Synthesis of *dl*-12,15-Ethylene-13,14-dihydro-prostaglandin-$F_{2\alpha}$ Methyl Ester

Nobuyuki HAMANAKA,* Hisao NAKAI, and Masayasu KURONO

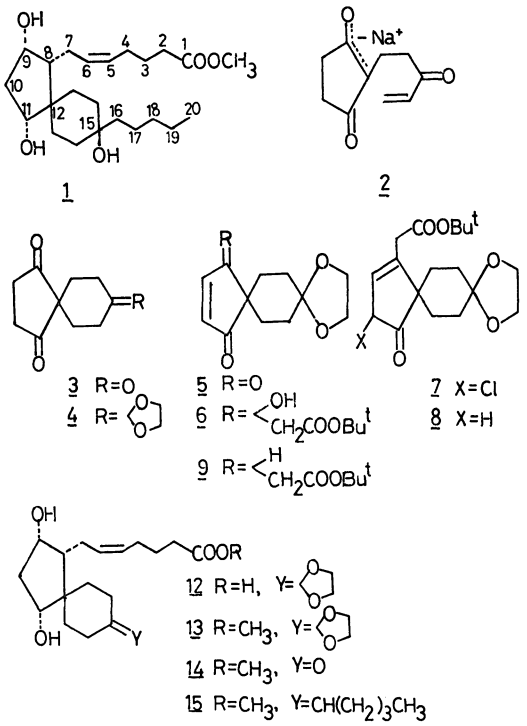
Ono Pharmaceutical Co., Ltd., Research Institute, 3-1-1, Sakurai, Shimamoto-cho, Mishima-gun, Osaka 618

(Received January 10, 1980)

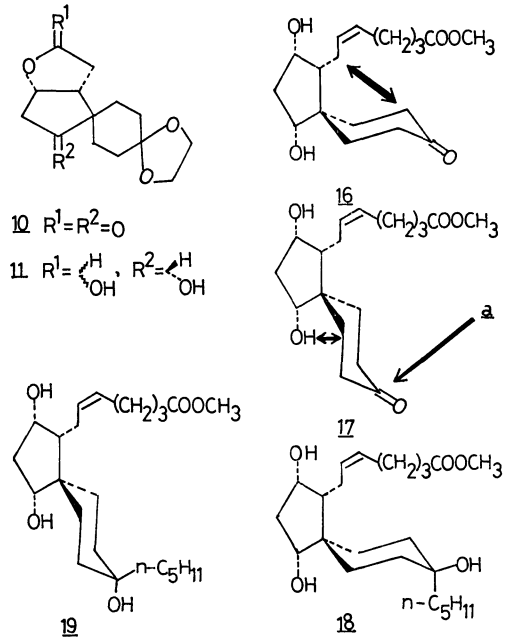
A report is given on the synthesis of a spiro prostaglandin analog *via* triketone obtained by the double Michael addition of 1,3-cyclopentanedione to 1,4-pentadien-3-one.

Prostaglandin (PG) is a highly active autacoid which might act as a mediator in many physiological activities.[1] The synthesis of 12-methyl[2] and that of 15-methyl PGs[3] have been described in investigations carried out to find stable PG analogs having higher biological activities than natural PG. In the present report we describe the synthesis of a spiro PG analog in which an ethylene linkage is introduced between the C-12 and C-15 positions, Δ^{13}-double bond being saturated.

The starting bicyclic triketone **3** was obtained as follows. The sodium salt of 1,3-cyclopentanedione was treated with 1,4-pentadien-3-one (1 equiv, −40 °C, 4 h, then −20 °C, 1.5 h) to afford the intermediate anion **2**. Cyclization of **2**, which rapidly polymerized during the course of isolation, was accomplished by treatment *in situ* with AcOH (5 equiv, −20 °C, 20 h) to give the bicyclic triketone **3**[4] in 56% yield on the basis of 1,3-cyclopentanedione. Selective protection of the C-8 carbonyl group in six-membered ring of **3** with ethylene glycol (1 equiv, TsOH, benzene, reflux, 30 min) afforded monoacetal **4** quantitatively. Dehydrogenation of **4** with SeO_2 in dioxane (92—93 °C, 20 h) gave 1,3-cyclopentanedione **5** in 88% yield. Addition of two carbon units (corresponding to C-6 and C-7 of PG) was achieved by treatment of **5** with $LiCH_2COOBu^t$[5] in benzene (1.2 equiv, 25 °C, 30 min) to give hydroxy ester **6** in 79% yield. Treatment of **6** with $SOCl_2$ (4.4 equiv)–pyridine (5.6 equiv) in CH_2Cl_2 at −40 °C for 30 min gave the deconjugated α-chloro ketone **7** quantitatively. Reductive dechlorination of **7** with Zn–CH_3OH (40—43 °C, 3.5 h) gave the conjugated ketone **9** in 84% yield. Treatment of **9** with TsOH in toluene gave unstable lactone **10** which was directly reduced with *i*-Bu_2AlH in toluene (−70 °C, 5 min) to give the hydroxy hemiacetal **11** in 77% yield on the basis of **9**. Condensation of **11** with $Ph_3P{=}CH(CH_2)_3COONa$ (9.5 equiv) in DMSO (34 °C, 75 h) followed by esterification with CH_2N_2 gave methyl ester **13** in 50% yield. Geometry of the two hydroxyl groups of **13** was confirmed by lanthanoid induced ^1H NMR shifts (Fig. 1). Since the proton signals at C-9 and C-11 of **13** showed the same gradient while two protons of C-10 showed different gradients, 9- and 11-hydroxyl groups of **13** are *cis* as expected from the synthetic route of **13**. Compound **13** was deprotected with TsOH–acetone (reflux, 2 h) to give **14** quantitatively. The α-chain was introduced by treatment of **14** with *n*-$C_5H_{11}MgBr$ to give the desired *dl*-12,15-ethylene-13,14-dihydro-$PGF_{2\alpha}$ methyl ester **1** in 60% yield. Treatment of **1** with AcOH (50 °C, 2 h) exclusively gave **15** possessing exocyclic double bond [*m/e* 378 (M^+), 335 ($M^+-C_3H_7$)]. *m/e* 321 ($M^+-C_4H_9$) was not observed among fragment ion peaks of **15**. This suggests that the hydroxyl group of C-15 occupies an equatorial position, and **18**



Scheme 1.



Scheme 2.

Table 1. Spectral data of new compounds

Compound	Mp/°C	IR cm^{-1} ($CHCl_3$)	NMR δ ($CDCl_3$)
1	oil	3400, 1735	5.43(2H, m), 4.22(1H, m)
3	98—100(AcOEt-Et_2O)[a]	1755, 1720, 1715	2.01(4H, t, J=7.2Hz), 2.61(4H, t, J=7.2Hz)
4	100—101 (Et_2O)[a]	1760, 1721	1.84(8H, bs), 2.28(4H, s), 3.95(4H, s)
5	129—130 (Et_2O)[a]	1750, 1710	1.70—2.65(8H, A_2B_2), 3.97(4H, s),7.15(2H, s)
6	80—81.5 (i-Pr_2O)[a]	3480, 1725, 1600	2.34 and 2.69 (each 1H, AB, J=15 Hz), 6.09 and 7.39 (each 1H, d, J=5.0 Hz), 1.50(9H,bs)
7	oil	1755, 1725	6.14(1H, m), 4.70(1H, m), 3.06(2H, m), 1.50(9H, bs)
8	oil	1735	5.95(1H, m), 2.94(2H, m), 1.50(9H, bs)
9	81—83 (i-Pr_2O)[a]	1725, 1710, 1600	6.06(1H, quart, J=1.8, 6.0 Hz), 7.58(1H, quart, J=2.5, 6.0 Hz), 1.50 (9H, bs)
10	137—140 (i-Pr_2O)[a]	1780, 1735, 3500	5.18(1H, m)
11	oil	3500	5.02(1H, bt, J=5.0Hz), 4.65(1H, m)
12	oil	1710	
13	oil	3500, 1730	5.38(2H, m), 4.15(2H, m), 3.92(4H, s), 3.67(3H, s)
14	oil	3500, 1730, 1710	5.40(2H, m),4.20(2H, m) 3.70(3H, s)

a) Recrystallization solvents.

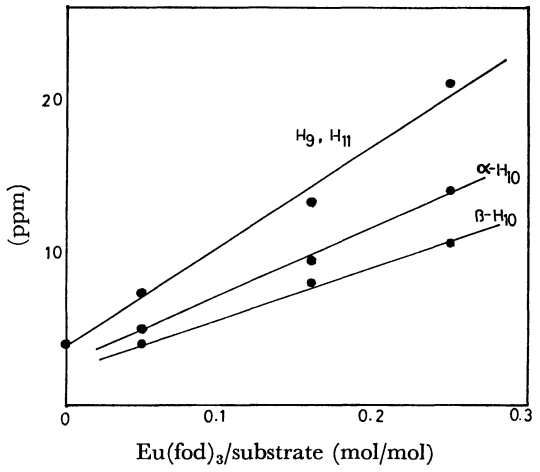


Fig. 1. Lanthanoid induced ^{1}H-NMR shifts of **13**.

or **19** are the possible stereoisomers of **1**. We tentatively assigned the stereochemistry of **1** to **19** on the basis of the following. i) Conformer **17** is more stable as compared with **16**, the steric repulsions between the C-11 OH and six-membered ring of **17** being less than those between α-chain carbons and the six-membered ring of **16**; ii) Axial attack of Grignard reagent to the six-membered cyclic ketone **17** favors approach from axis a.

After intravenous administration, PG analog **1** showed no effect on uterine contractile activity in a pregnant rat at a dose of 200 γ/kg or on blood pressure in rabbit and dog at a dose of 50 γ/kg.

Experimental

General. Melting and boiling points are uncorrected. ^{1}H-NMR spectra were recorded on a Varian XL-100 spectrometer with Me_4Si as an internal standard, and IR spectra on a Hitachi EPI-G2 spectrophotometer. MS data were obtained on a JEOL JMS-01 SG at 75 eV.

Spiro[4.5]decane-1,4,8-trione (3). To a suspension of 230 mg (10.0 mmol) of NaH in DMF (90 ml) was added 980 mg (10.0 mmol) of 1,3-cyclopentanedione at −35 °C over a period of 10 min. To the resulting mixture was added a solution of 820 mg (10.0 mmol) of 1,4-pentadien-3-one in DMF (10 ml) at −35 °C over a period of 5 min. The resulting solution was allowed to stand at −35 °C for 4 h, then at −20 °C for 1.5 h and then treated with AcOH (3 ml) at −20 °C for 20 h. The reaction mixture was poured into 1 mol dm^{-3} HCl (300 ml) and extracted with CH_2Cl_2. The organic layer was washed with H_2O and dried (Na_2SO_4). After removal of the solvent, the residue obtained was purified by column chromatography on silica gel using a mixture of benzene and AcOEt as an eluent to afford 1.01 g (56%) of **3** as colorless crystals; MS *m/e* 180 (M^+).

8,8-(Ethylenedioxy)spiro[4.5]decane-1,4-dione (4). A mixture of 100 mg (0.556 mmol) of triketone **3**, 34.5 mg (0.556 mmol) of ethylene glycol, 1 mg of TsOH and benzene (5 ml) was refluxed for 1 h. The resulting mixture was diluted with benzene (20 ml) and was shaken with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to afford 125 mg (100%) of **4** as colorless crystals; MS *m/e* 224 (M^+).

8,8-(Ethylenedioxy)sprio[4.5]dec-2-ene-1,4-dione (5). A solution of 70 mg (0.312 mmol) of monoacetal **4** in dioxane (2 ml) was treated with 35 mg (0.315 mmol) of SeO_2 at 92—93 °C for 20 h. The resulting mixture was diluted with AcOEt (15 ml) and washed with H_2O and saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to afford 82 mg of oily residue which was purified by column chromatography on silica gel using Et_2O as an eluent to afford 61 mg (88%) of **5** as colorless crystals; MS *m/e* 222 (M^+).

1-(t-Butoxycarbonylmethyl)-1-hydroxy-8,8-(ethylenedioxy)spiro-[4.5]dec-2-en-4-one (6). To a stirred solution of 30 mg (0.135 mmol) of **5** in benzene (1 ml) was added dropwise a solution of 20 mg (0.164 mmol) of $LiCH_2COOBu^t$ in benzene (2 ml) at 0 °C over a period of 30 min. The resulting solution was diluted with benzene (20 ml) and washed with water and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue obtained was purified by thin layer chromatography on silica gel using Et_2O as a developing solvent to afford 36 mg (79%) of **6** as colorless crystals; MS *m/e* 338.1707 (Calcd for $C_{18}H_{26}O_6$: 338.1729).

1-(t-Butoxycarbonylmethyl)-3-chloro-8,8-(ethylenedioxy)spiro[4.5]-dec-1-en-4-one (7). To a stirred solution of 150 mg (0.443 mmol) of **6** in CH_2Cl_2 (1 ml) were added dropwise a solution of 155 mg (1.96 mmol) of $SOCl_2$ in CH_2Cl_2 (7 ml)

and then a solution of 195 mg (2.45 mmol) of pyridine in CH_2Cl_2 (7 ml) at −40 °C over a period of 30 min. The resulting mixture was diluted with CH_2Cl_2 (20 ml) and washed with H_2O, dried (Na_2SO_4) and evaporated under reduced pressure to afford an oily residue which was purified by thin layer chromatography on silica gel using Et_2O as a developing solvent to give 151 mg (100%) of **7** as an oil; MS *m/e* 356.1376 (Calcd for $C_{13}H_{25}O_5Cl$: 356.1390).

1-(t-Butoxycarbonylmethyl)-8,8-(ethylenedioxy)spiro[4.5]dec-1-en-4-one (8). A solution of 580 mg (1.63 mmol) of **7** in MeOH (25 ml) was treated with 4.00 g (61.2 mmol) of Zn dust at 60 °C for 2 h. After removal of the Zn dust by filtration, the filtrate was evaporated. The resulting residue was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4) and evaporated. Purification of the residue by column chromatography on silica gel using Et_2O as an eluent afforded 520 mg (100%) of **8** as an oil; MS *m/e* 322.1780 (Calcd for $C_{18}H_{26}O_5$: 322.1780).

1-(t-Butoxycarbonylmethyl)-8,8-(ethylenedioxy)spiro[4.5]dec-2-en-4-one (9). A solution of 50 mg (0.155 mmol) of **8** and 5.04 mg (0.0933 mmol) of NaOMe in MeOH (3 ml) was treated at 40—43 °C for 3.5 h. After removal of MeOH *in vacuo*, the residue was extracted with AcOEt. The organic layer was washed with H_2O, dried ($MgSO_4$) and evaporated. Purification of the residue by column chromatography on silica gel using a mixture of benzene and AcOEt as an eluent gave 42 mg (84%) of **9** as colorless crystals; MS *m/e* 322.1800 (Calcd for $C_{18}H_{26}O_5$: 322.1780).

(4S,8S)-4',4'-Ethylenedioxy-5-oxaspiro[bicyclo[3.3.0]octane-1,1'-cyclohexane]-2,6-dione (10). A solution of 120 mg (0.372 mmol) of **9** in benzene (10 ml) was treated with 2 mg of TsOH at 60 °C for 16 h. The resulting solution was diluted with benzene (30 ml), washed with H_2O and saturated aqueous $NaHCO_3$ solution and dried ($MgSO_4$). After removal of benzene *in vacuo*, the residue obtained was purified by column chromatography on silica gel using AcOEt as an eluent to afford 62 mg (63%) of **10** as colorless crystals; MS *m/e* 266.1130 (Calcd for $C_{14}H_{18}O_5$: 266.1154).

(4S,6R,8S,2R)- and/or (4S,6S,8S,2R)-4'4'-Ethylenedioxy-6-oxospiro[bicyclo[3.3.0]octane-1,1'-cyclohexane]-3,7-diol (11) Directly from (9). A solution of 100 mg (0.310 mmol) of **9** in toluene (3 ml) was treated with 64 mg (0.340 mmol) of TsOH at 40 °C for 3 h and then cooled to −70 °C. To the resulting solution was slowly added 4.80 mmol of *i*-Bu_2AlH in toluene (3 ml) over a period of 30 min. After the addition of MeOH (3 ml), the reaction mixture was treated with H_2O (9 ml) at 25 °C and stirred vigorously. After removal of the gel by filtration, the filtrate was dried ($MgSO_4$) and evaporated *in vacuo* to afford 65 mg (77% based on **9**) of **11** as an oil.

1-(cis-6-Methoxycarbonyl-2-hexenyl)-8,8-(ethylenedioxy)spiro-[4.5]decane-2,4-diol (13) Directly from (11). To a stirred solution of 2.5 g (5.65 mmol) of (4-carboxybutyl)triphenylphosphonium bromide in DMSO (3 ml) was added a solution of 2.0 mmol of sodium methylsulfinylmethide in DMSO (5 ml) at 10 °C. To the above solution was added a solution of 160 mg (0.592 mmol) of the crude hemiacetal **11** in DMSO (5 ml) at 25 °C. The resulting solution was allowed to stand at 34 °C for 45 h. The reaction mixture was quenched with H_2O (50 ml) and then extracted with a mixture of Et_2O and AcOEt (1: 1). The aqueous layer was acidified with oxalic acid (≈pH 5) and then extracted with a mixture of Et_2O and pentane (1: 1). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by thin layer chromatography on silica gel using a mixture of AcOEt and AcOH (98: 2) as a developing solvent to afford 120 mg of **12** which was treated with CH_2N_2 in MeOH and then evaporated *in vacuo* to afford 109 mg (50% based on **11**) of **13** as an oil after purification by column chromatography on silica gel using AcOEt as an eluent; MS *m/e* 368.2188 (Calcd for $C_{20}H_{32}O_6$: 368.2198).

1-(cis-6-Methoxycarbonyl-2-hexenyl)-2,4-dihydroxyspiro[4.5]-decan-8-one (14). A solution of 56 mg (0.152 mmol) of **13** and 1 mg of TsOH in acetone (5 ml) was refluxed for 5 h. The resulting solution was diluted with AcOEt and washed with saturated aqueous $NaHCO_3$ solution. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to give 52 mg (100%) of **14** as an oil; MS *m/e* 324 (M^+).

dl-*12,15-Ethylene-13,14-dihydro-PGF$_{2\alpha}$ Methyl Ester (1).* To a stirred solution of 52 mg (0.160 mmol) of **14** in Et_2O (10 ml) was added dropwise a solution of 0.500 mmol of *n*-$C_5H_{11}MgBr$ in Et_2O (1 ml). After being left to stand at 25 °C for 30 min, the resulting mixture was diluted with AcOEt, washed with aqueous NH_4Cl solution and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue obtained was purified by thin layer chromatography on silica gel using AcOEt as a developing solvent to afford 36 mg (60%) of **1** as an oil; MS *m/e* 396.2866 (Calcd for $C_{23}H_{40}O_5$: 396.2875).

References

1) J. W. Hinman, *Ann. Rev. Biochem.*, **41**, 161 (1972); J. R. Weeks, *Ann. Rev. Pharmacol.*, **12**, 317 (1972).

2) E. J. Corey, C. S. Shiner, R. P. Volante, and C. R. Cyr, *Tetrahedron Lett.*, **1975**, 1161.

3) E. W. Yankee, U. Axen, and G. L. Bundy, *J. Am. Chem. Soc.*, **96**, 5865 (1974).

4) H. A. P. de Jongh and H. Wynberg, *Recl. Trav. Chim.*, **82**, 202 (1963).

5) M. W. Rathke and D. F. Sullivan, *J. Am. Chem. Soc.*, **95**, 3050 (1973).