Tetrahedron Letters No. 3, pp 251 - 254.

0040-4039/79/0115-0251$02.00/0

SYNTHESIS OF PROSTAGLANDINS AND THEIR CONGENERS I.
(+)-11-DEOXY-11α-HYDROXYMETHYL PROSTAGLANDIN $F_{2\alpha}$ FROM AUCUBIN[1)]

M. Naruto, K. Ohno*, N. Naruse, and H. Takeuchi
Basic Research Laboratories, Toray Industries Inc.,
Tebiro, Kamakura, 248, Japan

There have been current interests in the developed synthesis of optically active prostaglandins without resolution[2)]. The successful results reported by several laboratories include microbiological process[2a)], assymmetric induction process[2b)], or the use of chiral starting materials such as 2,3-isopropylidene-L-erythrose[2c)], S-(-)-malic acid[2d)], or D-tartalic acid[2e)]. We also devoted some efforts to the synthesis of chiral prostanoids which would not require separation of enantiomers. We wish to describe herein the synthesis of an optically active prostaglandin analog 1, (+)-11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$[3)], from aucubin 2[4a)], a predominant glycoside in Aucuba Japonica.

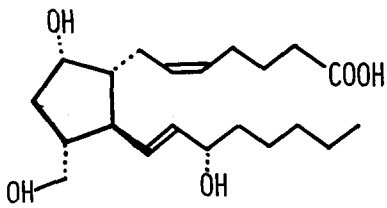
Catalytic hydrogenation of aucubin 2, followed by treatment with phosphoric acid, produced the known tetrahydroanhydroaucubigenin 3[4b)]. Collins oxidation[5)] of 3, followed by $LiAlH_4$ reduction, afforded predominantly its epimer 4[4c)], which was converted into the benzoate 5[6,7)] in a high yield using benzoyl chloride and pyridine(mp 60-61°C, $[\alpha]_D^{25}$ +33°(c 1.04, methanol)). The benzoate 5 in dichloromethane was added to the pale yellow mixture of 1.1 equiv of 2-acetoxy-1-heptene and 1.1 equiv of titanium tetrachloride in dichloromethane at -5°C under an argon atmosphere, and this reaction mixture was stirred for additional 2 hr at -5°C.[8)] After work up with aqueous alkaline solution, a mixture of the hydroxy ketone 6[6,7)] and its acetate 7[6,7)] were obtained. These were readily separated by silica gel column chromatography with ethyl acetate-dichloromethane as eluent (6; 66% yield, $[\alpha]_D^{25}$ +69°(c 1.1, methanol), 7; 14% yield, $[\alpha]_D^{25}$ +34°(c 0.909, methanol)). The acetate 7 was selectively converted into 6 using trifluoroacetic acid in methanol.

Reaction of the hydroxy ketone 6 with chloroacetyl chloride and pyridine in ether afforded the chloroacetate 8[6)] in 87% yield($[\alpha]_D^{23}$ +52°(c 1.16, methanol)). Treatment of the chloroacetate 8 with *p*-toluenesulfonic acid(0.4 equiv) in acetic anhydride at 70°C for 2.5 hr, gave the enone 9[6)], which was purified in 65% yield by silica gel column chromatography($[\alpha]_D^{28}$ +23°(c 1.06, methanol), IR:

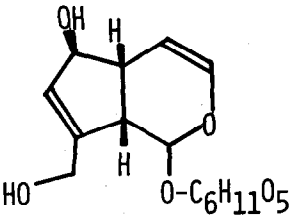
$\nu(cm^{-1})$ 1670, 1625, NMR: δ (ppm) 6.19(d, 1H, J=16 Hz), 7.03(dd, 1H, J= 16 Hz, 11 Hz)). Isomerization of the enone 9 using catalytic amount of *p*-toluenesulfonic acid in acetic acid at 105°C for 4 hr produced the stable isomeric enone 10[6] in 60% yield($[\alpha]_D^{25}$ +47°(c 1.00, methanol), IR: $\nu(cm^{-1})$ 1670, 1625, NMR: δ (ppm) 6.20(d, 1H, J=16 Hz), 6.69(dd, 1H, J=16 Hz, 8 Hz)).

Treatment of the stable enone 10 with excess zinc borohydride in dimethoxyethane at 20°C for 2 hr afforded in 60% yield a mixture of the (15S) alcohol 11[6] (more polar) and the (15R) epimer 12[6] (ratio *ca.* 6:4). Separation of the desired (15S) isomer 11 from the mixture was accomplished by silica gel column chromatography, using benzene-ethyl acetate as eluent. Further, the (15R) isomer 12 reverted to the precursor 10 upon treatment with activated manganese dioxide in dichloromethane. The (15S) alcohol 11 was converted into the tetrahydropyranyl drivative 13[6] using dihydropyran (5 equiv) in dichloromethane containing catalytic amount of *p*-toluenesulfonic acid in a high yield. Selective hydrolysis of 13 with thiourea and sodium bicarbonate in ethanol at 70°C for 5 hr yielded the alcohol 14[6] in 70% yield. Collins oxidation[5] of 14 produced the aldehyde 15[6] in 90% yield, which was treated with potassium carbonate in methanol at 20°C to form the hemiacetal 16[6] in 92% yield.

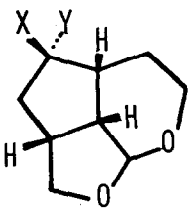
Condensation of 16 with the Wittig reagent derived from (4-carboxybutyl)-triphenylphosphonium bromide[9] and sodium methylsulfinylmethide in dimethyl sulfoxide followed by hydrolysis using acetic acid-water(2:1) at 40°C afforded 35% yield of 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$ 1[3a, 6,7] after purification by silica gel column chromatography($[\alpha]_D^{25}$ +23°(c 0.26, tetrahydrofuran), NMR: δ (ppm) 0.89(t, 3H), 1.1-2.6(21H), 3.6(m, 2H), 4.1(m, 2H), 5.3-5.6(m, 4H), 5.7(s, 4H)). By analogy to the t.l.c. behavior[10] and biological activity between natural prostaglandins and their 15-epimers, the compound 1, being more polar than its epimer which was derived from the intermediate 12 using essentially the same experimental conditions as described above, has tentatively been assigned the (15S) configuration.



1



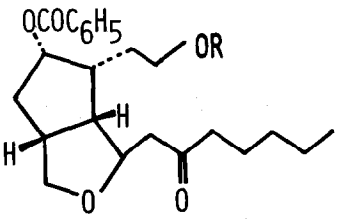
2



3 X=OH, Y=H

4 X=H, Y=OH

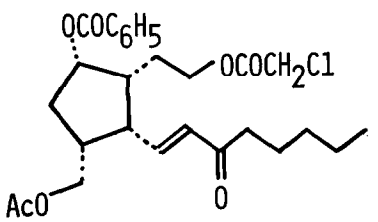
5 X=H, Y=$OCOC_6H_5$



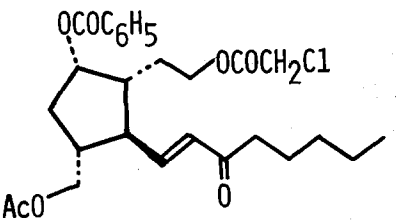
6 R=H

7 R=$COCH_3$

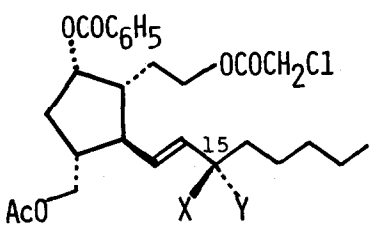
8 R=$COCH_2Cl$



9



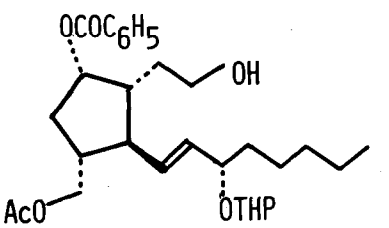
10



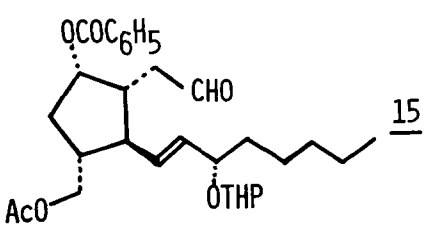
11 X=H, Y=OH

12 X=OH, Y=H

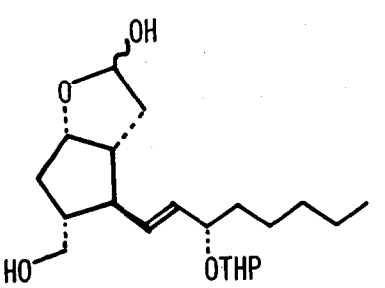
13 X=H, Y=THP



14



15



16

References and Notes

1) The synthesis of several prostanoids from aucubin has already been disclosed by the authors; Japan Kokai, 83435/1977, 83436/1977, 83437/1977, 83452/1977, 83453/1977, 85150/1977, 89654/1977, 89663/1977, 97943/1977, 97944/1977 (CA., 87, 184358y, 88, 6410x, 6411y, 6412z, 22218w, 22226x, 89198h, 89199j).

2a) T. Tanka, S. Kurozumi, T. Toru, S. Miura, M. Kobayashi, and S. Ishimoto, Tetrahedron, 32, 1713(1976).
C.J. Sih, J.B. Heather, G.P. Peruzzotti, P. Price, R. Sood, and L.F.H. Lee, J. Am. Chem. Soc., 95, 1676(1973).

b) E.J. Corey and H.E. Ensley, ibid., 97, 6908(1975).

c) G. Stork and S. Rauscher, ibid., 98, 1583(1976).

d) K.G. Paul, F. Johnson, and D. Favara, ibid., 98, 1285(1976).

e) K. Ogura, M. Yamashita, and G. Tsuchihashi, Tetrahedron Lett., 1976, 759.

3a) G.L. Bundy, Tetrahedron Lett., 1975, 1957.

b) 11-Deoxy-11α-hydroxymethyl prostaglandins have been obtained by several other methods;
F. Kienzle, G.W. Holland, J.L. Jernow, S. Kwoh, and P. Rosen, J. Org. Chem., 38, 3440(1973).
K. Sakai, J. Ide, and O. Oda, Tetrahedron Lett., 1975, 3021.

4a) H. Uda, M. Maruyama, K. Kabuki, and S. Fujise, Nippon Kagaku Zasshi, 85, 279(1964).

b) S. Fujise, ibid., 74, 725(1953).

c) S. Fujise, M. Maruyama, and H. Uda, ibid., 82, 367(1961).

5) J.C. Collins, W.W. Hess, and F.J. Frank, Tetrahedron Lett., 1968, 3363.

6) Infrared and NMR(100 MHz, in $CDCl_3$) spectra were in agreement with the assigned structure.

7) Satisfactory elemental or mass spectral analytical data were obtained.

8) Lewis acid promoted aldol-type condensation of acetal with enol acetates; T. Mukaiyama, T. Izawa, and K. Saigo, Chem. Lett., 1974, 323.

9) E.J.Corey, N.M. Weinschenker, T.K. Schaaf, and W. Huber, J. Am. Chem. Soc., 91, 5675(1969).
R. Greenwald, M. Chaykovsky, and E.J. Corey, J. Org. Chem., 28, 1128(1963).

10) N.H. Andersen, J. Lipid Res., 10, 316(1969).

(Received in Japan 20 October 1978)