The Preparation of Dioxaprostacyclin Analogues from D-(—)-Ribose

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Using D-(−)-ribose as chiral starting material, we have prepared 1-deoxy-D-ribofuranose by a novel route, and then employed both compounds as precursors of the dioxaprostacyclin analogues (2).

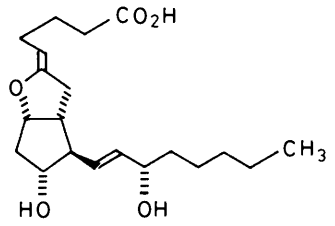
Since the discovery of prostacyclin (PGI_2) (1) in 1976,[1a] there has been a flurry of research activity directed towards the synthesis of PGI_2 itself, and of more stable analogues.[1b] The ultimate prize would be a molecule of reasonable biological half-life which had, like PGI_2, the ability to prevent aggregation of blood platelets. Such a compound would have obvious potential in the treatment of arteriosclerosis and other diseases of the cardiovascular system.

We sought to prepare analogues of general structure (2) by a short and flexible synthetic sequence commencing with D-(−)-ribose. This molecule has the right relative stereochemistry at three contiguous chiral centres (C-2, C-3, and C-4) for elaboration into the desired analogues. It is also reasonably inexpensive and readily available, and there is ample precedent in the literature for the use of sugars as chiral starting materials for the synthesis of prostanoids and other natural products.[2]

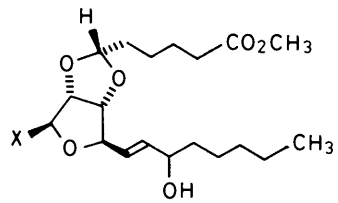
Methyl β-D-ribofuranoside (3a) was prepared in 98% yield from D-(−)-ribose using methanol, and concentrated sulphuric acid as catalyst—the ratio of anomers (β : α) was *ca.* 4 : 1. This mixture was treated with methyl, 6,6-dimethoxyhexanoate in refluxing 1,2-dichloroethane, containing a catalytic quantity of pyridinium tosylate.† Two products were obtained, and the major one (42% isolated yield) has been assigned structure (4a) (*vide infra*). The anomeric proton appeared as a singlet at δ 4.98 in the ^1H n.m.r. spectrum, and the acetal proton as a triplet at δ 4.87 (*J* 4 Hz). Formation of acetals under conditions of kinetic or thermodynamic control is known to favour production of the *endo* isomer (acetal proton *exo*),[3] and it is usually possible to assign the configuration if both products are obtained since the *endo*-proton resonates at lower field.[4] Unfortunately, the minor product (isolated in 8% yield) had an α-methoxy group (anomeric proton at δ 4.95, doublet, *J* 4 Hz), and although the acetal proton appeared as a triplet (*J* 5 Hz) at lower field (δ 5.28), it is impossible to assign structures on the basis of this evidence alone. N.O.e. experiments were carried out, but were not conclusive.

Although the major product (4a) was crystalline, crystals suitable for an *X*-ray crystallographic analysis could not be obtained. The same was true for the 5-*O*-benzoyl, 5-*O*-(3-nitrobenzoyl), and 5-*O*-(4-phenylbenzoyl) derivatives, which were obtained as oils or microcrystalline products.

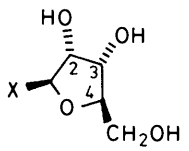
In order to try to ascertain the likely chemical shift for *endo*- and *exo*-acetals of this type, we treated (3a) with 1,1-dimethoxyethane under the same conditions. Once again there was one major product (acetal proton at δ 4.97, quartet, *J* 5 Hz; anomeric proton at δ 4.99, singlet), but small amounts of a second acetal with a β-methoxy group were also isolated (acetal proton at δ 5.30, quartet; anomeric proton at δ5.00, singlet), and it seems reasonable to assign structures (5a) and (5b) to the major and minor isomers respectively. On this basis, the assigned structure (4a) would seem most likely in the light of the similarity in the chemical shifts of the acetal proton of this major product and that of the major product (5a).



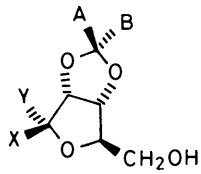
(1)



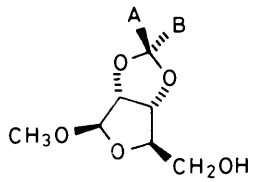
(2) a ; X = OCH_3
b ; X = H



(3) a ; X = OCH_3
b ; X = H



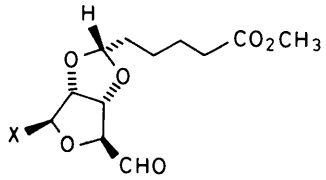
(4) a ; X = OCH_3, Y = A = H, B = $[CH_2]_4CO_2CH_3$
b ; X = Y = A = H, B = $[CH_2]_4CO_2CH_3$



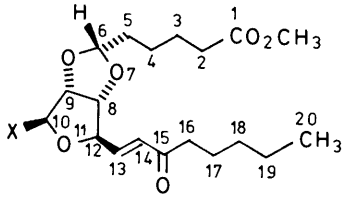
(5) a ; A = H, B = CH_3
b ; A = CH_3, B = H

The primary hydroxy group of (4a) was oxidised to the aldehyde (6a) (isolated as its hydrate) using freshly prepared Collins' reagent, and the eight-carbon appendage was applied using a Wittig reaction between (6a) and the sodio derivative of dimethyl 2-oxoheptylphosphonate. Finally, the vinyl ketone thus formed, compound (7a) [36% overall from (4a)],

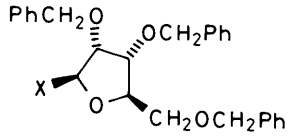
† Tosylate = toluene-*p*-sulphonate.



(6) a; X = OCH_3
b; X = H



(7) a; X = OCH_3
b; X = H



(8) a; X = OH
b; X = H
c; X = OCH_3

was reduced with sodium borohydride to produce (6*R*)-11-deoxy-10β-methoxy-7,11-dioxa-PGI_1* methyl ester (2a) as a *ca.* 1 : 1 mixture of stereoisomers at C-15 (two ester singlets were discernible in the ^1H n.m.r. spectrum).

A similar sequence of reactions, using 1-deoxy-D-ribofuranose (3b) as chiral starting material, produced (6*S*)-11-deoxy-7,11-dioxa-PGI_1 methyl ester (2b), again racemic at C-15. Only one acetal was formed upon reaction of (3b) with methyl 5-formylpentanoate, and this is assigned structure (4b) since the acetal proton resonated at δ 4.95.

For this second route a new synthesis of (3b) was required, since established routes [5] were either tedious or low-yielding. We had noted the report by Kikugawa [6] on the synthesis of non-symmetrical ethers from aldehydes using pyridine–borane complex in the presence of trifluoroacetic acid, *viz.* equation (1). It seemed to us that a similar reaction might

$$RCHO + R'CHO \longrightarrow RCH_2OCH_2R' \quad (1)$$

yield 1-deoxy-D-ribose from a suitably protected D-ribose derivative. Indeed treatment of 2,3,5-tri-*O*-benzyl-β-D-ribofuranose (8a) with pyridine–borane complex [7] (3.5 mmol per mmol of substrate) in trifluoroacetic acid (3 ml per mmol of substrate) at room temperature produced (within 10 min) a 64% isolated yield of 2,3,5-tri-*O*-benzyl-1-deoxy-D-ribofuranose (8b). Hydrogenolysis of this gave 1-deoxy-D-ribofuranose (3b) in quantitative yield as a white crystalline solid, m.p. 97—99 °C (lit.,[5] 100—101 °C). A similar result [60% yield of (8b)] was obtained using methyl 2,3,5-tri-*O*-benzyl-β-D-ribofuranoside (8c). When borane–tetrahydrofuran complex was used with either substrate (in trifluoroacetic acid), (8b) was produced in lower yield (*ca.* 30%).

Preliminary biological testing of (2a) and (2b) showed that both had agonist activity: analogue (2a) had 4 times, and (2b) 60 times, the potency of $PGF_{2\alpha}$ as constrictors of bronchial smooth muscle from guinea pig lung. Unfortunately, neither compound had any effect upon preparations of blood platelets.

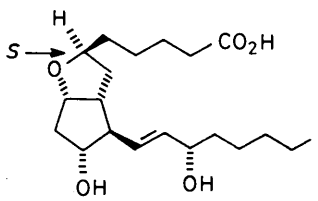
Experimental

I.r. spectra were recorded with a Perkin-Elmer 157 double-beam grating spectrophotometer (for liquid films unless otherwise stated). ^1H N.m.r. spectra were recorded with a Varian T-60 (60 MHz) or Varian HA 100 (100 MHz) instrument (tetramethylsilane as internal reference); ^{13}C n.m.r. spectra were recorded by Dr. Brian Wood at the City of London Polytechnic on a Jeol FX90Q (90 MHz) instrument; and mass spectra were recorded on a A.E.I. MS 12 instrument. Kieselgel $GF_{254+354}$ (Merck) was used for analytical t.l.c., and flash chromatography was performed using Merck Kieselgel 60 (230—400 mesh). Organic solvents were dried by distillation from calcium hydride when required anhydrous. High-resolution mass spectra (exact mass data) were obtained (by P.C.M.U.) for all new liquid compounds, and these were judged to be pure if they produced single spots in several different t.l.c. systems, and showed no spurious resonances in 100 MHz spectra. Light petroleum refers to that fraction boiling in the range 40—60 °C).

Methyl β-D-*Ribofuranoside* (3a).—D-Ribose (23.1 g, 154 mmol) was dissolved in methanol (150 ml) and the solution was cooled to 0 °C. Concentrated H_2SO_4 (2 ml) was added and, after being kept overnight at 0 °C, the solution was passed over Amberlite IR-45 (OH) resin until neutral to universal indicator paper. The eluate was dried and concentrated to yield a golden syrup (25.0 g, 98%). T.l.c. analysis showed two spots [major—R_F 0.62, minor—R_F 0.51; Et_2O–MeOH (9 : 1) with two elutions] which appeared to be in the ratio *ca.* 4 : 1. This is in accord with literature precedent for typical β : α ratios produced by this method. The mixture was used without further purification and had $\nu_{max.}$ 3 350br (OH), 1 645br, and 1 035br cm^{-1}; δ(D_2O) 3.4 (3 H, s, OMe) and 3.6—4.2 (6 H, m, CH).

Methyl 6-*Hydroxyhexanoate*.—Caprolactone (22.8 g, 0.2 mol) was added to a solution of $LiOH \cdot H_2O$ (8.4 g, 0.2 mol) in methanol–water (60 ml and 40 ml) and the solution was stirred at 45 °C for 20 h, then cooled and washed with di-

* According to *Chemical Abstracts*, PGI_1 is (6*S*,9α,11α,13*E*,15*S*)-6,9-epoxy-11,15-dihydroxyprost-13-en-1-oic acid (shown here), *i.e.* with a 6α-hydrogen atom. However, other workers in this



PGI_1 (*Chem. Abstr.*)

field have used the name PGI_1 to imply the acid with *unspecified* stereochemistry at C-6; individual epimers were then given the appropriate *R* or *S* stereochemical designator (*e.g.* see A. Johnson, F. H. Lincoln, E. G. Nidy, W. P. Schneider, J. L. Thompson, and U. Axen, *J. Am. Chem. Soc.*, 1978, **100**, 7690).

chloromethane. The aqueous layer was cooled to 0 °C, acidified to pH 1 with 6M HCl, and extracted with ethyl acetate to yield a yellow oil after concentration. The hydroxy acid thus formed was esterified by treatment with methanol (95 ml) and concentrated H_2SO_4 (5 ml) at room temperature for 48 h. After concentration, washing with water, and neutralisation with saturated aqueous $NaHCO_3$, the hydroxy ester was extracted into dichloromethane. After being dried and evaporated the solution yielded an oily product (17.3 g, 58%) which was used without further purification and had $\nu_{max.}$ 3 400br (OH) and 1 735 (ester C=O) cm^{-1}; δ ($CDCl_3$) 1.8 (6 H, m, 3-, 4-, and 5-H_2), 2.6 (2 H, t, *J* 3 Hz, 2-H_2), 3.45 (1 H, s, OH), 3.7 (2 H, m, 6-H_2), and 3.9 (3 H, s, OMe).

Methyl 5-Formylpentanoate.—(i) A solution of the preceding hydroxy ester (1.8 g, 12.5 mmol) in benzene (30 ml) was stirred with pyridinium chlorochromate (PCC) adsorbed onto alumina (26 g; equivalent to 25 mmol of PCC) at room temperature for 2 h. After filtration and rough chromatography using a column of $MgSO_4$, an oily product (1.55 g, 87%) was obtained after evaporation of the eluate. This product was pure by t.l.c.

(ii) Oxalyl dichloride (11.0 g, 86.8 mmol) was cooled to −60 °C in dichloromethane (150 ml), and dimethyl sulphoxide (DMSO) (14.8 g, 189 mmol) was added. The solution was stirred for 20 min, and then the previously prepared hydroxy ester (11.2 g, 79 mmol) was added dropwise, at −60 °C, during 15 min. The solution was stirred for 30 min, then triethylamine (39.9 g, 395 mmol) was added and the solution was allowed to warm to room temperature. Water (200 ml) was added, and after being stirred for 15 min, the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 ml), and the combined organic extracts washed successively with 2M HCl, water, saturated aqueous Na_2CO_3, and water. After drying and concentration of the extracts a red oil (10.4 g, 96%) was obtained, R_F 0.79 (Et_2O), and this was used without further purification since no organic impurities were discernible. Spectroscopic data were as follows. $\nu_{max.}$ 2 705 (CHO) and 1 735 (ester and aldehyde C=O) cm^{-1}; δ ($CDCl_3$) 1.7 (4 H, m, 3- and 4-H_2), 2.4 (4 H, m, 2- and 5-H_2), 3.7 (3 H, s, OMe), and 9.8 (1 H, br m, CHO).

Methyl 6,6-Dimethoxyhexanoate.—Methyl 5-formylpentanoate (2.5 g, 17.5 mmol) and trimethyl orthoformate (26.7 g, 0.25 mol) were added to $CeCl_3.7H_2O$ (11.7 g, 31 mmol) in methanol (50 ml). After being stirred for 1 h at room temperature the mixture was poured into saturated aqueous $NaHCO_3$ and the product was extracted into diethyl ether (3 × 50 ml). The extract was dried and concentrated to give the acetal (2.4 g, 70%). This was pure by t.l.c. [R_F 0.43; light petroleum–diethyl ether (2 : 1)]; $\nu_{max.}$ 2 950, 1 740 (ester C=O), 1 140, 1 365, 1 170, 1 075, and 960 cm^{-1}; δ ($CDCl_3$) 1.4—1.7 (6 H, m, 3-, 4-, and 5-H_2), 2.2—2.5 (2 H, t, *J* 6 Hz, 2-H_2), 3.3 (6 H, s, acetal OMe), 3.7 (3 H, s, ester OMe), and 4.35 (1 H, t, *J* 5 Hz, 6-H).

Methyl 2,3-O-5′-Methoxycarbonylpentylidene-β-D-ribofuranoside (4a).—The previously prepared ester acetal (1.4 g, 7.4 mmol) was added to a solution of methyl β-D-ribofuranoside (3a) (mixture of anomers, *ca.* 4 : 1 β : α) (1.21 g, 7.4 mmol) in refluxing anhydrous 1,2-dichloroethane (40 ml). Pyridinium tosylate (0.2 g, 0.8 mmol) was then added and the mixture was heated under reflux for 7 h. After 2 h only one product was clearly discernible, but at the end of the reflux period another product was also visible. After concentration the reaction mixture was extracted with diethyl ether, and the products were purified by flash chromatography with diethyl ether as eluant to produce the major product (4a) (0.91 g, 42%) and a minor product (0.16 g, 8%). *Major product* (R_F 0.31; diethyl ether), white crystalline solid, m.p. 44 °C; $[\alpha]_D$ −47° (*c* 0.12, $CHCl_3$); $\nu_{max.}$ 3 450br (OH), 1 735 (ester (C=O), 1 440, 1 365, 1 200, 1 170, 1 140, 1 140, 1 110, 1 085, 1 045, and 975 cm^{-1}; δ_H ($CDCl_3$) 1.4—1.85 (6 H, m, 2′-, 3′-, and 4′-H_2), 2.2—2.4 (2 H, t, *J* 6 Hz, 5′-H_2), 3.2 (1 H, br, OH), 3.42 (3 H, s, 1-OMe), 3.64 (3 H, s, ester OMe), 3.58—3.82 (2 H, m, 5-H_2), 4.45 (1 H, m, 4-H), 4.5 (1 H, d, *J* 6 Hz, 2-H), 4.7 (1 H, d, *J* 6 Hz, 3-H), 4.87 (1 H, t, *J* 4 Hz, 1′-H), and 4.98 (1 H, s, 1-H); δ_C ($CDCl_3$) 173.672 (C=O), 109.211 (C-1′), 105.867 (C-1), 87.634 (C-4), 85.585 (C-2), 81.701 (C-3), 63.624 (C-5), 55.292 (ester methyl C), 51.230 (OMe at C-1), 33.761 (C-5′), 32.55 (C-2′), 24.531 (C-4′), and 23.096 (C-3′); *m/z* 259.119 (40% $C_{12}H_{19}O_6$) (Found: C, 53.4; H, 7.7. $C_{13}H_{22}O_7$ requires C, 53.77; H, 7.64%).

Minor product (R_F 0.15; diethyl ether), an oil; $\nu_{max.}$ 3 450, 1 735 (ester C=O), 1 440, 1 330, 1 140, and 1 060 cm^{-1}; δ ($CDCl_3$) 1.3—1.9 (6 H, m, 2′-, 3′-, and 4′-H_2) 2.4 (2 H, t, *J* 6 Hz, 5′-H_2), 3.45 (3 H, s, OMe at C-1), 3.65 (3 H, s, ester OMe), 3.6—3.8 (2 H, m, 5-H_2), 4.1—4.3 (1 H, br m, OH), 4.5—4.6 (2 H, m, 2- and 3-H), 4.95 (1 H, d, *J* 4 Hz, 1-H), and 5.2 (1 H, t, *J* 4 Hz, 1′-H).

(6R)-11,15-*Dideoxy*-10β-*methoxy*-15-*oxo*-7,11-*dioxa-PGI*$_1$ *Methyl Ester* (7a).—Chromium trioxide–dipyridine complex was prepared by stirring CrO_3 (1.2 g, 12 mmol) in a mixture of pyridine (1.2 ml, 24 mmol) and dichloromethane (25 ml) for 30 min at room temperature. A solution of the bicyclic alcohol (4a) (0.29 g, 1 mmol) in dichloromethane (5 ml) was then added, and the mixture was stirred for 30 min. Aqueous $NaHCO_3$ was added and the layers were separated; the organic layer was then washed with cold water, dried and, concentrated to yield the crude oxidation product. This was taken up in 1,2-dimethoxyethane (DME) (5 ml) and added at 0 °C to a stirred suspension of 50% sodium hydride in oil (60 mg, 1.5 mmol) and dimethyl 2-oxoheptylphosphate (330 mg, 1.5 mmol) in DME (20 ml) which had been previously stirred for one hour at room temperature. The mixture was stirred for one additional hour at 0 °C, and then at room temperature for 30 min. The solvent was removed and the product was purified by flash chromatography with diethyl ether as eluant. This yielded the ketone (7a) [141 mg, 36% from (4a)] (R_F 0.68, diethyl ether) which was rather unstable and was reduced immediately to yield (2a). Alternatively, immediate i.r. and n.m.r. data were obtained: $\nu_{max.}$ 1 740 (ester C=O), 1 700 (ketone C=O), 1 635, 1 460, 1 440, 1 135, 1 110, 1 090, and 980 cm^{-1}; δ ($CDCl_3$) 0.8—1.9 (15 H, m, 3-, 4-, 5-, and 17-, 18-, 19-H_2 and 20-H_3), 2.35 (2 H, t, *J* 6 Hz, 2-H_2), 2.55 (2 H, t, *J* 6 Hz, 16-H_2), 3.4 (3 H, s, acetal OMe), 3.7 (3 H, s, ester OMe), 4.1 (1 H, d, *J* 7 Hz, 12-H), 4.6—4.8 (3 H, m, 6-, 8-, and 9-H), 5.1 (1 H, s, 10-H), 6.25 (1 H, d, *J* 15 Hz, 14-H), and 6.8 (1 H, dd, *J* 15 and 7 Hz, 13-H).

(6R,15RS)-11-*Deoxy*-10β-*methoxy*-7,11-*dioxa-PGI*$_1$ *Methyl Ester* (2a).—A solution of the vinyl ketone (7a) (215 mg, 0.56 mmol) in methanol (2 ml) was added to a stirred solution of $NaBH_4$ (40 mg, 1.05 mmol) in methanol (5 ml) at −20 °C under nitrogen. After 90 min at this temperature the reaction was complete and the mixture was quenched with aqueous HCl (0.5M; 6 ml). After concentration, the oily product mixture was taken up in ethyl acetate (30 ml) and washed with aqueous H_2SO_4 (0.2M; 10 ml). The aqueous layer was extracted with ethyl acetate (3 × 10 ml) and the combined organic phases were then washed successively with saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and water. After flash chromatography the alcohol (racemic at C-15) (169 mg, 80%) was obtained, R_F 0.27 [diethyl ether–light petroleum (2 : 1)]; $\nu_{max.}$ 3 460br (OH), 1 735 (ester C=O), 1 140, 1 380, 1 135,

1 105, 1 080, 1 025, and 965 cm^{-1}; δ ($CDCl_3$) (220 MHz) 0.9 (3 H, t, *J* 6 Hz, 20-H_3), 1.2—1.8 (15 H, m, 3-, 4-, 5-, 16-, 17-, 18-, and 19-H_2 and OH), 2.33 (2 H, t, *J* 6 Hz, 2-H_2), 3.35 (3 H, s, acetal OMe), 3.7 (3 H, s, ester OMe), 4.55 (2 H, s, 8- and 9-H), 4.70 (1 H, d, *J* 5 Hz, 12-H), 4.9 (1 H, t, *J* 4 Hz, 6-H), 5.02 (1 H, s, 10-H), and 5.75 (2 H, m, 13- and 14-H); *m/z* 315.145 (2%, $M^+ - C_5H_{11}$. Calc. for $C_{15}H_{23}O_7$: *m/z* 315.144).

2,3,5-*Tri*-O-*benzyl*-1-*deoxy*-D-*ribofuranose* (8b).—2,3,5-Tri-*O*-benzyl-D-ribose (0.84 g, 2.0 mmol) was dissolved in trifluoroacetic acid (TFA) (6 ml) and cooled in an ice-bath prior to the dropwise addition of pyridine–borane [7] (0.66 g, 7 mmol). The solution was kept for 10 min, and then the TFA was removed under reduced pressure. The residual mixture was then treated with aqueous NaOH (8%; 38 ml) at reflux for 1 h. After being cooled the solution was extracted with diethyl ether and the extract was then washed in turn with dilute HCl and water. After drying and concentrating the extract, a crude product (0.7 g) was obtained which provided pure product (0.52 g, 64%) (R_F 0.56) after flash chromatography using light petroleum–diethyl ether (1 : 1) as eluant; $\nu_{max.}$ 1 500, 1 450, 1 370, 1 210, 1 130—1 070br, 1 030, 740, and 700 cm^{-1}; δ ($CDCl_3$) 3.3—3.7 (2 H, m, 5-H_2), 3.8—4.3 (5 H, m, 1-H_2 and 2-, 3-, and 4-H), 4.3—4.5 (6 H, m, $PhCH_2$) and 7.3 (15 H, s, Ph).

1-*Deoxy*-D-*ribofuranose* (3b).—Compound (8b) (5.6 g, 13.9 mmol) was dissolved in ethanol, the solution was added to palladium–charcoal (10%; 3.87 g), and the mixture was stirred vigorously while being exposed to an atmosphere of hydrogen. The mixture took up 99% of the theoretical volume of hydrogen (30 ml) during 3 h, and after filtration and concentration an orange oil (2.85 g, 99%) was obtained which crystallised with time, m.p. 97—100 °C (lit.,[5] 100—101 °C) (Found: C, 44.5; H, 7.25. Calc. for $C_5H_{10}O_4$: C, 44.77; H, 7.52%); $\nu_{max.}$ (Nujol) 3 500—3 050br (OH), 1 510, 1 380, 1 345, 1 325, 1 305, 1 230, 1 120, 1 090, 1 010, 970, 935, 895, 850, 735, 685, 640, and 510 cm^{-1}; δ_H ([$^2H_4$]MeOH) 3.25—6.3 (m); δ_C (DMSO) 84.6 (d, C-4), 73.5 (t, C-1), 73.1 and 71.9 (d and d, C-2 and C-3), and 63.3 p.p.m. (t, C-5).

1-*Deoxy*-2,3-O-5′-*methoxycarbonylpentylidene*-D-*ribofuranose* (4b).—1-Deoxy-D-ribofuranose (3b) (0.905 g, 6.75 mmol) and methyl 6,6-dimethoxyhexanoate (1.26 g, 6.75 mmol) were dissolved in refluxing anhydrous 1,2-dichloroethane (300 ml) and treated with pyridinium tosylate (0.17 g, 0.7 mmol). The mixture was refluxed for 6 h and then distilled with constant replenishment of the dichloroethane, for a further 5 h. After concentration and flash chromatography (diethyl ether as eluant), an off-white solid (0.87 g) was obtained. This microcrystalline material was recrystallised from diethyl ether to provide an analytical sample, R_F 0.23 (diethyl ether); m.p. 59 °C (Found: C, 55.15; H, 7.9. $C_{12}H_{20}O_6$ requires C, 55.36; H, 7.75%); $\nu_{max.}$ (Nujol) 3 490—3 350br (OH), 1 735 (ester C=O), 1 470, 1 440, 1 380, 1 365, 1 310, 1 240, 1 190, 1 180, 1 140, 1 100, 1 045, and 955 cm^{-1}; δ ($CDCl_3$) 1.2—2.0 (6 H, m, 2′-, 3′-, and 4′-H_2), 2.2 (1 H, m, OH), 2.4 (2 H, t, *J* 6 Hz, 5′-H_2), 3.5—3.7 (2 H, m, 5-H_2), 3.65 (3 H, s, ester OMe), 3.9—4.05 (2 H, m, 1-H_2), 4.1—4.25 (1 H, dd, *J* 3 and 5 Hz, 4-H), 4.45—4.55 (1 H, dd, *J* 7.5 and 3 Hz, 3-H), 4.6—4.85 (1 H, m, 2-H), and 4.95 (1 H, t, *J* 4 Hz, 1′-H).

(6S)-11,15-*Dideoxy*-15-*oxo*-7,11-*dioxa*-*PGI*$_1$ *Methyl Ester* (7b).—DMSO (0.14 ml, 1.9 mmol) was added to a solution of oxalyl dichloride (0.07 ml, 0.9 mmol) in dichloromethane (1.5 ml) at −60 °C. After the mixture had been stirred for 15 min, a solution of the alcohol (4b) (0.2 g, 0.8 mmol) in dichloromethane (1 ml) was added to the suspension, and the mixture was stirred for a further 20 min. Triethylamine (0.5 ml, 4 mmol) was then added and the solution was allowed to warm to room temperature. After the addition of water (2 ml), the organic phase was separated, and the aqueous phase was further extracted with CH_2Cl_2. The combined organic phases were then washed successively with dilute HCl, water, and aqueous Na_2CO_3. On drying and concentrating the organic phase, an oil (180 mg, 90% calculated for aldehyde) was obtained, and this was homogeneous by t.l.c. (R_F 0.44, diethyl ether).

To a suspension of sodium hydride (99 mg, 2.08 mmol) in DME (15 ml) was added a solution of dimethyl 2-oxoheptylphosphonate (0.46 g, 2.08 mmol) in DME (4 ml). This mixture was stirred for 1 h at room temperature, then cooled to 0 °C prior to the addition of a solution of the aldehyde (6b) (350 mg, 1.4 mmol, from two preparations as described above) in DME (5 ml). The temperature of the reaction mixture was maintained at 0 °C for 30 min, then the reaction temperature was allowed to rise to room temperature and was held there for 2 h. After flash chromatography with light petroleum–diethyl ether (2 : 1) as eluant the pure product (7b) (180 mg, 45%) was obtained. This was relatively unstable and was reduced immediately to (2b), apart from a small sample which was used immediately for i.r. and n.m.r. analysis. R_F 0.42 [light petroleum–diethyl ether (2 : 1)]; $\nu_{max.}$ 1 740 (ester C=O), 1 680 (ketone C=O), 1 635, 1 375, 1 410, 1 135 cm^{-1}; δ ($CDCl_3$) 0.88 (3 H, t, *J* 6 Hz, 20-H_3), 1.1—1.8 (12 H, m, 3-, 4-, 5-, 17-, 18-, and 19-H_2), 2.3 (2 H, t, *J* 6 Hz, 2-H_2), 2.5 (2 H, t, *J* 6 Hz, 16-H_2), 3.7 (3 H, s, ester OMe), 3.8 (1 H, dd, *J* 4 and 11 Hz, 10-H_α), 4.05 (1 H, d, *J* 11 Hz, 10-H_β), 4.4—4.8 (3 H, m, 8-, 9-, and 12-H), 4.95 (1 H, t, *J* 4 Hz, 6-H), 6.35 (1 H, dd, *J* 2 and 15 Hz, 14-H), and 6.7 (1 H, dd, *J* 4 and 15 Hz, 13-H).

(6S,15RS)-11-*Deoxy*-7,11-*dioxa*-*PGI*$_1$ *Methyl Ester* (2b).—A solution of the vinyl ketone (7b) (200 mg, 0.56 mmol) in methanol (1.5 ml) was added to a stirred solution of $NaBH_4$ (34 mg, 0.9 mmol) in methanol (3 ml) at −20 °C under nitrogen. After 30 min at −20 °C the reaction was quenched with HCl (4.5 ml; 0.5M), and the mixture was then concentrated and taken up into ethyl acetate and washed successively with H_2SO_4 (0.5M), water, and aqueous $NaHCO_3$. After drying and concentration of the solution the racemic alcohol (145 mg, 73%) was obtained, R_F 0.34 (diethyl ether), and this was further purified by preparative t.l.c. to provide an analytical sample as an oil, $\nu_{max.}$ 3 450 (OH), 1 740 (ester C=O), 1 440, 1 135, 970 cm^{-1}; δ ($CDCl_3$) 0.9 (3 H, t, *J* 6 Hz, 20-H_3), 1.1—1.9 (14 H, m, 3-, 4-, 5-, 16-, 17-, 18-, and 19-H_2), 2.3 (2 H, t, *J* 6.5 Hz, 2-H_2), 2.45 (1 H, br s, OH), 3.65 (3 H, s, ester OMe), 3.7—4.2 (3 H, m, 15-H and 10-H_2), 4.4—4.75 (3 H, m, 8-, 9-, and 12-H), 4.95 (1 H, t, *J* 4 Hz, 6-H), 5.55 (1 H, dd, *J* 4 and 15 Hz, 13-H), and 5.8 (1 H, dm, *J* 15 Hz, 14-H); *m/z* 285.132 (15%, $M^+ - C_5H_{11}.C_{14}H_{21}O_6$ requires *m/z* 285.133).

Acknowledgements

We thank Glaxo and the S.E.R.C. for a C.A.S.E. award (for E. B. W.), and Professor J. Grant Buchanan for helpful discussions concerning the stereochemistry of the acetals.

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Received 24*th March* 1983; *Paper* 3/462