saponification, Osmium tetroxide hydroxylation, periodate cleavage, excess Grignard treatment, esterification, Collins oxidation, vigorous *m*-chloroperbenzoic acid oxidation and in addition, departed smoothly when desired. another attractive feature of the present work is that the more readily available C-11 synthon related to 5 not only served as an ideal substrate for model studies, but also led to the synthesis of the novel homo $PGF_1\alpha$.

Indian castor oil (2, R = glyceride) was *trans*-esterified to methyl ricinoleate (2, R=Me)[2], in 85% yields, in MeOH containing catalytic methoxide.[3] The transformation of 2 to methyl 10-undecenoate (3) and heptaldehyde (4) can be best achieved by heating, admixed with sand, over a luminous flame. Surprisingly, other procedures[4] gave unreliable results. The procedure developed in the

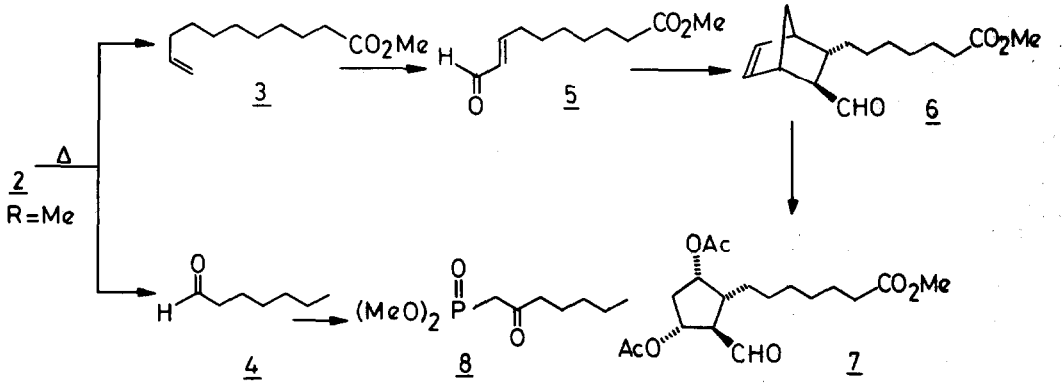

Chart 1.

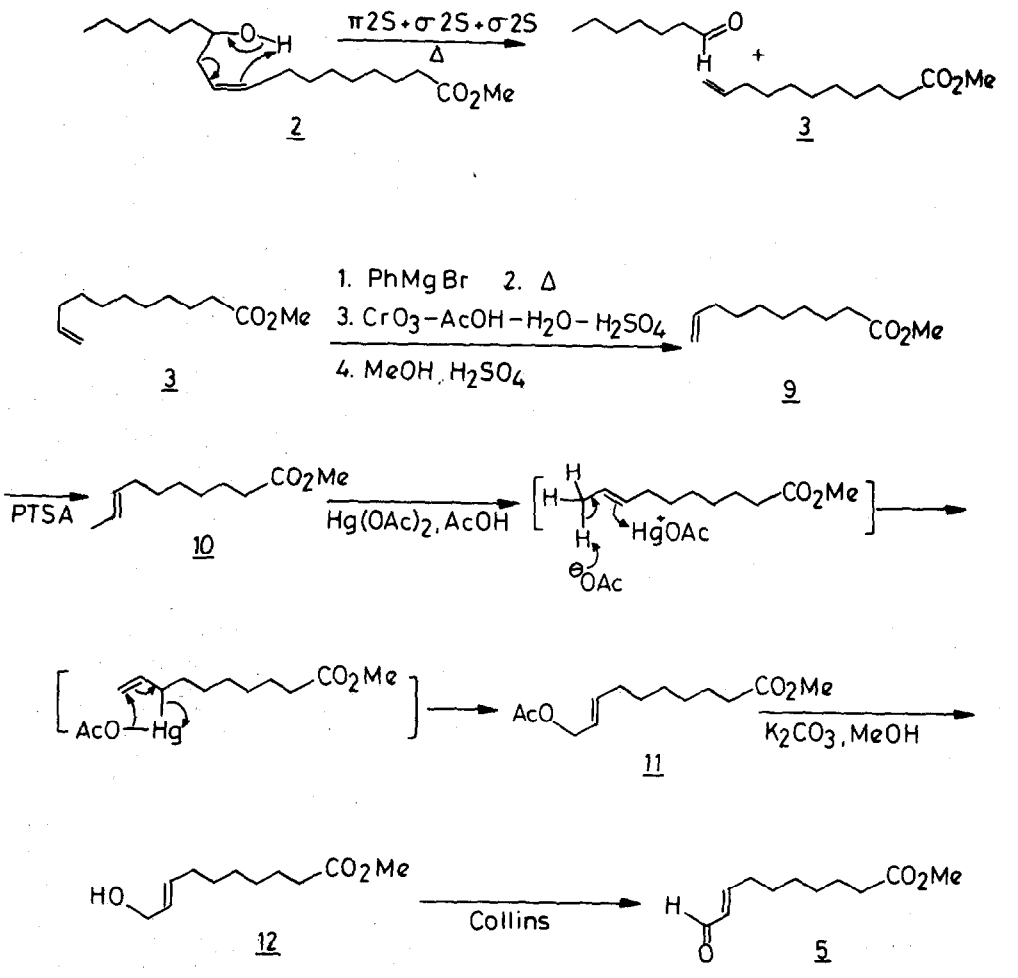

Chart 2.

present work gave 49% of 3+4, based on unchanged 2, which was recycled. 75 Litres of castor oil was thus pyrolysed, in batches. The fragmentation proceeds, most likely by a cyclic pathway (Chart 2). In agreement with a cyclic pathway, the acetylenic ester related to 2 gave the allene, methyl undeca 9,10-diene.

The methyl 10-undecenoate (3)→methyl 9-decenoate (9) change was accomplished by a modified degradation procedure in an overall yield of 49%[5,6] (Chart 2).

Attempted preparation of methyl 10-acetoxy-8-E-decenoate (11) from 9 with $Hg(OAc)_2$ in refluxing AcOH gave predominantly the undesired 8-acetoxy isomer,[7] thus indicating a regioselectivity from the process. Therefore, 9 was smoothly isomerised (PTSA) to methyl 8E-decenoate (10), which, in turn, underwent acetoxylation to give the desired 11 as the major product along with the 8-acetoxy isomer in the ratio 3:1 (Chart 2).

Although 11 can be separated from the 8-acetoxy isomer by chromatography, it was convenient to effect this operation after transformation to the key synthon 5, via *trans*-esterification to methyl 11-hydroxy 8-decenoate (12) followed by Collins oxidation[8] (Chart 2).

The $\alpha\beta$ unsaturated aldehyde 5, whose structure was rigorously established, can be obtained in 13% overall yield from castor oil.

The minor fragmentation product 4 was correlated to dimethyl 2-oxoheptyl phosphonate (8) and triphenyl 2-oxoheptyl phosphonium bromide (13), two synthons that have been used in the generation of the lower chain of prostaglandins. Heptaldehyde was transformed to 1-acetoxy heptene[9] and then, by a novel degradation to hexanoic acid, which was transformed to the phosphonate 8 by known procedures.[10] Alternately, 4 was converted via reduction, dehydration and epoxidation, to, 1-heptene oxide which has been recently converted to, by an unusually interesting regiospecific reaction to, 1 bromo-2-oxo heptane,[11] a precursor to 13[12] (Chart 3).

The cycloaddition of the C_{10} synthon 5 with cyclopentadiene gave a 73% yield of a separable[13] mixture of adducts, 2:1 in favour of the desired *exo* aldehyde adduct 6 (Chart 4). An observation of practical use was made in handling *exo, endo* isomers related to series arising from the (4+2) addition. Although compound 6 can be separated from the *endo* aldehyde isomer with considerable difficulty, this process was progressively made easier on compounds arising from further reactions on the aldehyde function. Thus, the MEM ester 15 related to 6 can be quite easily separated from the *endo* isomer. Apart from accumulated differences in polarity, a preference for reactivity with the *exo* isomer related to 6 also contribute to this phenomenon. For example, Wittig reaction, as monitored by tlc, nearly exclusively consumes the *exo* aldehyde 6, initially. The *exo* aldehyde assignment for 6 is fully supported by NMR data.[14] MEM ester 15 was prepared from 6 via borohydride reduction followed by reaction with MEM chloride[15,16]

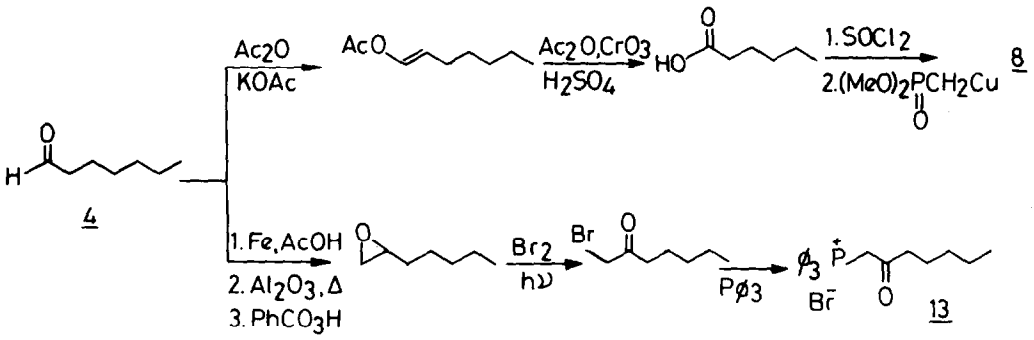

Chart 3.

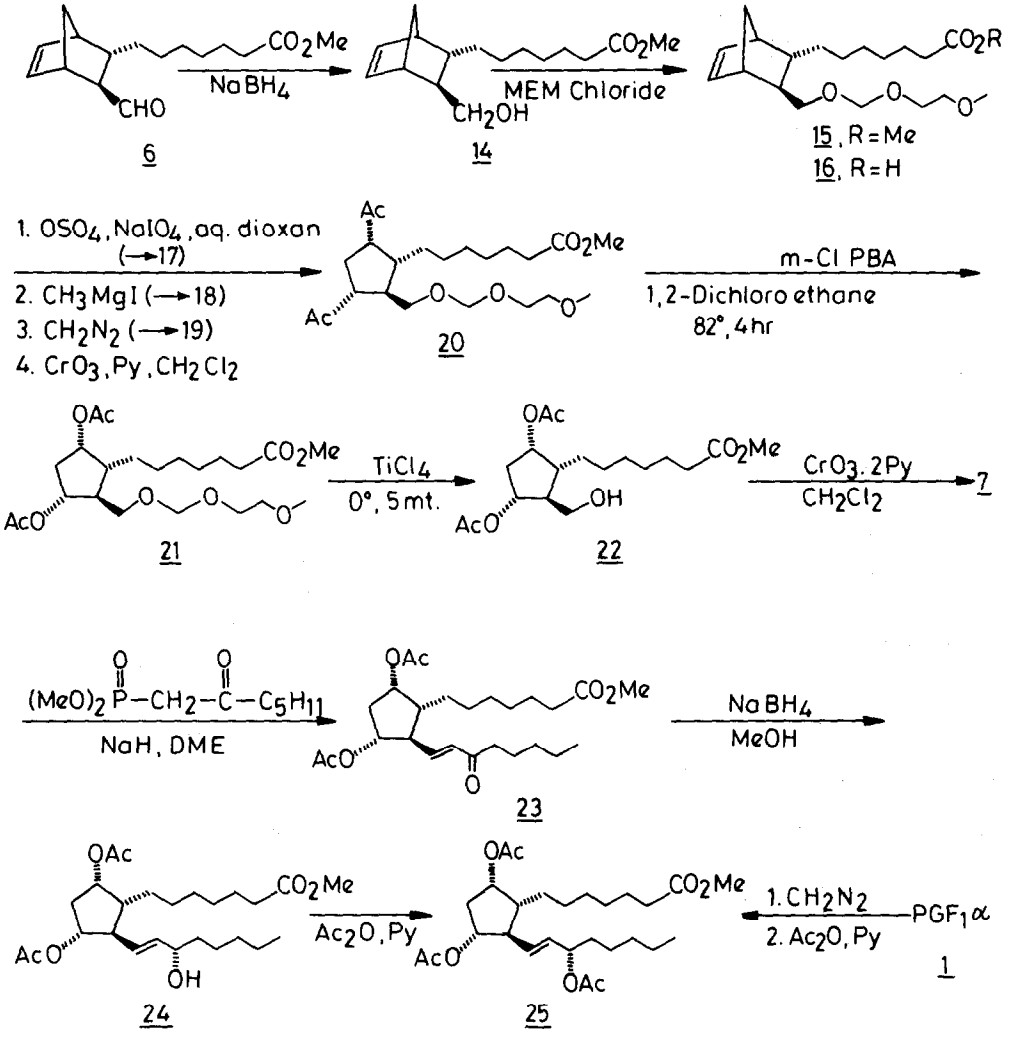

Chart 4.

(Chart 4). Pure MEM ester was saponified with 2N KOH to **16** to protect the carboxyl function and then smoothly transformed to the prostanoid **20**, by sequence, dialdehyde **17**, Grignard adduct **18**, and ester **19** (Chart 4).

The transformation of **20** to corresponding diacetoxy compound **21**, associated with the generation of the correctly functionalised prostanoid nucleus, required extensive experimentation. From a large number of trial experiments, where the solvent, equivalents of reagents and the temperature was varied and the reactions monitored by tlc and NMR, it was possible to achieve an optimum conversion to the key diacetoxy compound **21**. Parenthetically, the twenty atom frame work present in **21** bears a similarity to the C-20 prostaglandins. The MEM protecting group was smoothly removed by $TiCl_4$ under rigorously controlled conditions,[17] the resulting alcohol **22**, oxidised to aldehyde **7** and then subjected to Horner–Wittig reaction with **8** and the enone **23** thus

obtained transformed to PGF$_1\alpha$ diacetate (**24**)[18] by borohydride reduction (Chart 4).

The triacetate **25**, obtained from acetylation of **24** was found to be identical to that obtained from authentic PGF$_1\alpha$ via esterification and acetylation (Chart 4).

The optimum conditions for the above series was intially worked out with **3**, since this C_{11} synthon possessing only an additional methylene group was more readily available. This led to the synthesis of the novel homo-PGF$_1\alpha$ diacetate methyl ester via intermediates homologous to compounds **5–23**.

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EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra were recorded on Perkin–Elmer Model-137, 157 and 521 spectrophotometers as neat liquids or solids as KBr discs. NMR spectra were obtained on approximately 10–15% solutions mostly in $CDCl_3$ on A-60D, and TR-90 spectrometers. The chemical shifts are reported in ppm downfield from internal TMS at 0.00 as internal standard. Elemental analysis were carried out in Coleman automatic, C, H and N analysers. Silica-gel G(acme) was used for tlc and column chromatography was done on silica gel (Acme), columns being prepared from its slurry in petroleum ether (60–66°). Reactions were monitored, whenever possible, by tlc.

I. *Trans-esterification of castor oil*

Preparation of methyl ricinoleate **2** (R=Me). Castor-oil (932 g, 1 mol) was added to MeOH (3.5 L), to which Na (1 g, 0.043 g atom) had already been added and the mixture was refluxed on the water bath for 1 hr. Solvents were evaporated and the residue washed with 50% aqueous MeOH (300 ml), the upper layer dried over $MgSO_4$ and distilled b.p. 128–130°/0.02 mm to give 795.60 g (85%) of **2** (R=Me). (Found: C, 73.18; H, 11.48. Calcd for $C_{19}H_{36}O_3$: C, 73.07; H, 11.53%). IR: ν_{max}(neat)(cm^{-1}): 3571 (OH), 1742 (ester). NMR: $\delta_{(CDCl_3)}$: 5.45 (m, olefinic protons), 3.65 (s, $COOCH_3$).

II. *Pyrolysis of methyl ricinoleate*

Isolation of methyl-10-undecenoate (**3**) *and n-heptaldehyde* (**4**). Under a set-up for downward distillation, a mixture of **2** (R = Me; 100 g) and sand (50 g) was pyrolysed using a Bunsen burner for 0.75 hr, during which 87.0 g of a light-green distillate was collected. The small amount of water was separated, the residue distilled to give heptaldehyde (152°/1 atm), methyl undec-10-enoate (12.5 g, 49%; b.p. 80–81°/0.9 mm), and unchanged methyl 12-hydroxy *cis*-9-octadecenoate (60.0 g). (Found: C, 72.9; H, 11.24. Calcd for $C_{12}H_{22}O_2$: C, 72.72; H, 11.1%). IR: ν_{max}(neat) (cm^{-1}): 1742 (ester), 1658 (double bond). NMR: $\delta_{(CDCl_3)}$: 5.78 (m, 1 H, olefinic), 4.98 (m, 2 H, olefinic), 3.68 (s, 3 H, ester).

III. *Degradation of methyl-10-undecenoate* (**3**) *to methyl-9-decenoate* (**9**)

(a) *Addition of* PhMgBr. A soln of methyl-undec-10-enoate (50.0 g, 0.25 mol), in ether (500 ml), was added, in drops, at 20°, to a stirred soln of C_6H_5MgBr from 12.15 g Mg (0.50 g atom) and 78.5 g bromobenzene (0.50 mol), in ether (500 ml), over 1 hr, the mixture refluxed for 2.5 hr, the Grignard complex decomposed by the addition of ice-cold 2NH_2SO_4 and extracted in ether. The ether extract was washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated to yield 77.0 g (95%) of the desired alcohol. It was used as such, without purification, for dehydration. IR: ν_{max}: (neat)(cm^{-1}): 3597 (OH), 1650 (double bond), 1608 (phenyl).

(b) *Dehydration.* The crude alcohol (77.0 g) was heated at 200° for 30 min and fractionated to give 60.0 g (78%) of diene b.p. 163–165°/0.07 mm. IR: ν_{max}(neat)(cm^{-1}): 1653 (double bond), 1600 (phenyl). NMR: $\delta_{(CDCl_3)}$: 7.23 (m, aromatic), 5.83 (m, 1 H, olefinic), 5.0 (m, 2 H, olefinic).

(c) *Degradation of diene*: *preparation of 9-decenoic acid.* A soln of CrO_3 (19.0 g, 0.19 mol), in water (20 ml), was added, during 1.5 hr, to a vigorously stirred soln of the diene (25.0 g, 0.082 mol), in glacial AcOH (250 ml), at 35°. After additional 0.5 hr, ~70 ml AcOH was removed *in vacuo*. The residue was treated with 2NH_2SO_4 (500 ml), extracted with benzene and solvents evaporated. The mixture was then treated with sat $NaHCO_3$aq, extracted with ether, the aqueous layer–carefully acidified with ice-cold 2NHCl and extracted with ether. Evaporation of the dried ($MgSO_4$) ether extract gave 8.8 g (63%) of the dec-9-enoic acid, b.p. 93–95°/0.8 mm. IR: ν_{max}: (neat) (cm^{-1}): 1709 (carboxyl), 1658 (double, bond). NMR: $\delta_{(CDCl_3)}$: 5.8 (m, 1 H, olefinic), 5.0 (m, 2 H, olefinic).

(d) *Esterification of 9-decenoic acid*: *preparation of methyl-9-decenoate.* Dec-9-enoic-acid (100 g, 0.58 mol) was refluxed for 4 hr, in 1 L of abs MeOH (approx 50 molar excess), containing conc H_2SO_4 (2 g) as catalyst. MeOH was distilled off, the residue poured into 500 ml water, the upper oily layer extracted with ether (3 × 200 ml), the ether extract washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated to yield 105.2 g (98%) of methyl-dec-9-enoate; b.p. 60–61°/0.3 mm. (Over all yield from methyl undec-10-enoate; 49%). (Found: C, 71.52; H, 11.19. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.93%). IR: ν_{max}(neat)(cm^{-1}): 1740 (ester), 1658, 905 (double bond). NMR: $\delta_{(CDCl_3)}$: 5.8 (m, 1 H, olefinic), 4.92 (m, 2 H, olefinic), 3.66 (s, 3 H, ester).

IV. *Isomerisation of methyl-9-decenoate*

Preparation of methyl E-8-*decenoate* (**10**). Under stirring, a soln of methyl-dec-9-enoate (100 g, 0.54 mol) and *p*-toluenesulphonic-acid (10 g), in dry benzene (75 ml), was refluxed for 10 hr. Solvents were evaporated and the residue was distilled to give 96.8 g (97%) of **10** b.p. 60–61°/0.2 mm. (Found: C, 71.54; H, 11.04. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.93%). IR: ν_{max}(neat)(cm^{-1}): 1740 (ester), 1639, 966 (double bond). NMR: $\delta_{(CDCl_3)}$: 5.4 (m, 2 H, olefinic), 3.66 (s, 3 H, ester).

V. *Reaction of methyl-8-decenoate* (**10**) *with* $Hg(OAc)_2$

Regioselective preparation of methyl 10-*acetoxy* E-*dec*-8-*enoate* (**11**). A mixture of **10** (45 g, 0.24 mol), mercuric-acetate (114.69 g, 0.36 mol) and glacial AcOH (100 ml), was refluxed for 15 hr, (bath temp 120°), decanted, evaporated, diluted with water, extracted with ether, the ether layer washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated and fractionated to give 33.1 g of pure **11**; b.p. 115°/0.13 mm; 15.1 g **10** was recovered unchanged, yield, on the basis of recovered starting material, 85%. (Found: C, 64.34; H, 9.25. Calcd for $C_{13}H_{22}O_4$: C, 64.43; H, 9.15%). IR: ν_{max}(neat)(cm^{-1}): 1740 (ester), 1733 (acetate). NMR: $\delta_{(CDCl_3)}$: 5.68 (m, 2 H, olefinic), 4.5 (d, J = 5 Hz, 2 H, CH_2OAc), 3.66 (s, 3 H, ester), 2.0 (s, 3 H, $-OCOCH_3$).

VI. *Hydrolysis of methyl* 10-*acetoxy* E-*dec*-8-*enoate* (**11**)

Isolation of methyl 10-*hydroxy*-E-*dec*-8-*enoate* (**12**). Under efficient stirring, a soln of **11** (30 g, 0.124 mol) in abs MeOH (25 ml), was mixed with a suspension of freshly ignited K_2CO_3 (20.7 g, 0.55 mol), in abs MeOH (30 ml). The mixture left stirred for 2 hr decanted, solvents evaporated under reduced pressure, the residue neutralised with ice cold 2NHCL and extracted repeatedly with CH_2Cl_2. The organic extract was washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) solvents evaporated and distilled to give 23.3 g (94%) of **12**, b.p. 115°/0.04 mm. (Found: C, 65.84; H, 10.10. Calcd for $C_{11}H_{20}O_3$: C, 65.96; H, 10.06%). IR: ν_{max}(neat)(cm^{-1}): 3636 (hydroxyl), 1740 (ester). NMR: $\delta_{(CDCl_3)}$: 5.62 (m, 2 H, olefinic), 4.05 (m, 2 H, $-CH_2-OH$), 3.66 (s, 3 H, ester).

VII. *Oxidation of* 10-*hydroxy* E-*dec*-8-*enoate*

Preparation of key αβ-unsaturated aldehyde synthon (**5**). Under N_2, and at 0°, CrO_3 (16.0 g, 0.16 mol) was added in lots to a stirred soln of dry pyridine (30 ml), in dry CH_2Cl_2 (50 ml). After

0.5 hr, a soln of allylic alcohol (2.0 g, 0.01 mol), in CH_2Cl_2 (30 ml), was added in drops. The mixture was left stirred for additional 2 hr, decanted from the black tarry deposit, filtered, the residue washed repeatedly with CH_2Cl_2 and the organic extract washed with 5% sodium meta-bisulphite, sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was passed quickly through a short column of silica-gel (15 g). Elution with PhH: CH_2Cl_2 (1:1) gave **5** as an almost colorless liquid (1.59 g, 80%). A sample was further purified by bulb distillation 108–113°/0.1 mm $R_f = 0.5$ (90% PhH: 10% EtOAc). (Found: C, 66.74; H, 9.19. Calcd for $C_{11}H_{18}O_3$: C, 66.63; H, 9.15%). IR: ν_{max}(neat)(cm^{-1}): 1738 (ester), 1695 (aldehyde), 1639 (double bond).

NMR: $\delta_{(CDCl_3)}$: 9.4 (D, J = 9 Hz, 1 H, CHO), 6.75 (m, 1 H, olefinic), 5.8 (m, 1 H, olefinic), 3.66 (s, 3 H, ester). Semicarbazone: m.p. 130–131°: IR: ν_{max}(KBr)(cm^{-1}): 3282 (–NH), 1726 (ester), 1694 (amide), 1654 (double bond); NMR: $\delta_{(CDCl_3)}$: 9.88 (b, 1 H, –CH=N–), 7.50 (b, 1 H, NH), 6.20 (b, 2 H, $CONH_2$), 5.78 (b, 2 H, olefinic), 3.78 (s, 3 H, ester). *m/e* = 255.

VIII. *Reaction of 1-acetoxy heptene with* CrO_3

Preparation of hexanoic acid. CrO_3 (38 g, 0.38 mol) was added, in small lots, to ice-cooled and stirred Ac_2O (400 ml). The mixture was allowed to attain rt slowly (CAUTION !). 1-Acetoxy heptene (20.0 g, 0.13 mol), was then added dropwise, over 0.25 hr, and the mixture stirred for 3 hr. Solvents were evaporated *in vacuo*, the residue admixed with $2NH_2SO_4$ (1 L), extracted with benzene. The dried ($MgSO_4$) benzene extract was evaporated, the residue treated with sat $NaHCO_3$aq, extracted with ether, the aqueous layer carefully acidified with ice-cold 2NHCl and the liberated oil extracted with ether. Evaporation of the dried ($MgSO_4$) ether extract gave 9.87 g of the hexanoic acid (67%, b.p. (45–46°/0.9 mm). It was characterised as its anilide and was compared with an authentic sample. Anilide: m.p. 93–94° (colourless crystals); mixed m.p. with authentic sample 93°C. Mass: *m/e* 191.

IX. *Transformation of n-heptaldehyde* (**4**) *to heptene oxide*

1-Heptene. An intimate mixture of activated alumina (90 g) and n-heptanol (15 g, 0.13 mol)—prepared by Fe/AcOH reduction of n-heptaldehyde[19]—was heated at 500°, under set-up for downward distillation, for 0.5 hr. The organic layer was separated, dried ($MgSO_4$) and the crude product (1-heptene content ~80% by NMR) distilled to give 6.5 g (51%) of 1-heptene, b.p. 92–94°.

1-Heptene oxide. To an ice cooled and stirred soln of perbenzoic acid (14 g, 0.1 mol) in $CHCl_3$ (235 ml) was added, in drops, a soln of 1 heptene (9 g, 0.09 mol) in $CHCl_3$ (10 ml). The mixture was stirred for 1.5 hr, washed with 2 N NaOH, water, dried ($MgSO_4$), solvents evaporated and the residue fractionated to give 7 g (69%) of 1-heptene oxide, b.p. 137°. NMR: $\delta_{(CDCl_3)}$: 2.65 (br, t proton), 2.5 (q), 2.2 (q) (epoxide methylene).

X. *Reaction of* C_{10}-$\alpha\beta$-*unsaturated aldehyde synthon with cyclopentadiene*

Isolation of adduct (**6**). Under N_2 and stirring a soln of the aldehyde (6.4 g, 0.032 mol), in xylene (25 ml), was admixed with freshly cracked cyclopentadiene (5 × 7 ml); and the mixture refluxed for 15 hr. Solvents were evaporated *in vacuo* and the residue was chromatographed over silica-gel. Elution with benzene: EtOAc (95:5) gave 6.2 g (73%) of the adduct bp 150–155°/0.2 mm; $R_f = 0.6$ (90% PhH: 10% EtOAc). A pure sample of **6** was prepared by careful preparative tlc on silicagel with multiple development (97% PhH: 3% EtOAc). (Found: C, 72.68; H, 9.19. Calcd for $C_{16}H_{24}O_3$: C, 72.69: H, 9.15%). IR: ν_{max}(neat)(cm^{-1}): 1740 (ester), 1715 (aldehyde). NMR: $\delta_{(CDCl_3)}$: 9.65 (d, J = 2.5 Hz, 1 H, CHO), 6.04 (m, 2 H, olefinic), 3.66 (s, 3 H, ester).

XI. *Preparation of triethyl methoxy ethoxy methyl ammonium chloride (MEM salt)*

Under stirring, a steady stream of dry HCl was passed through a mixture of 2-methoxy ethanol (45.6 g, 0.6 mol) and paraformaldehyde (19.8 g, 0.66 mol), until the mixture became homogeneous, then diluted with hexane (270 ml), dried (overnight at 5° over 30 g $MgSO_4$) and solvents evaporated *in vacuo* to give 65.2 g (87%) of almost colourless MEM chloride which was used, without purification, for the next reaction.

Under stirring and anhydrous conditions, a soln of freshly distilled triethylamine (68.27 g, 0.67 mol), in dry ether (100 ml), was added, in drops, to a soln of MEM-chloride (65.2 g, 0.52 mol), in dry ether (150 ml), the mixture left stirred overnight, solvents decanted and the residual crystalline mass washed with dry petroleum ether (40–60°) and dried *in vacuo*, yield 88.56 g (75%); m.p. 59–61°C.

XII. *Sodium borohydride reduction of key* C_{10}-*adduct* **6**

Preparation of alcohol (**14**). Under stirring and ice-cooling, a soln of aldehyde (15 g, 0.056 mol) in MeOH (30 ml), was added, in drops, to a suspension of $NaBH_4$ (5.5 g, 0.15 mol), in MeOH (15 ml). The mixture was stirred over night at rt, neutralised with AcOH, solvents evaporated *in vacuo*, the residue diluted with water and repeatedly extracted with CH_2Cl_2, the organic extract washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and solvents evaporated to yield 14.88 g (97.9%) of nearly pure (tlc) alcohol. A sample was further purified by preparative tlc and "bulb-distillation"; b.p. 160–165°/0.2 mm; $R_f = 0.5$, (85% PhH: 15% EtOAc). (Found: C, 72.05; H, 9.81. Calcd for $C_{16}H_{26}O_3$: C, 72.18; H, 9.77%). IR: ν_{max}(neat)(cm^{-1}): 3380 (hydroxyl), 1734 (ester). NMR: $\delta_{(CDCl_3)}$: 6.05 (m, 2 H, olefinic), 3.78 (m, 2 H, $-CH_2-OH$), 3.66 (s, 3 H, ester).

XIII. *Reaction of alcohol* (**14**) *with triethyl methoxy ethoxymethyl ammonium chloride*

Preparation of MEM ester (**15**). A soln of **14** (14.48 g, 0.054 mol) and MEM salt (13.53 g, 0.06 mol), in dry acetonitrile (75 ml), was refluxed for 2 hr, solvents evaporated *in vacuo*, the residue diluted with water and extracted with CH_2Cl_2, dried ($MgSO_4$) and solvents evaporated to give 17.5 g (91%) of MEM ester. Chromatography on silicagel followed by elution (PhH: EtOAc: 95:5) gave 9 g of pure **15**, b.p. 170–175°/0.18 mm. (Found: C, 67.68; H, 9.54. Calcd for $C_{20}H_{34}O_5$: C, 67.79: H, 9.60%). IR: ν_{max}(neat)(cm^{-1}): 1720 (ester).

NMR: $\delta_{(CDCl_3)}$: 6.05 (m, 2 H, olefinic), 4.68 (s, 2 H, $-O-CH_2-O-$). 3.69 (s, 3H, $COOCH_3$), 3.60 (m, 6H, $-CH_2-O-CH_2-CH_2-O$), 3.37 (s, 3H, $-OCH_3$).

XIV. *Saponification of MEM ester* (**15**)

Preparation of MEM acid (**16**). To a stirred suspension of **15** (18.0 g, 0.051 mol), in 150 ml 2N KOH (16.8 g in 150 ml soln), at room temp. (20°), was added, in drops, MeOH, until the soln became clear (~120 ml). The mixture was stirred for 48 hr, concentrated *in vacuo* to ~100 ml, extracted repeatedly with ether, the aqueous layer was carefully acidified with ice-cold 2NHCl and extracted repeatedly with CH_2Cl_2. The dried ($MgSO_4$) organic extract on evaporation gave 16.26 g (94%) of **16**. (Found: C, 66.92; H, 9.44. Calcd for $C_{19}H_{32}O_5$ (Mol. Wt. 340): C, 67.06; H, 9.41%). IR: ν_{max}(neat)(cm^{-1}): 1700 (carboxyl).

NMR: $\delta_{(CDCl_3)}$: 6.05 (m, 2H, olefinic), 4.68 (s, 2H, $-O-CH_2-O-$), 3.58 (m, 6 H, $-CH_2O$, $-O-CH_2-CH_2-O-$), 3.35 (s, 3 H, $-OCH_3$).

XV. *Cleavage of MEM acid* (**16**)

Isolation of dialdehyde (**17**). Under stirring and protection from light, OsO_4 (0.1 g) was added to a soln of the MEM-acid (3.5 g, 0.0102 mol), in dioxan (25 ml), the mixture stirred for 0.25 hr, then admixed with, in drops, a soln of $NaIO_4$ (4.5 g, 0.021 mol), in water (35 ml), over 1 hr, stirred overnight, filtered, the residue (sodium-iodate) washed with ether, the combined filtrate and washings evaporated *in vacuo*, the residue extracted repeatedly with CH_2Cl_2, the organic extract washed with brine, dried ($MgSO_4$) and solvents evaporated to yield 3.45 g (90%) of **17**, $R_f = 0.5$, (PhH: dioxan: AcOH, 80:40:1), which was used immediately, without purification, for Grignard reaction. IR: ν_{max}(neat) cm^{-1}): 1706 (Carbonyl).

XVI. *Reaction of dialdehyde* (**17**) *with* MeMgI

Preparation of diol (**18**).

Under N_2, a soln of **17** (3.52 g, 0.0094 mol), in dry ether (35 ml), was added, at rt (25°), over 0.25 hr, to stirred ethereal MeMgI made from Mg (1.14 g, 0.047 g atom), and MeI (6.67 g, 0.047 mol),

in 50 ml ether. After 1 hr, at rt, 1,2-dimethoxyethane (50 ml) was introduced, the mixture refluxed for 6 hr, the Grignard complex decomposed with ice-cold sat NH_4Cl aq, extracted with ether and the dried ($MgSO_4$) ether extract on evaporation gave 3.21 g (84%) of **18**. (Found: C, 62.51; H, 9.84. Calcd for $C_{21}H_{40}O_7$: C, 62.37; H, 9.9%). IR: ν_{max}(neat)(cm^{-1}): 3440 (hydroxyl), 1705 (carboxyl).

NMR: $\delta_{(CDCl_3)}$: 4.72 (s, 2 H, $-O-CH_2-O-$), 3.62 (m, 6 H, $-CH_2-O-$, $-O-CH_2-CH_2-O-$), 3.39 (s, 3 H, $-OCH_3$).

XVII. *Esterification of diol acid* (**18**)

Preparation of ester (**19**). A soln of **18** (3.5 g, 0.0086 mol), in ether (20 ml), was treated with ethereal diazomethane, till slight excess was indicated by the yellow colour. The excess reagent was destroyed with dil AcOH, the mixture washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and solvents evaporated to yield 3.55 g (98%) of **19** b.p. 190–195°/0.05 mm. (Found: C, 63.39; H, 10.16. Calcd for $C_{22}H_{42}O_7$: C, 63.15; H, 10.04%). Ir; ν_{max}(neat)(cm^{-1}): 3534 (hydroxyl), 1738 (ester).

NMR: $\delta_{(CDCl_3)}$: 4.72 (s, 2 H, $-O-CH_2-O$), 3.62 (m, 9 H, $-CH_2-O$, $-O-CH_2-CH_2-O-$, $COOCH_3$), 3.39 (s, 3 H, $-OCH_3$).

XVIII. *Collins oxidation of diol* (**19**)

Preparation of the diacetyl compound (**20**). Solid CrO_3 (8 g, 0.08 mol) was added gradually, to a stirred soln of dry pyridine (15 ml), in dry CH_2Cl_2 (20 ml). After 0.25 hr, a soln of **19** (2.0 g, 0.0049 mol), in CH_2Cl_2 (20 ml), was added gradually and then stirred for 48 hr during which a black solid separated. The mixture was decanted, the residue repeatedly extracted with CH_2Cl_2, the combined extracts and the decanted portion washed with 5% sodium-metabisulphite, sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and solvents evaporated. The crude product was passed quickly through a short column of silica-gel. Elution with 40% CH_2Cl_2: 60% PhH gave 1.6 g (81%) of **20**: b.p. 200°/0.1 mm; R_f = 0.8 (50% acetone: 50% hexane). (Found: C, 63.83; H, 9.06. Calcd for $C_{22}H_{38}O_7$: C, 63.76; H, 9.17%. IR: ν_{max}(neat)(cm^{-1}): 1730 (ester), 1700 (carbonyl).

NMR: $\delta_{(CDCl_3)}$: 4.70 (s, 2 H, $-OCH_2-O$), 3.6 (m, 9 H, $-CH_2-O-$, $-O-CH_2-CH_2-O$, $-COOCH_3$), 3.38 (s, 3 H, $-OCH_3$), 2.18 (s, 6 H, $-COCH_3$).

XIX. *Bayer Villiger oxidation of diacetyl compound* (**20**)

Preparation of key di-acetate (**21**). A stirred soln of **20** (400 mg, 0.00096 mol) and *m*-chloroperbenzoic acid (496 mg, 0.00288 mol, ~3 equiv) in 1,2-dichloroethane (15 ml), was kept at 80–82°, for 4 hr, diluted with CH_2Cl_2 and centrifuged at −20°. The supernatant was evaporated *in vacuo*, the residue triturated with sat $NaHCO_3$aq, extracted repeatedly with CH_2Cl_2 and solvents evaporated to give nearly pure (tlc) **21** (341 mg, 79%). (Found: C, 59.04; H, 8.46. Calcd for $C_{22}H_{38}O_9$: C, 59.19; H, 8.52%). IR: ν_{max}(neat)(cm^{-1}): 1730 (carbonyl).

NMR: $\delta_{(CDCl_3)}$: 5.47 (m, 2 H, ), 4.66 (s, 2 H, $-O-CH_2-O-$), 3.6 (m, 9 H, $-CH_2-O-$, $O-CH_2-CH_2-O-$, $COOCH_3$), 3.36 (s, 3 H, $-OCH_3$), 2.17 (s, 6 H, $-OCOCH_3$).

XX. *Cleavage of MEM grouping from* **21**

Preparation of diacetate alcohol **22**. Under stirring and ice-cooling, a 10% soln of $TiCl_4$ in hexane (3.8 ml, 0.0034 mol), was added to a soln of **21** (800 mg, 0.0017 mol), in CH_2Cl_2 (10 ml). The mixture was stirred for 5 min, quenched with 10% NH_4OH (3 ml), centrifuged at −20°, the supernatant diluted with CH_2Cl_2, washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated to yield almost pure (tlc) **22**, yield, 536 mg (83%). (Found: C, 60.27; H, 8.45. Calcd for $C_{18}H_{30}O_7$: C, 60.33; H, 8.37%). NMR: $\delta_{(CDCl_3)}$:

5.7 (m, 2 H, ), 3.6 (s, 3 H, $COOCH_3$), 2.09 (s, 6 H, $-OCOCH_3$).

XXI. *Collins oxidation of alcohol* **22**

Isolation of aldehyde **7**. Under N_2, stirring and at 0°, CrO_3 (0.6 g, 0.006 mol), was added, in lots, to a soln of dry pyridine (1 ml), in dry CH_2Cl_2 (5 ml). After 0.5 hr, a soln of **22** (400 mg, 0.001 mol) in CH_2Cl_2 (5 ml), was introduced. The mixture was stirred for 0.5 hr, decanted from the black deposit, which was washed repeatedly with CH_2Cl_2 and the combined organic extracts and decanted liquid washed with 5% sodium-metabisulphite, sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and evaporated *in vacuo*. The crude product was passed quickly through a short column of silica gel (15 g) and elution with 50% PhH: 50% CH_2Cl_2 gave 295 mg (74%) of the aldehyde as an almost colourless liquid which was immediately used in the Wittig reaction.

XXII. *Reaction of aldehyde* **7** *with sodium dimethyl (2-oxo-heptyl) phosphonate*

Isolation of enone **23**. Under N_2 and stirring, a soln of dimethyl 2-oxo heptyl phosphonate (115 mg, 0.0006 mol) in dimethoxyethane (5 ml), was added, in drops, to a suspension of NaH (48 mg; 0.001 mol; 50% dispersion in oil), in dimethoxy ethane (5 ml), when a thick white ppt appeared. The mixture was stirred for 1 hr, and admixed with, in drops, with a soln of **7** (200 mg, 0.00059 mol), in dimethoxy ethane (10 ml), when most of the white ppt disappeared. The mixture was then refluxed for 6 hr, neutralised with AcOH, solvents evaporated and the residue on preparative tlc and elution with 20% MeOH: 80% PhH gave 207 mg of **23** (81%). IR: ν_{max}(neat)(cm^{-1}): 1740 (ester), 1680 (α,β-unsaturated ketone), 1630 (double bond). NMR: $\delta_{(CDCl_3)}$: 6.86 (1 H, m, $CH=$), 6.14 (1 H, m, $=CHCO$), 3.66 (s, 3 H, ester), 2.16 (s, 6 H, $COCH_3$).

XXIII. *Sodium borohydride reduction of enone* **23**

Preparation of $PGF_1\alpha$ diacetate methyl ester (**24**). To a well stirred slurry of $NaBH_4$ (210 mg, 0.0057 mol), in MeOH (10 ml), at rt, was added a soln of **23** (150 mg, 0.00033 mol), in MeOH (4 ml), the mixture stirred for 3 hr, neutralised with AcOH, solvents evaporated and the residue extracted repeatedly with CH_2Cl_2. The organic phase was washed with sat bicarbonate, brine, dried ($MgSO_4$) and evaporated to yield 140 mg (94%) of **24** IR: ν_{max}(neat)(cm^{-1}): 3486 (OH), 1738 (ester).

XXIV. *Acetylation of* **24**

Preparation of $PGF_1\alpha$-tri-acetate methyl ester (**25**). A soln of **24** (9 mg; 0.000022 mol), in Ac_2O (0.5 ml), was admixed with 1 drop of pyridine and the mixture left aside for 1 hr. Solvents were evaporated *in vacuo* to yield 9 mg of **25**. IR: ν_{max}(neat) (cm^{-1}): 1752 (ester).

XXV. *Preparation of authentic $PGF_1\alpha$ tri-acetate methyl ester*

(a) *$PGF_1\alpha$ methyl ester.* An ether soln of $PGF_1\alpha$ (10 mg) was treated with ethereal diazomethane till slight excess was present. The excess reagent was destroyed with dil AcOH, the ether layer washed with sat $NaHCO_3$aq, brine, dried ($MgSO_4$) and solvents evaporated to yield 10 mg of the desired $PGF_1\alpha$-methyl ester; R_f = 0.8 ($CHCl_3$: MeOH: H_2O: 80:20:2).

(b) *Preparation of $PGF_1\alpha$ triacetate methyl ester.* 4 Drops of Ac_2O (first) and 2 drops of pyridine were added to $PGF_1\alpha$-methyl ester (neat), from the previous experiment. The mixture was left at rt for 1 hr and solvents evaporated *in vacuo*, to yield tri-acetoxy $PGF_1\alpha$-methyl ester (10 mg); R_f = 0.9 ($CHCl_3$: MeOH: H_2O: 80:20:2). IR: ν_{max}(neat)(cm^{-1}): 1752 (ester).

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