Total Synthesis of 12-Hydroxymethylprostaglandin $F_{2\alpha}$ Methyl Ester

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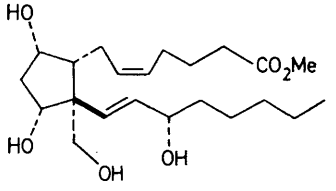
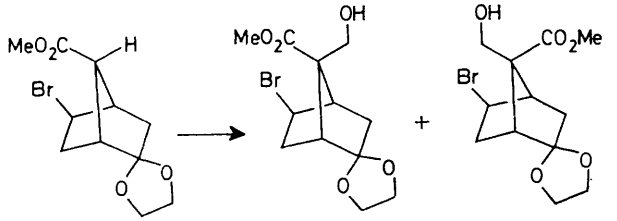
Summary The hydroxymethylation of the ester enolate derived from the ester (**2**) provided the hydroxymethylated adducts (**3**) snd (**4**) both of which have been successfully converted into 12-hydroxymethylprostaglandin $F_{2\alpha}$ methyl ester(**1**).

INTEREST in C-12 substituted prostaglandins has culminated in the synthesis of 12-methylprostaglandins,[1] 12-fluoro-$PGF_{2\alpha}$ methyl ester,[2] and 11-deoxy-12-hydroxymethyl-PGE_2.[3] We report the total synthesis of 12-hydroxymethylprostaglandin $F_{2\alpha}$ methyl ester [12-hydroxymethyl-$PGF_{2\alpha}$ methyl ester (**1**)] from the previously described bicyclo[2.2.1]heptane derivative (**2**).[4]

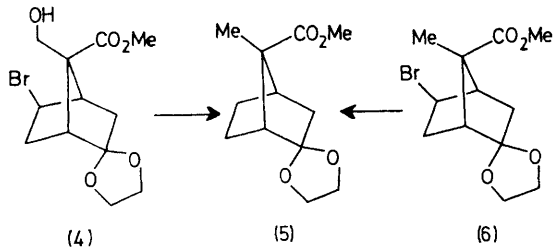


(1)



(2) (3) (4)

Hydroxymethylation[5] of the ester enolate of compound (**2**) employing excess of dry gaseous formaldehyde, obtained from depolymerization of paraformaldehyde, gave, in 96% yield, a pure mixture of the hydroxymethylated ester (**3**) m.p. 130·5—131·5 °C (R_f 0·20) [ether–hexanes (2:1)] and the isomeric hydroxymethylated ester (**4**), m.p. 116·5—117·5 °C (R_f 0·29) in a ratio of *ca.* 1:1. Despite the lack of selectivity in the hydroxymethylation, the two isomers could be readily separated by chromatography on silica



(4) (5) (6)

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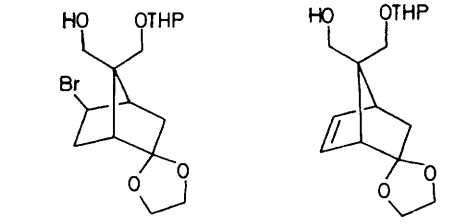
gel and each in turn converted into 12-hydroxymethyl-$PGF_{2\alpha}$ (**1**) (*vide infra*). The structure assigned to compound (**4**) was based on its conversion [(a) $MeSO_2Cl$–pyridine, (b) NaI–acetone, and (c) Bu_3SnH–PhH] into the bicyclo[2.2.1]heptane derivative (**5**) which was prepared (Bu_3SnH–PhH) from the known ester (**6**)[4] (Scheme).

Tetrahydropyranylation (dihydropyran; *p*-$MeC_6H_4SO_3H$; CH_2Cl_2) of the alcohol (**3**) followed by reduction ($LiAlH_4$; Et_2O; reflux) gave, in 87% yield, the new alcohol (**7**). Dehydrobromination of (**7**) with 1,5-diazabicyclo-[5.4.0]undec-5-ene (DBU) in refluxing toluene provided (**8**) in 92% yield. Collins oxidation[6] followed by treatment[7] with the sodio derivative of dimethyl 2-oxoheptylphosphonate[8] in tetrahydrofuran (THF) gave, in 45% yield from (**8**), the enone (**9**). Reduction ($NaBH_4$–EtOH; 0 °C) of (**9**) gave a *ca.* 1:1 mixture of the epimeric alcohols at the eventual C-15 carbon atom. Deacetalization (30% aq. acetic acid; 90 °C) gave, in 50% overall yield, the keto diol (**10**).



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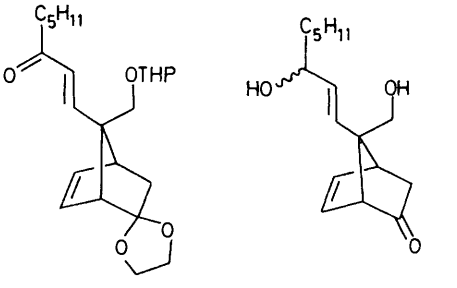
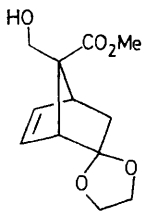


(9) (10)

THP = Tetrahydropyranyl

As indicated, the isomeric alcohol (**4**) has successfully been converted into the keto diol (**10**) and 12-hydroxymethyl-$PGF_{2\alpha}$ (**1**). The crystalline alcohol (**11**), m.p. 100–101 °C, available by the dehydrobromination (DBU–toluene; reflux) of the alcohol (**4**) in near quantitative yield, was oxidized [CrO_3·2Py (Py = pyridine)][6] to its corresponding aldehyde, which was treated (22 h, 52 °C) with the sodium salt of dimethyl 2-oxoheptylphosphonate in dry THF. The enone (**12**), obtained in 66% overall yield from (**11**), was reduced sequentially with $NaBH_4$ (EtOH; −20 °C) and $LiAlH_4$ (Et_2O; 25 °C) providing in >90% yield the diol (**13**) which, upon deacetalization, gave the compound (**10**), identical in all respects with the sample prepared from the alcohol (**3**). The overall yield

for the conversion (**4**)→(**10**) is far superior to that for the transformation (**3**)→(**10**) (*vide supra*).



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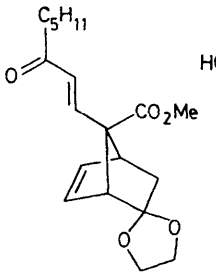

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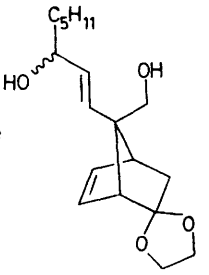
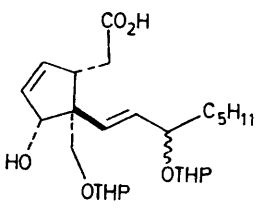


(13)

Tetrahydropyranylation of the diol (**10**) followed by Baeyer–Villiger oxidation[9] with 30% hydrogen peroxide in aqueous methanol containing sodium hydroxide (5 °C, 5 days) afforded the hydroxy acid (**14**) (85%). Using standard synthetic techniques, the hydroxy acid (**14**) was subjected to iodolactonization, deiodination, and tetrahydropyranylation which gave rise to the bicyclic lactone (**15**) (55% overall yield). Reduction (Bu^i_2AlH; toluene; −78 °C) and condensation with the standard Wittig reagent gave a hydroxy carboxylic acid (75%) which was directly esterified with ethereal diazomethane. Removal of the tetrahydropyranyl groups of compound (**16**) under acidic conditions gave a *ca.* 1:1 mixture of 12-hydroxymethyl-$PGF_{2\alpha}$ methyl ester (**1**) and its C-15 epimer which were separated by column chromatography on silica gel. The more polar isomer has been tentatively assigned the (15*S*) natural configuration in keeping with the t.l.c. behaviour of natural prostaglandins and the (15*R*) unnatural isomers.[10]



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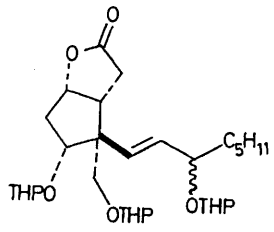

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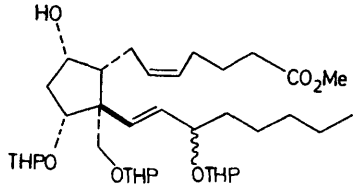

(16)

Preliminary results obtained with 12-hydroxymethyl $PGF_{2\alpha}$ methyl ether and its C-15 epimer indicate that both compounds are ineffective in terminating pregnancy in hamsters when dosed (125 ug) subcutaneously on day 5 of pregnancy.

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