CHEMISTRY LETTERS, pp. 1419-1422, 1978. Published by the Chemical Society of Japan

# THE SYNTHESIS OF USEFUL CHIRAL PROSTANOID INTERMEDIATES AND NATURALLY OCCURRING PROSTAGLANDINS FROM AUCUBIN

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

The synthesis of optically active intermediate 9 for prostanoids from aucubin 1 was described, in which stepwise cleavage of intramolecular cyclic acetal of tetrahydroanhydroaucubigenin 2 by ethanethiol in the presence of boron trifluoride was successfully accomplished. The synthesis of naturally occurring prostaglandins was also described.

Previously we have reported[1] a stereocontrolled synthesis of optically active prostanoids from aucubin 1[2], which includes Lewis acid promoted cross aldol-type condensation between acetal and enol acetate. Herein we wish to describe alternative synthetic approach to prostanoids from aucubin 1.

The known tosylate 3[3,4,5] was treated with excess ethanethiol in dimethoxyethane in the presence of boron trifluoride etherate(2.4 equiv) at 20°C to give the monothioacetal 4[4] in quantitative yield. Cornforth oxidation of 4 produced the lactone 5[4,5] (47% yield, mp 98-100°C, $[\alpha]_D^{23}$ +218°(c 1.00, chloroform)), which was treated with boron trifluoride etherate(2.0 equiv) in ethanethiol at 20°C to produce the dithioacetal 6[3] quantitatively. Benzoylation of 6 afforded the corresponding benzoate 7[4,5] (mp 79.5-80°C, $[\alpha]_D^{23}$ -40°(c 1.04, chloroform)) in 75% yield from 5.

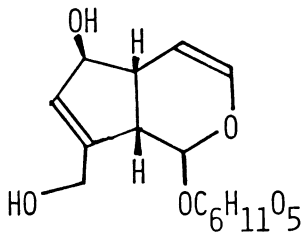
Treatment of the benzoate 7 with N-chlorosuccinimide-silver nitrate in acetonitrile-water[6] at 0°C gave a mixture of the aldehyde 8(more polar) and the epimer 9(less polar). The mixture was converted upon treatment with potassium acetate in methanol into the stable isomer 9[4,5] (68% yield from 7, mp 132-133.5°C, $[\alpha]_D^{24}$ -24°(c 1.00, chloroform), NMR:aldehyde proton $\delta$=9.78 ppm(d)). This aldehyde

is a useful intermediate for the synthesis of 11-deoxy-11α-hydroxymethyl prostaglandins. For example, 11-deoxy-11α-hydroxymethyl $PGF_{2\alpha}$[7] ($[\alpha]_D^{25}$ +23°(c 0.26, tetrahydrofuran)) was derived from 9 using essentially the same experimental conditions as those of the conventional methods[8].

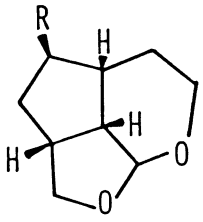
Synthesis of naturally occurring prostaglandins was accomplished in the following way. Condensation of the aldehyde 9 with sodio derivatives of dimethyl 2-oxoheptylphosphonate in dimethoxyethane at 20°C produced the *trans*-enone 10[4] (88% yield, $[\alpha]_D^{25}$ -25°(c 1.312, chloroform)). Treatment of the enone 10 with excess zinc borohydride in dimethoxyethane at 20°C afforded a mixture of the (15S) alcohol 11[4] (less polar) and the (15R) epimer 12[4] (more polar). These were readily separated by column chromatography on silica gel using ethyl acetate as eluent (11; 47% yield, $[\alpha]_D^{24}$ -36°(c 1.1, chloroform), 12; 33% yield, $[\alpha]_D^{24}$ -56°(c 1.3, chloroform)). The desired (15S) alcohol 11 was converted into the tetrahydropyranyl(THP) derivative 13[4] using dihydropyran(5 equiv) in dichloromethane containning catalytic amount of *p*-toluenesulfonic acid. Methanolysis of 13 with an equimolar amount of potassium carbonate in methanol at 20°C gave the alcohol 14[4], which was converted by the reaction with Cornforth reagent[9] at 20°C to the carboxylic acid 15[4]. The carboxylic acid 15 was converted into 17[4] *via* 16[4] by the known procedure[10] (condensation with *m*-chloroperbenzoic acid, followed by decarboxylative rearrangement).

Methanolysis of 17 with potassium carbonate in methanol at 20°C followed by hydrolysis in acetic acid-water(2:1) at 40°C afforded the diol 18[4,5] (20% yield from 11 after chromatographic purification(silica gel, ethyl acetate)). The diol 18, thus obtained, exhibited the same IR and NMR spectra, and thin layer chromatographic behavior in all respects as those of an authentic sample which was prepared according to the conventional method[8], and had $[\alpha]_D^{23}$ -7.1°(c 0.491, chloroform) as compared with $[\alpha]_D^{27}$ -7.0°(c 1.43, chloroform) found for an authentic sample[8b].

The synthesis of naturally occurring forms of prostaglandins from the diol 18 has been reported by E.J. Corey *et al.*[8b], and the synthesis of the diol 18 constitutes indirect total synthesis of naturally occurring prostaglandins.

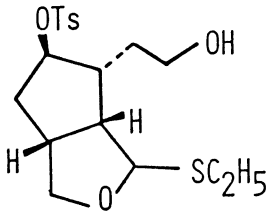



1

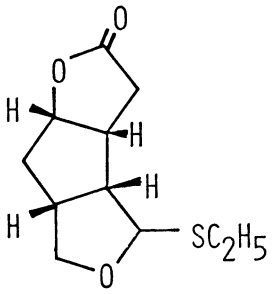



2 R=OH

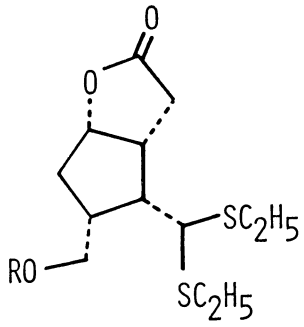
3 R=OTs




4

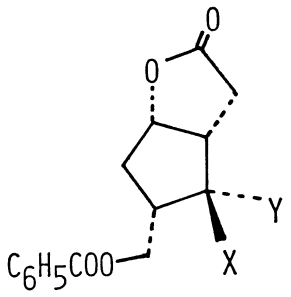



5



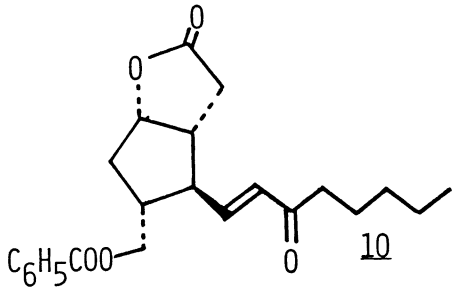

6 R=H

7 R=$C_6H_5CO$

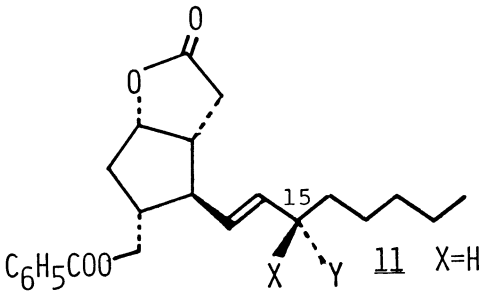



8 X=H, Y=CHO

9 X=CHO, Y=H



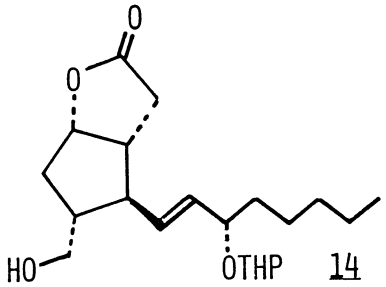

10



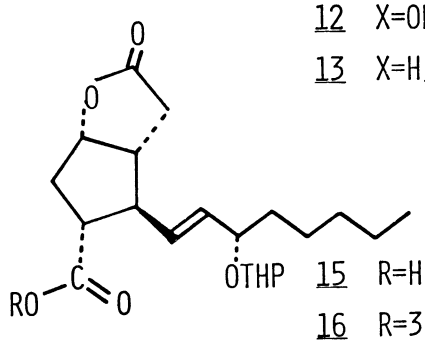

11 X=H, Y=OH

12 X=OH, Y=H

13 X=H, Y=OTHP

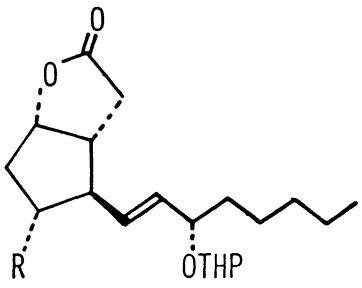



14

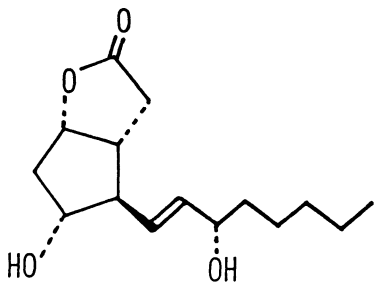



15 R=H

16 R=3-Cl$C_6H_4COO$




17 R=3-ClC$_6$H$_4$COO




18

References and Notes

1) M. Naruto. K. Ohno, N. Naruse, and H. Takeuchi, Tetrahedron Lett., submitted for publication.

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

3) H. Uda, ibid., 81, 1723(1960)

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

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

6) E.J. Corey and B.W. Erickson, J. Org. Chem., 36, 3553(1971).

7a) The synthesis of this compound from aucubin has already been disclosed by the authors; K. Ohno, M. Naruto, H. Takeuchi and N. Naruse, Japan Kokai,83436/1977 and 83453/1977 (CA., 88, 6412z and 6410x).

b) 11-Deoxy-11α-hydroxymethyl-prostaglandins have been obtained by several methods C.V. Grudzinskas and M.J. Weiss, Tetrahedron Lett., 1973, 141.
K. Sakai, J. Ide, and O. Oda, ibid., 1975, 3021.

8a) E.J. Corey, N.M. Weinschenker, T.K. Schaaf, and W. Huber, J. Am. Chem. Soc., 91, 5675(1969).

b) E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker, and N.M. Weinchenker, ibid., 92, 397(1970).

9) R.H. Cornforth, J.W. Cornforth, and G. Popjak, Tetrahedron, 18, 1351(1962).

10) F. Kienzle, G.W. Holland, J.L. Jernow, S. Kwoh, and P. Rosen, J. Org. Chem., 38, 3440(1973).

(Received October 21, 1978)