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(+)-11-DEOXY-13,14-DIHYDRO-13β,11α-EPOXYMETHANO-12-ISOPROSTAGLANDIN $F_{2\alpha}$ FROM AUCUBIN

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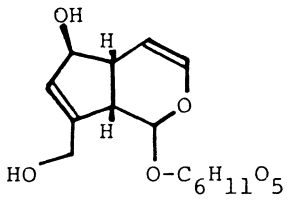
Synthesis of (+)-11-deoxy-13,14-dihydro-13β,11α-epoxymethano-12-isoprostaglandin $F_{2\alpha}$ from aucubin 1 is described. An aldol-type condensation of cyclic acetal 3a with 2-acetoxy-1-heptene in the presence of $TiCl_4$ is a key step of this synthesis.

During the synthetic study[1,2] of prostaglandins from aucubin 1[3a], we have been interested in the synthesis and biological properties of various kinds of prostanoids which could be derived from aucubin 1[3a]. And herein we wish to report the synthesis of the title prostanoid, (+)-11-deoxy-13,14-dihydro-13β,11α-epoxymethano-12-isoprostaglandin $F_{2\alpha}$ 2.

Condensation of the benzoate 3a, which has been derived from the known alcohol 3b[3b], with 2-acetoxy-1-heptene[4] in the presence of $TiCl_4$[5] in dichloromethane at -5°C afforded the hydroxy ketone 4[2,6,7], which was converted into the acetal 5[6] in a quantitative yield(excess ethylene glycol and catalytic amount of *p*-toluenesulfonic acid in benzene under azeotropical reflux) and thence to the aldehyde 6[6] (Collins oxidation[8]) in 94% yield from 4. Condensation of 6 with the Wittig reagent derived from (4-carboxybutyl)-triphenylphosphonium bromide[9] and sodium methylsulfinylmethide in dimethyl sulfoxide followed by esterification using diazomethane, and treatment with catalytic amount of *p*-toluenesulfonic acid in acetone afforded the ester-ketone 7[6,7] (65% yield from 6, $[\alpha]_D^{25}$ +65°(c 1.046, chloroform).

Treatment of 7 with excess sodium borohydride in methanol gave a mixture of the (15S) alcohol 8(more polar) and the (15R) epimer. Separation of the desired (15S) isomer 8[6,7] from the mixture was accomplished by column chromatography on silica gel, using benzene-ethyl acetate as eluent(41% yield). Hydrolysis of 8 using 0.5M KOH in methanol-water(1:1) at 60°C produced (+)-11-deoxy-13,14-dihydro-13β,11α-epoxymethano-12-isoprostaglandin $F_{2\alpha}$ 2[6,7] (IUPAC nomenclature; (Z)-7-[(3R, 3aR,4R,5S,6aR)-hexahydro-5-hydroxy-3-((S)-2-hydroxyheptyl)-1*H*-cyclopenta[*c*]furan-4-yl]-5-heptenoic acid) in 87% yield. By analogy to the TLC behavior[10] and biological activity between natural prostaglandins and their 15-epimers, the more polar isomer 2 has tentatively been assigned the (15S) configulation[11].

2; $[\alpha]_D^{24}$ +38.2° (c 1.00, methanol)
MS:(m/e) 368(M^+), 350, 297
IR:(ν cm^{-1}) 3500-2500, 1705
NMR:(δ ppm, $CDCl_3$) 0.9(3H, t), 1.1-2.6(22H), 2.8(1H, m), 3.6-4.2(4H), 4.35(1H, m), 5.35(3H, s), 5.4(2H, m)



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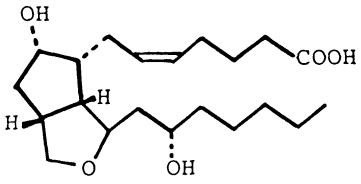

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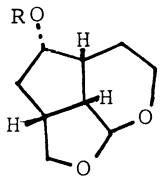
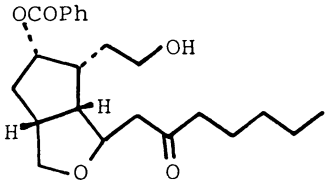


3a: R=PhCO

3b: R=H



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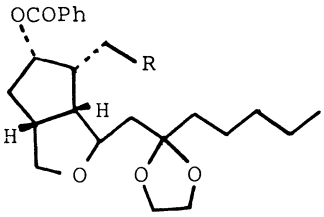
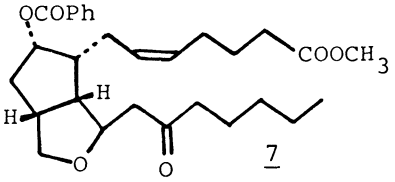


5: R=CH_2OH

6: R=CHO



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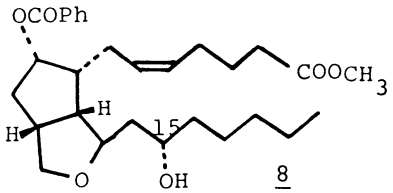

8

References and Notes

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11) Bioassay of 2 on the relaxation of isolated tracheal muscle(guinea pig) exhibited about 5% activity of PGE_2. Biological activity was measured by Mr. S. Nishio in our laboratory. Full bioassay details for similar prostanoids from aucubin will be reported elsewhere.

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