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A SIMPLE SYNTHESIS OF (+)-11-DEOXY-11α-HYDROXYMETHYL $PGF_{1\alpha}$ AND ITS 12-ISOMER FROM AUCUBIN

Kiyotaka OHNO* and Masanobu NARUTO
Basic Research Laboratories, Toray Industries, Inc., Tebiro, Kamakura 248

A simple synthesis of the titled prostanoids, (+)-11-deoxy-11α-hydroxymethyl $PGF_{1\alpha}$ 9 and its 12-isomer 6, from aucubin 1 is described. The latter prostanoid 6 is characterized by its all-*cis* configuration on the cyclopentane ring.

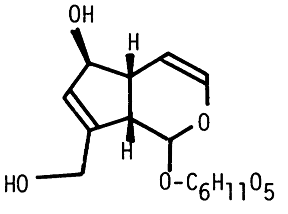
Previously we have reported stereocontrolled syntheses of optically active prostanoids,[1,2)] including naturally occurring ones,[1b)] from tetrahydroanhydroaucubigenin 2[3a)] which is easily obtained from aucubin 1,[3b)] a predominant glycoside in *Aucuba Japonica*. In a large scale preparation, crystalline and almost pure 2 was directly obtained from the fresh fruits of the plant without isolation of 1 by the sequence (1) hydrogenation of crude extracts of 1 over Raney-nickel (ethanol-water) (2) hydrolysis of glucoside with phosphoric acid and subsequent ring closure (3) extraction with chloroform. In the course of our study on the structure-activity relationships, we have been interested in the synthesis and the biological properties of various prostanoids to be derived from aucubin 1. We wish to report a simple and efficient synthesis of the titled prostanoids, (+)-11-deoxy-11α-hydroxymethyl $PGF_{1\alpha}$ 9[7)] and its 12-isomer 6, from the olefin ketone 3,[1c)] the intermediate for the synthesis of 13,11-epoxymethano-type prostanoids.[1c)]

Catalytic hydrogenation of 3 using palladium on charcoal(5 %) gave the saturated ketone 4.[4)] The dehydrative tetrahydrofuran ring fission of 4 was successfully effected by treating the ketone 4 with p-toluenesulfonic acid(2.2 equiv) in acetic anhydride at 70°C for 1.5 hr to produce the enone 5[4)](attempted similar ring fission of 3 was unsuccessful). Isomerization of the enone 5 was achieved by treatment with 2 equiv of p-toluenesulfonic acid in acetic acid at 110°C for 9 hr to give the stable isomer 8.[4)]

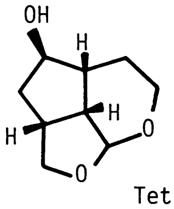
Reduction of the stable enone 8 with an excess of sodium borohydride in methanol, followed by hydrolysis using potassium hydroxide(1 M) in methanol-water(1:1), afforded a mixture of the (15S)-alcohol 9(more polar) and the epimeric counterpart, (15R)-alcohol 10(less polar). These were readily separated on silica gel column with methanol-benzene as eluent(9[4,5)]; 29% yield, 10[4,5)]; 34% yield). By analogy to the tlc behaviors[6)] as well as the relative biological activities between natural prostaglandins and their 15-epimers, the end product 9, being more polar than 10, has tentatively been assigned the (15S) configuration, 11-deoxy-11α-hydroxymethyl $PGF_{1\alpha}$ (mp64-68°C, $[\alpha]_D^{24.5}$+28.3°(c 0.865, methanol), NMR:δppm 0.87(3H), 1.0-2.5(25H), 3.57(m, 2H), 3.9-4.3(m, 2H), 5.46(m, 2H), 7.0(4H)).[7)]

Similarly the enone 5 was converted to the 12-isomeric prostanoid 6[4,5)](more polar) and its 15-epimer 7[4,5)] under essentially the same experimental conditions(6; oil, $[\alpha]_D^{23}$+9°(c 0.43, chloroform), NMR: 0.9(3H), 1.0-3.0(25H), 3.58(d, 2H), 3.9-4.4(m, 2H), 5.2(4H), 5.5-5.9(m, 2H), 7; mp 78-81°C, $[\alpha]_D^{23}$+18°(c 1.68, chloroform)). These prostanoids, 6 and 7, are characterized by the all-*cis* configuration on the cyclopentane ring structure. The biological properties of these prostanoids are currently in study.

Synthetic route to prostaglandin analogs, shown above, features (1)simple and efficient chiral synthesis, (2)easiness of large scale preparation, and (3)easily available optically active starting material(wide distribution of Aucuba Japonica in Japan).

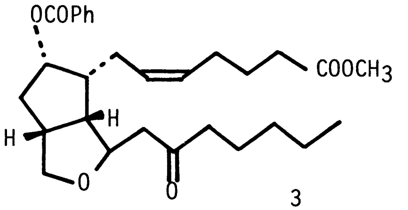


1 : Aucubin



2

Tetrahydroanhydroaucubigenin



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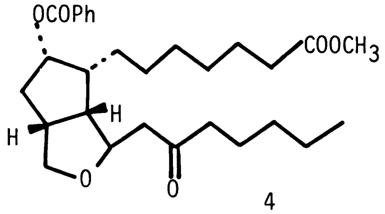

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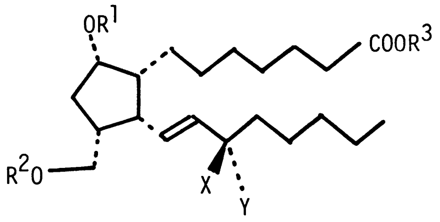
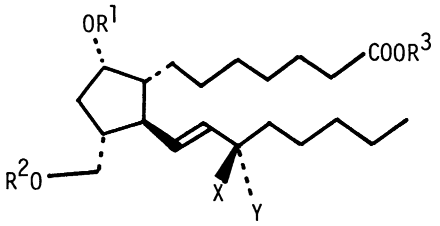


5 : X=Y=O, R^1=PhCO, R^2=CH_3CO, R^3=CH_3
6 : X=H, Y=OH, R^1=R^2=R^3=H
7 : X=OH, Y=H, R^1=R^2=R^3=H



8 : X=Y=O, R^1=PhCO, R^2=CH_3CO, R^3=CH_3
9 : X=H, Y=OH, R^1=R^2=R^3=H
10 : X=OH, Y=H, R^1=R^2=R^3=H

References and Notes

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2) Recently an alternate synthetic pathway to the intermediates for prostanoids from aucubin 1 has partly been reported.
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