CHEMISTRY LETTERS, pp. 23-26, 1979. Published by the Chemical Society of Japan

SYNTHESIS OF 15,17-METHYLENE-PROSTAGLANDINS

Haruki NIWA and Masayasu KURONO*

Research Institute, Ono Pharmaceutical Co. Ltd.,

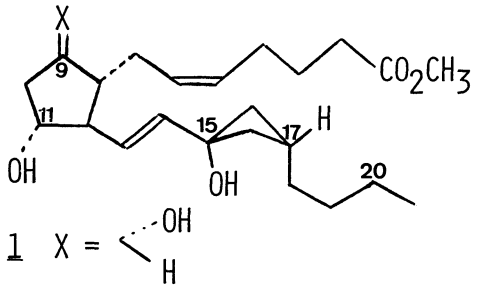
1-1, Sakurai 3-Chome, Shimamoto-cho, Mishima-gun, Osaka 618

20-Methyl-15,17-methylene-prostaglandin F2α and E2 methyl ester (1 and 2) and 15,17-methylene-17-phenoxy-ω-trinor-prostaglandin F2α methyl ester (3) were synthesized via pyrolysis of β-hydroxy sulfoxides obtained by the coupling reaction of 3,7-dioxy-6-phenylsulfinylmethyl-2-oxabicyclo-[3,3,0]-octane derivative (10) with 3-butylcyclobutanone and 3-phenoxycyclobutanone respectively.

An important pathway for *in vivo* deactivation of prostaglandins (PGs) involves enzymatic oxidation at the C-15 hydroxyl group (prostanoid numbering) to 15-oxo-PGs[1]. It was anticipated that PG analogs which cannot be transformed to the corresponding 15-oxo-PGs might afford more sustained biological activities. In the previous paper, we reported the synthesis of 15,19-methylene-ω-tetranor-PGs which showed less biological activities than those of natural PGs.[2] In this communication we would like to describe the synthesis of 15,17-methylene-PGs 1, 2 and 3 which were expected to be new biological PG mimics with high potency.

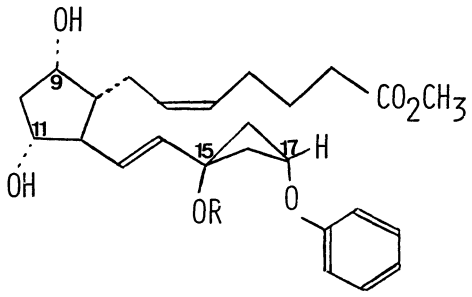
(-)-Lactone alcohol 4[3] was converted into the sulfoxide 10 by the sequential reactions as follows: (1) Tosylation of 4 with TsCl in pyridine at 25°C for 17 h to afford 5[4] (mp 91-92°C, $[\alpha]_D^{20}$ -51.3°(c 1.35, $CHCl_3$)), (2) substitution reaction of 5 with sodium iodide in reflux acetone to afford 6[4] ($[\alpha]_D^{23}$ -24.2°(c 5.90, $CHCl_3$)), (3) reduction of 6 with diisobutylaluminum hydride in toluene at -70°C for 30 min to afford 7[4] ($[\alpha]_D^{20}$ -35.3°(c 0.95, $CHCl_3$), mp 114-116°C), (4) treatment of 7 with CH_3OH and p-TsOH at 25°C for 30 min to afford 8[4,5] ($[\alpha]_D^{20}$ -50.7°(c 2.90, $CHCl_3$)), (5) treatment of 8 with dihydropyran and p-TsOH in CH_2Cl_2 at 25°C for 30 min to afford 9[4] ($[\alpha]_D^{20}$ -40.7°(c 5.60, $CHCl_3$)), (6) treatment of 9 with phenylsulfinylmethyllithium in THF at 20°C for 3 h to afford 10[4] ($[\alpha]_D^{20}$ -43.5°(c 4.30, $CHCl_3$), overall 76 % yield from 4).

The sulfoxide 10 was converted into the corresponding lithium salt upon treatment with 1.2 equiv of LDA in THF at -70°C for 30 min and allowed to react with 3-butylcyclobutanone[6] at -78°C for 10 min to give the desired adduct 11[4,7,8] in 83 % yield. Adduct 12[4,7,8] was also obtained in 85 % yield upon treatment with 3-phenoxycyclobutanone[9] under the essentially same procedure. Pyrolysis[10] of 11 and 12



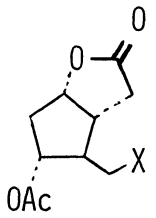
1 X =

2 X = =O



3 R = H

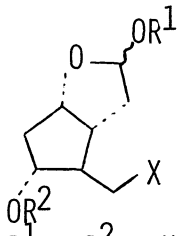
22 R = CH_2SCH_3



4 X = OH

5 X = OTs

6 X = I

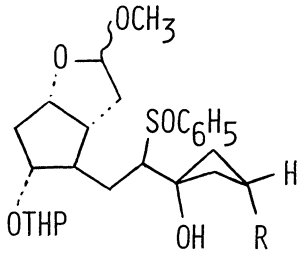


7 R^1 = R^2 = H, X = I

8 R^1 = CH_3, R^2 = H, X = I

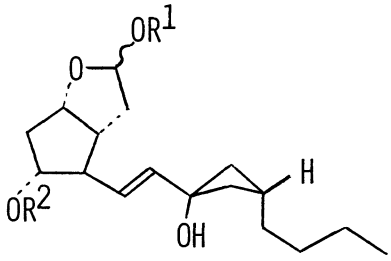
9 R^1 = CH_3, R^2 = THP, X = I

10 R^1 = CH_3, R^2 = THP, X = $CH_2SOC_6H_5$



11 R = n-C_4H_9

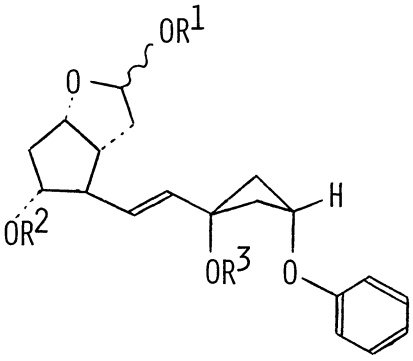
12 R = OC_6H_5



13 R^1 = CH_3, R^2 = THP

14 R^1 = CH_3, R^2 = H

15 R^1 = R^2 = H



16 R^1 = CH_3, R^2 = THP, R^3 = H

17 R^1 = CH_3, R^2 = H, R^3 = H

18 R^1 = R^2 = R^3 = H

19 R^1 = CH_3, R^2 = Ac, R^3 = H

20 R^1 = CH_3, R^2 = Ac, R^3 = CH_2SCH_3

21 R^1 = R^2 = H, R^3 = CH_2SCH_3

was carried out in benzene containing 5 equiv of pyridine at 78°C for 48 h to give the desired allylic alcohols 13[4] (76 % yield) and 16[4] (80 % yield) respectively.

Removal of THP group of 13 and 16 upon treatment with CH_3OH and p-TsOH at 25°C for 30 min afforded quantitatively the desired diols 14[4,5,11] and 17[4,5,11] respectively. The Wittig reaction of hemiacetal 15, derived from 14 by hydrolysis[12], was accomplished upon treatment with excess 4-carboxybutylidene-triphenylphosphorane in DMSO at 50°C for 19 h followed by esterification with excess diazomethane to give 20-methyl-15,17-methylene-PG $F_2\alpha$ methyl ester 1[4,13] ($[\alpha]_D^{28.5}$ +28.0°(c 1.80, $CHCl_3$), m/e calcd for $C_{23}H_{38}O_5$ (M^+) 394.2719; observed 394.2744) in 63 % yield.

On the other hand, 15,17-methylene-17-phenoxy-ω-trinor-PG $F_2\alpha$ methyl ester 3 was obtained by a series of the sequential reactions as follows. Acetylation of 17 with acetic anhydride and pyridine at 0°C for 4 h gave the desired monoacetate 19[4] in 70 % yield. Protection[14] of the tertiary hydroxyl group of 19 with a methylthiomethyl group[15] was accomplished upon treatment with acetic anhydride and DMSO at 40°C for 17 h to give the desired compound 20[4] in 80 % yield. Deacetylation followed by hydrolysis of 20 gave the corresponding hemiacetal 21. The Wittig reaction of 21 was accomplished upon treatment with excess 4-carboxybutylidenetriphenylphosphorane in DMSO at 25°C for 17 h followed by esterification with excess diazomethane to give the desired ester 22[4,13] (20 % yield). Removal of the methylthiomethyl group of 22 was carried out upon treatment with 4 equiv of chloramine-T in aqueous THF at 25°C for 10 min to give 15,17-methylene-17-phenoxy-ω-trinor-PG $F_2\alpha$ methyl ester 3[4,13] ($[\alpha]_D^{25}$ +21.8°(c 0.85, $CHCl_3$), m/e calcd for $C_{25}H_{32}O_5$ ($M^+ - H_2O$) 412.2250; observed 412.2252) in 50 % yield.

According to the essentially same procedure reported by E. W. Yankee et al[16], 20-methyl-15,17-methylene-PG $F_2\alpha$ methyl ester 1 was converted into the corresponding PG E_2 methyl ester 2[4,13] (overall 36 % yield, $[\alpha]_D^{28.5}$ -64.7°(c 2.25, $CHCl_3$), m/e calcd for $C_{23}H_{36}O_5$ (M^+) 392.2563; observed 392.2515) as follows: (a) selective silylation of C-11 hydroxyl group with N-trimethylsilyldiethylamine in dry acetone at -45°C for 6 h (b) oxidation of C-9 hydroxyl group with Collins reagent in dry CH_2Cl_2 at 25°C for 5 min (c) desilylation with AcOH-H_2O-CH_3OH at 25°C for 1 h.

These new PG analogs 1, 2 and 3 showed more potent biological activities than those of natural PGs: e.g. 15,17-methylene-17-phenoxy-ω-trinor-PG $F_2\alpha$ methyl ester 3 is 5 times more potent than natural $F_2\alpha$ in an antinidatory effect in pregnant rats.

REFERENCES AND NOTES

1. (a) E. Anggärd and B. Samuelsson, Ark. Kem., 25, 293 (1966).
(b) J. Nakano, E. Anggärd, and B. Samuelsson, European J. Biochem., 11, 386 (1969).
2. H. Niwa and M. Kurono, Chem. Lett., 1977, 1211.
3. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, J. Amer. Chem. Soc., 92, 397 (1970).
4. Satisfactory infrared, proton magnetic resonance and mass spectral data were obtained for each compound.
5. The product was an epimeric mixture (2:1) due to the configuration of the methoxyl group.
6. Prepared from diethyl butylmalonate (R. Adams and R. M. Kamm, Org. Syn., Coll. Vol. 1, 250 (1954)) using the sequential reactions as follows: 1) $LiAlH_4$ in Ether, 2) HBr-H_2SO_4, 3) $CH_3SOCH_2SCH_3$-BuLi, 4) HgO-aqueous H_2SO_4.[17]
7. The product should be a mixture of diastereoisomers due to four chiral centers including a sulfur atom and THP group.
8. The cis relationship between the hydroxyl and the substituent group on the cyclobutane ring was tentatively assigned, because it is reasonable that the bulky carbanion derived from 10 attacks the carbonyl group of the cyclobutanone from less hindered side. This prediction was apparently supported by the formation of only single product, 1 and 3 respectively, in the last step.
9. Prepared from 2-phenoxy-propane-1,3-diol (S. W. Chaikin, J. Amer. Chem. Soc., 70, 3522 (1948)) using the sequential reactions as follows: 1) TsCl-Py, 2) LiBr in acetone, 3) $CH_3SOCH_2SCH_3$-BuLi, 4) $CuCl_2 \cdot 2H_2O$ in DME.[17]
10. B. M. Trost, T. N. Saltzmann, and K. Hiroi, J. Amer. Chem. Soc., 98, 4887 (1976).
11. The trans geometry of the newly formed double bond was confirmed by the characteristic infrared absorption and the NMR spectrum of olefinic protons: 14; IR(film) 970 cm^{-1}, NMR($CDCl_3$) 5.35-5.95 ppm (ABX, J=15 and 7 Hz). 17; IR(film) 975 cm^{-1}, NMR($CDCl_3$) 5.4-5.9 ppm (ABX, J=15 and 7 Hz).
12. E. J. Corey and R. Noyori, Tetrahedron Lett., 1970, 311.
13. The product was homogeneous in several solvent systems on silica gel plate.
14. The Wittig reaction of 18 derived from 17 gave not desired product 3 but a complex mixture containing phenol. The result prompted us to protect the C-15 hydroxyl group with an appropriate protecting group in order to prevent from the decomposition of the cyclobutane ring.
15. K. Yamada, K. Kato, H. Nagase, and Y. Hirata, Tetrahedron Lett., 1976, 65.
16. E. W. Yankee, C. H. Lin, and J. Fried, J. Chem. Soc., Chem. Commun., 1972, 1120.
17. K. Ogura, M. Yamashita, M. Suzuki, and G. Tsuchihashi, Tetrahedron Lett., 1974, 3653.

(Received October 13, 1978)