Synthesis of the Prostaglandin H_2 Analogue DL-9,11-Ethano-9,11-dideoxaprostaglandin H_2

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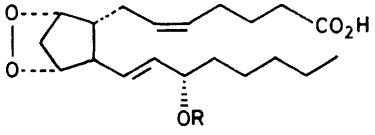
The total synthesis of the prostaglandin H_2 analogue, 9,11-ethano-9,11-dideoxaprostaglandin H_2 (3), starting from the known Diels–Alder adduct (4) is described.

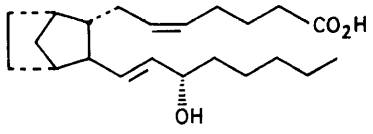
THE prostaglandin endoperoxides PGH_2(1) and PGG_2(2) are the precursors not only of the primary prostaglandins, but also of the thromboxanes (TXA_2 and B_2) and the prostacyclin (PGI_2) from arachidonic acid.[1-3]

Since these endoperoxides possess an interesting spectrum of biological activity coupled with their lability,[1,2] attention has been focused on obtaining stable PGH_2 analogues.

Here we report an efficient synthesis of the stable PGH_2 analogue (3), 9,11-ethano-9,11-dideoxaprostaglandin H_2 which may both facilitate studies on its mode of action and also be of clinical importance, in spite of other syntheses of PGH_2 analogues having already been reported.[4]



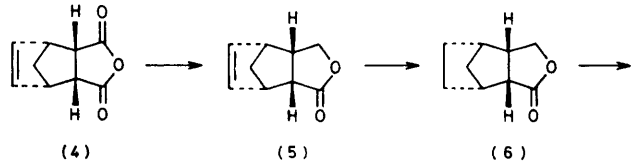
(1) R = H
(2) R = OH



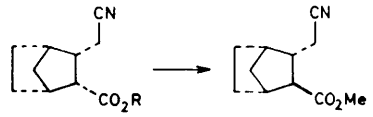
(3)

SCHEME 1

The initial synthetic target compound (9), was obtained as follows. The starting γ-butyrolactone (5) was obtained in 86.9% yield by sodium borohydride reduction of the known Diels–Alder adduct (4) [5] in dry dimethylformamide followed by acid treatment of the product at room temperature. Catalytic hydrogenation of compound (5) on 5% palladium–carbon in methanol afforded the dihydro-γ-butyrolactone (6) in quantitative yield. Introduction of a cyano-group by treatment of the γ-butyrolactone (6) with potassium cyanide afforded the desired carboxylic acid (7) which, without further purification, was treated with an excess of diazomethane to give the corresponding α-methyl ester (8) exclusively [77% overall yield from the γ-butyrolactone (6)]. None of the β-methyl ester (9) was observed.[6] Epimerisation of the α-isomer (8) using methanolic potassium carbonate at room temperature proceeded smoothly to afford the desired β-methyl ester (9) in 82—94% yield.



(4) (5) (6)



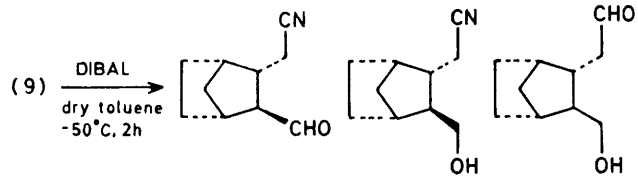
(7) R = H
(8) R = Me
(9)

SCHEME 2

Reduction of the methoxycarbonyl group in the presence of the cyano-group in the bicyclo[2.2.1]heptane derivative (9) by di-isobutylaluminium hydride was examined under several sets of conditions and the results are summarised in the Table. As can be seen, the use of four equivalents of di-isobutylaluminium hydride is most favourable to the production of the alcohol (11).

TABLE

Reduction of the bicyclo[2.2.1]heptane derivative (9) by di-isobutylaluminium hydride

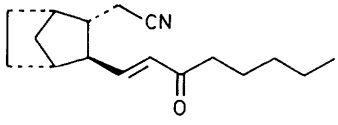


(9) DIBAL, dry toluene, -50°C, 2h

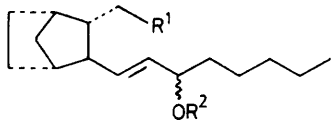
(10) (11) (12)

Reaction conditions DIBAL/methyl ester (mol ratio)	Products (yield %) (9)	(10)	(11)	(12)
1.2	27	0	26.4	0
2	27.6	6.8	53.6	0
4	0	0.92	96.9	0.9
6	0	0	50.1	12.5
8	0	0	38.8	24.5
10	0	0	39.5	26.8

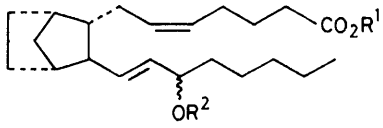
Oxidation [7] of the alcohol (11) and subsequent treatment of the resulting aldehyde (10) with the sodium-salt



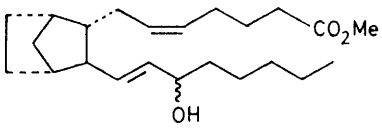
(13)



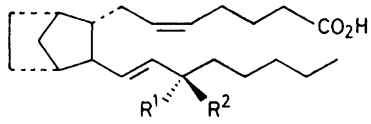
(14) R^1 = CN; R^2 = H
(15) R^1 = CN; R^2 = THP
(16) R^1 = CN; R^2 = Bu^tMe_2Si
(17) R^1 = CHO; R^2 = THP
(18) R^1 = CHO; R^2 = Bu^tMe_2Si



(19) R^1 = H; R^2 = THP
(20) R^1 = H; R^2 = Bu^tMe_2Si
(21) R^1 = Me; R^2 = THP
(22) R^1 = Me; R^2 = Bu^tMe_2Si



(23)



(3) R^1 = OH; R^2 = H
(24) R^1 = H; R^2 = OH

SCHEME 3

of dimethyl 2-oxoheptylphosphonate in benzene gave the enone (13) in 61.8% overall yield. Reduction of the latter with sodium borohydride in methanol at room temperature afforded the allyl alcohol (14) as a mixture of separable diastereoisomers. Without separation of this mixture, the hydroxy-group was protected as its tetrahydropyranyl or t-butyldimethylsilyl ether.[8] Introduction of the α side-chain was accomplished as follows. The reduction of both protected alcohols (15) and (16) using four equivalents of di-isobutylaluminium hydride followed by treatment of the reaction mixture with saturated ammonium chloride solution afforded the aldehydes (17) and (18) in 83 and 93.8% yield, respectively. Wittig reaction of the aldehydes (17) and (18) with the ylide derived from (4-hydroxycarbonylbutyl)-triphenylphosphonium bromide and dimesylsodium in dimethyl sulphoxide[9] afforded the desired carboxylic acids (19) and (20) in 84.7 and 33.2% yield, respectively. After esterification with ethereal diazomethane and cleavage of the tetrahydropyranyl ether of the resultant methyl ester (21) gave the hydroxylmethyl ester (23) as a mixture of C_{15} (PG numbering) diastereoisomers which were difficult to separate on a silica-gel column. However, cleavage of the tetrahydropyranyl ether of the carboxylic acid (19) afforded, in 96.5% yield, an almost 1 : 1 mixture of 9,11-ethano-9,11-dideoxaprostaglandin H_2 (3) and 9,11-ethano-9,11-dideoxa-15-*epi*-prostaglandin H_2 (24); these could be separated either on a silica-gel column or by thin layer chromatography. The more-polar isomer has been tentatively assigned the (15*S*) natural configuration.[4,10]

The synthetic method described herein would provide a versatile method for preparing stable PGH_2 analogues which contain a bridgehead heteroatom such as oxygen, nitrogen, or sulphur.

EXPERIMENTAL

M.p.s were determined on a Yazawa microapparatus. I.r. spectra were recorded with Shimadzu IR-400 spectrophotometer. Mass spectra were obtained with Hitachi M-52G and JEOL-MJS-O1SG-2 spectrometers. N.m.r. spectra were taken for solution in deuteriochloroform (tetramethylsilane as internal standard) with a JEOL JNM-PMX-60 instrument. All products described in experimental section were homogeneous by t.l.c. and h.p.l.c.

Sodium Borohydride Reduction of the Diels–Alder Adduct (4).—To a stirred ice-cooled solution of sodium borohydride (461 mg) in dimethylformamide (7 ml) was added dropwise over 10 min a solution of the anhydride (4.2 g) in dry dimethylformamide (10 ml). The temperature was kept below 20 °C. After 3 h, the solvent was removed below 40 °C under reduced pressure and the residue was carefully treated with 2N-sulphuric acid (20 ml). The mixture was

stirred for 3 h at room temperature and then extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue which was subjected to chromatography on silica gel (30 g). The elution with chloroform afforded the carbolactone (5) (1.59 g) as a colourless syrup, $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1}; δ ($CDCl_3$) 1.40 (1 H, d, *J* 9 Hz), 1.62 (1 H, d, *J* 9 Hz), 2.92—3.40 (4 H, m), 3.70 (1 H, dd, *J* 8 and 3 Hz), 4.20 (1 H, t, *J* 8 Hz), 6.15 (1 H, d, *J* 2 Hz), and 6.18 (1 H, d, *J* 2 Hz).

cis-*Bicyclo*[2.2.1]*heptane*-1,2-*carbolactone* (6).—The carbolactone (5) (1 g) was hydrogenated over 5% palladium on carbon (300 mg) in methanol (30 ml) at room temperature. Catalyst was filtered off and the filtrate was washed with methanol. Removal of the solvent left the residue (6) (1.01 g) as a colourless solid which on recrystallisation from n-hexane afforded the *carbolactone* (6) as colourless prisms, m.p. 108—111 °C (Found: C, 71.1; H, 8.0. $C_9H_{12}O_2$ requires C, 71.0; H, 7.95%); $\nu_{max.}$ ($CHCl_3$) 1 740 cm^{-1}; δ ($CDCl_3$) 1.33—1.67 (4 H, m), 2.37br (1 H, s), 2.60br (1 H, s), 2.73—3.07 (2 H, m), 4.20 (1 H, d, *J* 2 Hz), and 4.28 (1 H, d, *J* 2 Hz); *m/e* 152 (M^+).

cis-1-*Cyanomethyl*-2-*methoxycarbonylbicyclo*[2.2.1]*heptane* (8) *via* the *Carboxylic Acid* (7).—A mixture of the carbolactone (6) (959 mg) and potassium cyanide (820 mg) in dimethyl sulphoxide (10 ml) was heated for 3 h with stirring at 180 °C under nitrogen. The mixture was cooled to room temperature and then acidified with 1N-hydrochloric acid solution. The mixture was then extracted with ethyl acetate. The extract was washed with a small amount of brine, dried ($MgSO_4$), and then evaporated to leave the carboxylic acid (7) as a brown syrup, $\nu_{max.}$ ($CHCl_3$) 2 240 and 1 700 cm^{-1}. This compound was used in the following reaction without further purification.

The crude carboxylic acid (7) was treated with an excess of ethereal diazomethane. After the usual work-up, the crude residue was subjected to chromatography on silica gel (20 g). The elution with ethyl acetate–n-hexane (3 : 7, v/v) afforded the methyl ester (8) (956 mg) as a colourless syrup, $\nu_{max.}$ ($CHCl_3$) 2 240 and 1 720 cm^{-1}; δ ($CDCl_3$) 1.40—1.63br (6 H, s), 2.23—3.10 (6 H, m), and 3.62 (3 H, s); *m/e* 193 (M^+).

trans-1-*Cyanomethyl*-2-*methoxycarbonylbicyclo*[2.2.1]*heptane* (9).—To a stirred solution of the *cis*-methyl ester (8) (916 mg) in absolute methanol (5 ml) was added in small portions potassium carbonate (700 mg) at room temperature and the mixture was stirred for 7 h at room temperature under nitrogen. The mixture was poured into ether and the ethereal layer was separated, washed with brine, dried ($MgSO_4$), and then evaporated to leave the practically pure *trans*-methyl ester (9) (750 mg) as a colourless syrup, $\nu_{max.}$ ($CHCl_3$) 2 240 and 1 720 cm^{-1}; δ ($CDCl_3$) 1.03—2.30 (8 H, s); *m/e* 193 (M^+).

Reduction of trans-1-*Cyanomethyl*-2-*methoxycarbonylbicyclo*[2.2.1]*heptane* (9) by *Di-isobutylaluminium Hydride*.—To a cold solution of the methyl ester (9) (1.55 g) in dry toluene (40 ml) was added dropwise a solution of di-isobutylaluminium hydride (1.76M in hexane; 18.3 ml) over 20 min under nitrogen. The mixture was stirred for 2 h at −50 °C, quenched with saturated ammonium chloride solution, and then stirred for an additional 30 min. The mixture was filtered through a short Celite pad and washed with ethyl acetate. The filtrate was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue as a pale yellow syrup which was subjected to chromatography on silica gel (20 g). The first elution with chloroform afforded the aldehyde (10) (12 mg), $\nu_{max.}$ ($CHCl_3$) 2 700, 2 240, and 1 710 cm^{-1}; δ ($CDCl_3$) 1.03—2.13 (8 H, m), 2.30—2.80 (4 H, m), and 9.67 (1 H, s); *m/e* 163 (M^+). The second eluate gave the alcohol (11) (1.276 g), $\nu_{max.}$ ($CHCl_3$) 3 200—3 600 and 2 240 cm^{-1}; δ ($CDCl_3$) 0.90—2.0 (8 H, m), 2.27br (1 H, s, exchanged with D_2O), 2.23 (1 H, dd, *J* 8 and 4 Hz) and 3.26 (2 H, d, *J* 8 Hz), *m/e* 165 (M^+); and then the aldehyde (12) (30 mg), $\nu_{max.}$ ($CHCl_3$) 3 600—3 200, 2 730 and 1 720 cm^{-1}; δ ($CDCl_3$) 2.50 (2 H, dd, *J* 7 and 2 Hz), 3.43 (2 H, d, *J* 7 Hz) and 9.63 (1 H, t, *J* 2 Hz), *m/e* 168 (M^+).

Reduction of trans-1-*Cyanomethyl*-2-*methoxycarbonylbicyclo*[2.2.1]*heptane* (8) *by Di-isobutylaluminium Hydride*.—To a cold solution of the methyl ester (9) (215 mg) in dry toluene (5 ml) was added dropwise a solution of di-isobutylaluminium hydride (1.76M in hexane; 6.33 ml) over 10 min under nitrogen. The mixture was stirred for 2 h at −50 °C, quenched with saturated ammonium chloride solution, and then stirred for an additional 30 min. The mixture was filtered through a short Celite pad and washed with ethyl acetate. The filtrate was washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue which was subjected to chromatography on silica gel (10 g). The elution with chloroform afforded the aldehyde (12) (50.2 mg) and the alcohol (11) (50.2 mg), the i.r. and n.m.r. spectra of which were identical with those of authentic samples.

trans-1-*Cyanomethyl*-2-*formylbicyclo*[2.2.1]*heptane* (10).—The oxidizing reagent was prepared by addition of dimethyl sulphide (500 mg) in toluene (10 ml) to a stirred solution of *N*-chlorosuccinimide (820 mg) in toluene (20 ml) at 0 °C under nitrogen. The mixture was stirred for 45 min at 0 °C and then cooled to −20 °C. To the above mixture was added dropwise a solution of the alcohol (11) (670 mg) in toluene (10 ml). Stirring was continued for 2 h at −20 °C and then a solution of triethylamine (630 mg) in toluene (10 ml) was added. The resulting mixture was stirred for 23 h at room temperature and then washed with brine and dried ($MgSO_4$). Evaporation of the solvent left a residue as a pale yellow syrup which was subjected to chromatography on silica gel (15 g). Elution with chloroform afforded the aldehyde (10) (530 mg), the i.r. and n.m.r. spectra of which were identical with those of authentic sample.

trans-1-*Cyanomethyl*-2-[(*E*)-3-*oxo*-*oct*-1-*enyl*]*bicyclo*[2.2.1]-*heptane* (13).—To a stirred suspension of 50% sodium hydride dispersion (166 mg) in dry benzene (8 ml) was added dropwise a solution of dimethyl 2-oxoheptylphosphonate (769 mg) in dry benzene (15 ml) at room temperature under nitrogen. After the solution had been stirred at room temperature for 10 min, the mixture was treated with the aldehyde (10) (470 mg) in dry benzene (15 ml). After 2 h at room temperature the reaction mixture was quenched with saturated ammonium chloride solution, diluted with ether, washed with brine, and dried ($MgSO_4$). Filtration and evaporation of the solvent provided the crude enone which was chromatographed on silica gel (20 g). Elution with n-hexane–ethyl acetate (8 : 2, v/v) gave the pure enone (13) (569 mg) as a colourless syrup, $\nu_{max.}$ ($CHCl_3$) 2 260, 1 695, 1 670, and 1 625 cm^{-1}; δ ($CDCl_3$) 6.0 (1 H, d, *J* 16 Hz) and 6.63 (1 H, dd, *J* 16 and 8 Hz) (Found: M^+, 259.1965. $C_{17}H_{25}NO$ requires 259.1935).

trans-1-*Cyanomethyl*-2-[3-*tetrahydropyran*-2-*yloxy*-(E)-*oct*-1-*enyl*]*bicyclo*[2.2.1]*heptane* (15) and trans-1-*Cyanomethyl*-2-[3-*t*-*butyldimethylsilyloxy*-(E)-*oct*-1-*enyl*)*bicyclo*[2.2.1]*heptane* (16).—Sodium borohydride (150 mg) was added to a solution of the *trans*-enone (13) (500 mg) in methanol (10 ml) cooled to 0 °C. After 1 h, the reaction mixture was quenched

with water at 0 °C and the solvent evaporated. The residue was taken up in water and the product was isolated by extraction with chloroform. The combined extracts were washed with a small amount of brine and dried ($MgSO_4$). The solvent was removed to leave the practically pure allyl alcohol (14) (514.7 mg) as a colourless syrup which was a mixture of C_{15}-epimers (PG numbering); $\nu_{max.}$ ($CHCl_3$) 3 600—3 200 and 2 240 cm^{-1}; *m/e* 261 (M^+). This allyl alcohol (14) was used in the next reaction without further purification.

A solution of the above allyl alcohol (14) (465 mg) in dry methylene chloride (20 ml) containing dihydropyran (375 mg) and a catalytic amount of toluene-*p*-sulphonic acid was stirred at 0 °C for 1.5 h under nitrogen. The reaction mixture was quenched by the addition of solid sodium hydrogen carbonate. Filtration, followed by evaporation of the solvent, gave the crude protected allyl alcohol which was subjected to chromatography on silica gel (20 g). The elution with n-hexane–ethyl acetate (8 : 2, v/v) provided the tetrahydropyranyl allyl alcohol (15) (498 mg) as a pale yellow syrup; $\nu_{max.}$ ($CHCl_3$) 2 260 cm^{-1}; δ ($CDCl_3$) 3.25—4.15 (3 H, m), 4.62br (1 H, s), and 5.52—5.08 (2 H, m); *m/e* 244 (M^+ − 101).

A solution of the allyl alcohol (14) (43 mg) in dry dimethylformamide (1 ml) was treated at room temperature with t-butyldimethylsilyl chloride (37 mg) and imidazole (17 ml). After 17 h, the solvent was evaporated under reduced pressure and the resultant residue was extracted with chloroform. The extract was washed with brine, dried ($MgSO_4$), and evaporated to leave a residue which was subjected to chromatography on silica gel (5 g). The elution with n-hexane–ethyl acetate (8 : 2, v/v) gave the pure t-butyldimethylsilylallyl alcohol (16) (61 mg), $\nu_{max.}$ ($CHCl_3$) 2 260 cm^{-1}; δ ($CDCl_3$) 0.03 (6 H, s), 0.83 (9 H, s), 3.77—4.10 (1 H, m), 5.15 (1 H, dd, *J* 17 and 2 Hz), and 5.48 (1 H, d, *J* 16 Hz); *m/e* 318 (M^+ − 57).

9,11-*Ethano*-9,11-*dideoxaprostaglandin* H_2 (3) via *the Aldehyde* (17).—To a cold solution of the nitrile (15) (478 mg) in dry toluene (20 ml) was added dropwise a solution of di-isobutylaluminium hydride (1.76M in hexane; 4.8 ml) at −50 °C under nitrogen. The mixture was stirred for 5 h at −50 °C and then quenched with saturated ammonium chloride solution. The mixture was stirred for an additional 30 min at room temperature and then extracted with ether. The combined extracts were washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue as a pale yellow syrup which was subjected to chromatography on silica gel (30 g). The elution with ethyl acetate–n-hexane (1 : 9 v/v) afforded the aldehyde (17) (400 mg) as a colourless syrup, $\nu_{max.}$ ($CHCl_3$) 2 740 and 1725 cm^{-1}; δ ($CDCl_3$) 9.66 (1 H, t, *J* 2 Hz).

A suspension of 50% sodium hydride dispersion (24 mg) in freshly distilled dimethyl sulphoxide (1.5 ml) was heated at 70 °C for 1 h under nitrogen. To the above solution cooled to room temperature was added (4-carboxybutyl)triphenylphosphonium bromide (1.1 g) in dry dimethyl sulphoxide (1.5 ml). After 30 min, a solution of the aldehyde (17) (217 mg) in dry dimethyl sulphoxide (1.5 ml) was added dropwise to the red ylide solution. After 2 h at room temperature, the reaction mixture was quenched by the addition of ice–water and carefully acidified to pH 5 with 0.5N-sodium hydrogen-sulphate. The product was isolated by extraction with ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue which was subjected to chromatography on silica gel (15 g). Elution with ethyl acetate–n-hexane (2 : 8, v/v) gave the tetrahydropyranyl ether (19) (223 mg) as a mixture of C_{15} epimers, $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1}; δ ($CDCl_3$) 5.0—5.70 (4 H, m, olefinic protons) (Found: M^+, 432.3247. $C_{27}H_{44}O_4$ requires *M*, 432.3240).

A mixture of the above tetrahydropyranyl ether (19) (210 mg) dissolved in acetic acid–water–tetrahydrofuran (20 : 10 : 3, v/v; 5 ml) was stirred at 40 °C for 5 h; it was then diluted with brine and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and then evaporated to leave a colourless syrup which was subjected to chromatography on silica gel (15 g). Elution with chloroform gave, in order of elution, a mixture (105 mg) of 9,11-ethano-9,11-dideoxa-1-*epi*-prostaglandin H_2 (24) (less polar) and 9,11-ethano-9,11-dideoxaprostaglandin H_2 (3) (more polar) in an approximate ratio of 2 : 1 and then the pure compound (3) (58.3 mg) (Found: C, 75.6; H, 10.2. $C_{22}H_{36}O_3$ requires C, 75.8; H, 10.4%); $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1}; δ ($CDCl_3$) 5.0—5.70 (4 H, m, olefinic proton) (Found: M^+, 348.2697. $C_{22}H_{36}O_3$ requires 348.2665).

A mixture of compounds (24) and (3) (30 mg) was separated by preparative thin layer chromatography on silica gel (chloroform–methanol, 9.5 : 0.5, v/v) to give the 15-epimer (24) (18 mg) [$\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1}; δ ($CDCl_3$) 5.0—5.67 (4 H, m, olefinic protons) (Found: M^+, 348,2691. $C_{27}H_{44}O_4$ requires 348.2665)] and (3) (9.3 mg).

9,11-*Ethano*-9,11-*dideoxaprostaglandin* H_2 *Methyl Ester* (23).—The carboxylic acid (19) (26.5 mg) was treated with an excess of diazomethane in ether. After the usual work-up, the residue was purified by thin layer chromatography on silica gel (ethyl acetate–n-hexane 2 : 8, v/v) to afford the corresponding methyl ester (21) (20.2 mg) as a mixture of C_{15} epimers; $\nu_{max.}$ 1 730 cm^{-1}; δ ($CDCl_3$) 3.64 (3 H, s), 4.49—4.79 br (1 H, s), and 5.06—5.53 (4 H, m); *m/e* 446 (M^+).

A mixture of the above methyl ester (21) (18.5 mg) dissolved in acetic acid–water–tetrahydrofuran (20 : 10 : 3, v/v; 1 ml) was stirred at 40 °C for 6.5 h, diluted with brine, and then extracted with ethyl acetate. The extract was washed with saturated aqueous sodium hydrogen carbonate and brine, dried ($MgSO_4$), and then evaporated. The resultant residue was purified by thin layer chromatography on silica gel (ethyl acetate–n-hexane, 2 : 8, v/v) to give the methyl ester (23) (10.2 mg) as a mixture of C_{15} epimers, $\nu_{max.}$ 1 720 cm^{-1}; δ ($CDCl_3$) 3.63 (3 H, s), 3.83—4.29 (1 H, m), and 5.03—5.35 (4 H, m) (Found: M^+, 362.2803. $C_{23}H_{38}O_3$ requires 362.2819).

9,11-*Ethano*-15-*t-butyldimethylsilyl*-9,11-*dideoxaprostaglandin* H_2 *Methyl Ester* (22).—To a cold solution of the t-butyldimethylsilylallyl alcohol (16) (46 mg) in dry toluene (2 ml) was added dropwise a solution of di-isobutylaluminium hydride (1.76M in hexane; 0.43 ml) at −50 °C under nitrogen. The mixture was stirred for 3 h at −50 °C, quenched with saturated ammonium chloride solution, stirred for an additional 20 min at room temperature, and then extracted with ether. The extract was washed with brine, dried ($MgSO_4$), and filtered. The filtrate was condensed and the resultant residue was chromatographed on silica gel. Elution with ethyl acetate–n-hexane (1 : 9, v/v) gave the aldehyde (18) (43.5 mg) as a pale yellow syrup, $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}; δ ($CDCl_3$) 9.60 (1 H, t, *J* 2 Hz); *m/e* 321 (M^+ − 57.)

A suspension of 50% sodium hydride dispersion (44 mg) in freshly distilled dimethyl sulphoxide (0.3 ml) was heated at 75 °C for 1 h under nitrogen. To the above solution

cooled to room temperature was added (4-carboxybutyl)-triphenylphosphonium bromide (202 mg) in dry dimethyl sulphoxide (0.4 ml). After 30 min, a solution of the aldehyde (18) (43 mg) in dry dimethyl sulphoxide (0.3 ml) was added dropwise to the red ylide solution. After 2 h at room temperature, the reaction mixture was quenched by the addition of ice and acidified with 0.5N-sodium hydrogensulphate. The mixture was extracted with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$), and then evaporated to leave a residue which was chromatographed on silica gel (5 g). The elution with ethyl acetate–n-hexane (1 : 9, v/v) afforded the carboxylic acid (20) (18 mg) as a mixture of C_{15} epimers, $\nu_{max.}$ ($CHCl_3$) 1 710 cm^{-1}.

The above carboxylic acid (20) (12 mg) was treated with an excess of diazomethane in ether. After the usual work-up, the residue was purified by thin layer chromatography on silica gel (ethyl acetate–n-hexane 1 : 9, v/v) to give the corresponding methyl ester (22) (10 mg) as a mixture of C_{15} epimers, $\nu_{max.}$ ($CHCl_3$) 1 730 cm^{-1}; δ ($CDCl_3$) 0.01 (6 H, s), 0.89 (9 H, s), 3.66 (3 H, s), 3.79—4.16 (1 H, m), and 5.09—5.46 (4 H, m) (Found: M^+, 476.3706. $C_{29}H_{52}O_3Si$ requires M, 476.3685).

We thank Miss Y. Enomoto, Mrs. C. Koyanagi, Mr. K. Kawamura, Miss K. Mushiake, Mrs. R. Kobayashi, Miss K. Kikuchi, Miss Y. Kato, and K. Otomo, Pharmaceutical Institute, Tohoku University, for microanalyses and spectral measurements and for preparation of the manuscript. We also thank Ono Pharmaceutical Co. Ltd. for the donation of (4-hydroxycarbonylbutyl)triphenylphosphonium bromide.

[1/148 *Received*, 2nd *February*, 1981]

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