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

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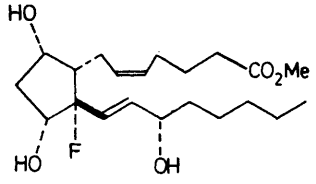
Summary The total synthesis of 12-fluoroprostaglandin $F_{2\alpha}$ methyl ester (**1**) from norbornadiene is described which involves the fluorination of the enolate derived from the ester (**3**) with perchloryl fluoride.

IT has been demonstrated[1] that the introduction of fluorine into the C-16 position of $PGF_{2\alpha}$ (*e.g.* 16ξ-fluoro $PGF_{2\alpha}$) markedly diminishes the ability of $PGF_{2\alpha}$ to serve as a 15-dehydrogenase substrate and results in a significant increase in antifertility activity in the golden hamster when compared with $PGF_{2\alpha}$. In view of the outstanding biological potency associated with fluorinated derivatives of naturally occurring prostaglandins,[1] we have developed a



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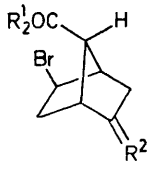
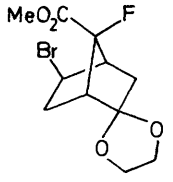


(2) R^1=H; R^2=O
(3) R^1=Me; R^2=-O[CH_2]$_2$O-



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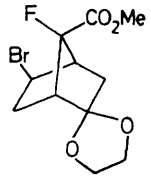
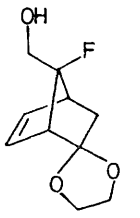


(5)

synthesis of 12-fluoroprostaglandin $F_{2\alpha}$ methyl ester [12-fluoro $PGF_{2\alpha}$ methyl ester (**1**)] which represents the first successful attempt at the introduction of fluorine into the five-membered ring nucleus of a natural prostaglandin. We detail below the total synthesis of 12-fluoro $PGF_{2\alpha}$ methyl ester (**1**).

Of prime importance to the success of our synthetic scheme was the ability of the enolate derived from the ester (**3**) to undergo fluorination with perchloryl fluoride† (**3** → **4**). We have previously described[2] the synthesis of the ester (**3**) from the keto acid (**2**)[3] which is readily available in three steps from norbornadiene. Activated methylene groups in 1,3-dicarbonyl systems undergo smooth fluorination with perchloryl fluoride;[4] however, only limited success has been reported with ester enolates.[5] Fluorination of the ester enolate [lithium di-isopropylamide–tetrahydrofuran (LDA–THF) at −78 °C] derived from (**3**) with perchloryl fluoride (−40 °C)‡ resulted in an 86% isolated yield of a pure mixture of the desired α-fluoro ester (**4**) (R_f 0·41) [hexane–ethyl acetate (4:1)] and the isomeric α-fluoro ester (**5**) (R_f 0·33) in a ratio of 1:1.§ Chromatography on silica gel easily provided the α-fluoro ester (**4**) which was reduced with lithium aluminium hydride in ether at room temperature and dehydrobrominated with 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing toluene. An 84% yield of the pure alcohol (**6**) (M^+ 200·0850) was obtained.



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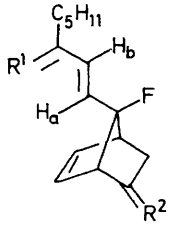
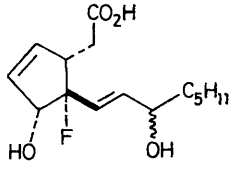


(7) R^1=O; R^2=-O[CH_2]$_2$O-
(8) R^1=H, OH; R^2=O



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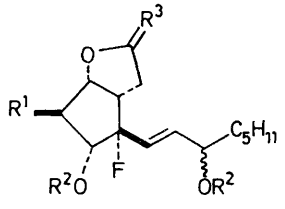


(10) R^1=I; R^2=H, R^3=O
(11) R^1=R^2=H; R^3=O
(12) R^1=H; R^2=THP; R^3=H,OH

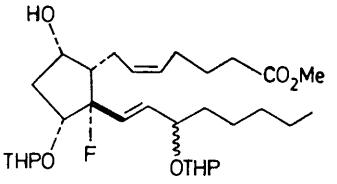
Collins oxidation[6] of the compound (**6**) followed by condensation with the sodium derivative of dimethyl 2-oxoheptylphosphonate[7] in dry tetrahydrofuran at 50 °C for 22 h produced the pure *trans*-enone (**7**) [J(H_a–H_b) 16 Hz, J(H_a–F) 18 Hz] in 51% yield. Reduction ($NaBH_4$–EtOH at −20 °C) with subsequent deacetalization (30% acetic acid, 25 °C) provided a 95% yield of the ketone (**8**), which upon Baeyer–Villiger oxidation[8] with 30% hydrogen peroxide and sodium hydroxide in aqueous methanol at 5 °C for 48 h afforded the hydroxy acid (**9**) in 75% yield. Iodolactonization of the hydroxy acid (**9**) gave the iodo-lactone (**10**) (84%) which with tri-n-butyltin hydride in benzene at

† Fluorinations with perchloryl fluoride can be extremely hazardous. Utilization of this reagent requires safety precautions.

‡ In an attempt to improve the ratio of **4** to **5** in favour of the desired compound, the reaction was, in one instance, cooled below −40 °C. Upon quenching the reaction with water, a violent explosion occurred.

§ We have found that enolates of α-substituted esters react with perchloryl fluoride providing excellent yields of the corresponding α-fluoro-α-substituted esters; *e.g.*, treatment of the enolate of methyl 2-n-butyloctanoate (generated from LDA at −20 °C in THF) with perchloryl fluoride at −20 °C gave a 90% yield of methyl 2-fluoro-2-n-butyloctanoate.

50 °C gives (**11**) in 70% yield. Treatment with dihydropyran and reduction with Bu^i_2AlH–toluene at −70 °C produced the hemiacetal (**12**) (70%) which, upon condensation with the Wittig reagent derived from $Ph_3P^+CH_2[CH_2]_3CO_2H$ and $MeSOCH_2^-\ Na^+$,[9] gave a hydroxy carboxylic acid (70%) which was directly esterified with ethereal diazomethane. Removal of the tetrahydropyranyl (THP) groups of compound (**13**) under acidic conditions [acetic acid–water–THF (20:10:3), 42 °C, 4·5 h] gave a *ca.* 1:1 mixture of the ester (**1**) and its C-15 epimer which were separated by column chromatography on silica gel.



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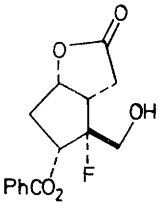

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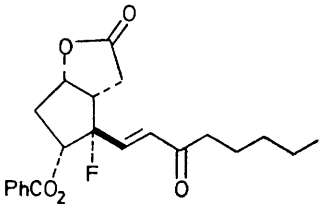

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Unlike the two-step sequence (**6** → **7**) *via* the corresponding α-fluoro aldehyde, we were unsuccessful in our attempt to convert the fluoro alcohol (**14**) into the *trans*-enone (**15**) *via* its corresponding α-fluoro aldehyde.

The stereochemistry of intermediates discussed above was established by n.m.r. analysis utilizing the known dependence of J_{HF} on dihedral angle[10] and long-range proton–fluorine coupling in rigid systems.[11]

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