CHEMISTRY LETTERS, pp. 1211-1214, 1977. Published by the Chemical Society of Japan

SYNTHESIS OF 15,19-METHANO-ω-NOR-PROSTAGLANDINS

Haruki NIWA and Masayasu KURONO*

Research Institute, ONO Pharmaceutical Co., Ltd.

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

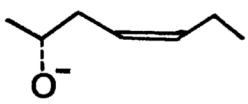
15,19-Methano-ω-nor-prostaglandin $F_{2\alpha}$ and E_2 methyl ester, 4 and 5, were synthesized from (-)-Corey's aldehyde 9 and the β-oxido ylide 6 via allylic rearrangement of the intermediate 17.

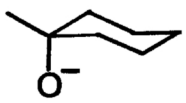
Recently, the Wittig reaction using the β-oxido ylide 1 has been successfully applied to the synthesis[1] of prostaglandin $F_{3\alpha}$ and E_3, 2 and 3. This communication reports the synthesis of 15,19-methano-ω-nor-prostaglandin $F_{2\alpha}$ and E_2 methyl ester, 4 and 5, using the β-oxido ylide 6, bearing an oxido group on a tertiary carbon atom, which was derived from the β-hydroxy phosphonium iodide 7.

The desired β-hydroxy phosphonium iodide 7 was prepared by the known procedure[2] as follows. Methylidenetriphenylphosphorane obtained from methyltriphenylphosphonium iodide 8 (1 equiv) and phenyllithium (1 equiv) in dry ether at 25°C for 30 min was treated with the freshly distilled cyclohexanone (1 equiv) at 0°C for 1 min, and immediately quenched with excess aqueous HI (9N) to give massy solids of the β-hydroxy phosphonium iodide 7 [50% yield from 8; pmr ($CDCl_3$) δ 3.90 ppm (2H, d, J=13 Hz, HO-C-C<u>H</u>$_2$-$P^+(C_6H_5)_3$)].

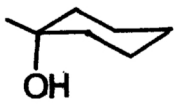
Treatment of 7 in dry THF with methyllithium (2 equiv) at -30°C for 20 min gave the reddish orange solution containing the β-oxido ylide 6.[1] The ylide solution was cooled down to -70°C and treated with (-)-aldehyde 9[1] (1 equiv) for 10 min and further at 0°C for 1 hr to give not a desired tertiary allylic alcohol 14 but a secondary allylic alchol 10[3] [30% yield from 9; pmr ($CDCl_3$) δ 4.29 (1H, dd, J=9 and 6 Hz, -C=CH-C<u>H</u>-OH) and 5.14 ppm (1H,bd, J=9 Hz, -C=C<u>H</u>-CH-OH); mass m/e 350 (M^+); ir ($CHCl_3$) 3600, 3450 and 1770 cm^{-1}; $[\alpha]_D^{23}$ -34.1° (c=1.98, $CHCl_3$)]. The secondary allylic alcohol 10 was easily converted into the tertiary allylic alcohol 15 under an aqueous acidic condition.[4] After reduction of 10 with diisobutyl-

$(C_6H_5)_3P{=}X$

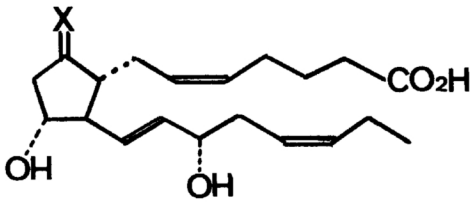
1 X = 

6 X = 

$(C_6H_5)_3\overset{+}{P}CH_2\text{-}X\ I^-$

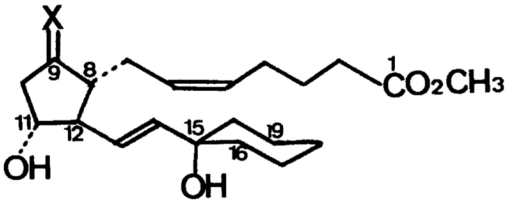
7 X = 

8 X = H



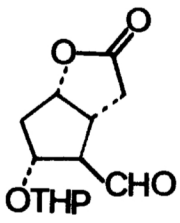
2 X = 

3 X = O

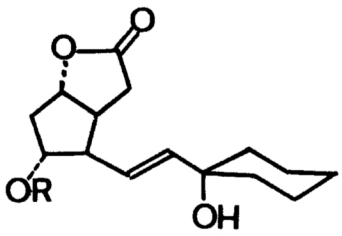


4 X = 

5 X = O

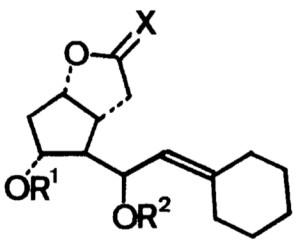


9



14 R = THP

15 R = H

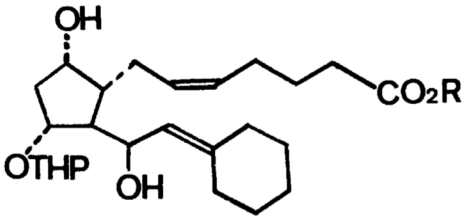


10 R^1 = THP, R^2 = H, X = O

11 R^1 = THP, R^2 = Ac, X = O

12 R^1=R^2= H, X= O

13 R^1 = THP, R^2 = H, X = 



16 R = H

17 R = CH_3

aluminun hydride (2 equiv) in toluene at -70°C for 15 min, the resulting mixture of diols 13[5] was treated with excess of 4-carboxy-n-butylidenetriphenylphosphorane in DMSO at 50°C for 2 days to give carboxylic acid 16 [ir ($CHCl_3$) 3400 and 1710 cm^{-1}; mass m/e 436 (M^+)] which was treated with diazomethane to afford the corresponding ester 17 [30% yield form 10; pmr ($CDCl_3$) δ 3.67 ppm (3H, s, $-COOCH_3$); mass m/e 365 (M^+-85); ir ($CHCl_3$) 3600, 3500, 1730 and 1240 cm^{-1}; $[\alpha]_D^{20}$ +38.0° (c=2.60, $CHCl_3$)]. Removal of THP group from 17 with AcOH-H_2O-THP at 37°C for 1 hr gave, via allylic rearrangement, 15,19-methano-ω-nor-prostaglandin $F_{2\alpha}$ methyl ester 4[4b] [60% yield; pmr ($CDCl_3$) δ 2.91 (3H, b, $(-OH)_3$), 3.90 (1H, m), 3.67 (3H, s, $-COOCH_3$), 5.42 (2H, m, $-CH_2-CH=CH-CH_2-$), 5.49 (1H, dd, J=16 and 7 Hz, $-CH=CH-C-OH$) and 5.71 ppm (1H, d, J=16 Hz, $-CH=CH-C-OH$); mass m/e 366 (M^+); ir ($CHCl_3$) 3600, 3400, 1730 and 980 cm^{-1}; $[\alpha]_D^{20}$ +31.7° (c=1.90, $CHCl_3$)].

According to essentially the same procedure as reported by E. W. Yankee et al.,[6] 15,19-methano-ω-nor-prostaglandin $F_{2\alpha}$ methyl ester 4 was converted into the corresponding E_2 methyl ester 5 [40% yield from 4; pmr ($CDCl_3$) δ 3.67 (3H, s, $-COOCH_3$), 4.05 (1H, m), 5.37 (2H, m, $-CH_2-CH=CH-CH_2$), 5.55 (1H, dd, J=16 and 7 Hz, $-CH=CH-C-OH$) and 5,78 ppm (1H, d, J=16 Hz, $-CH=CH-C-OH$); mass m/e 364 (M^+); ir ($CHCl_3$) 3550, 3400, 1740 and 980 cm^{-1}; $[\alpha]_D^{19}$ -70.0° (c=1.45, $CHCl_3$)] as follows: (a) selective silylation of the hydroxy group at C-11 (prostanoid numbering) with N-trimethylsilyldiethylamide in dry acetone at -45°C for 6 hr. (b) oxidation of C-9 hydroxy group with Collins reagent[7] (6 equiv) in dry CH_2Cl_2 at 25°C for 5 min. (c) desilylation with AcOH-H_2O-MeOH at 25°C for 1 hr.

These new 15,19-methano-ω-nor-prostaglandin $F_{2\alpha}$ and E_2 methyl ester, 4 and 5, showed less biological activities than those of the corresponding natural prostaglandins.

References and Notes

1) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu and T. K. Schaaf, J. Amer. Chem. Soc., 93, 1490 (1971), and references cited therein.

2) M. Schlosser and K. F. Christmann, Justus Liebigs Ann. Chem., 708, 1 (1971).

3) The structure of 10 was reliably confirmed by acetylation of the secondary allylic hydroxy group of 10 with Ac_2O-Py to give the corresponding acetate 11 [pmr ($CDCl_3$) δ 5.01 (1H, bd, J=9 Hz, -C=C<u>H</u>-CH-OAc) and 5.43 ppm (1H, dd, J=9 and 8 Hz, -C=CH-C<u>H</u>-OAc); ir ($CHCl_3$) 1770 and 1730 cm^{-1}].

4) (a) Treatment of 10 with MeOH-TsOH gave the diol 12 [pmr ($CDCl_3$) δ 4.41 (1H, dd, J=9 and 6 Hz, -C=CH-C<u>H</u>-OH) and 5.18 ppm (1H, bd, J=9 Hz, -C=C<u>H</u>-CH-OH); mass m/e 266 (M^+)].

(b) On the other hand, treatment of 10 with AcOH-H_2O-THF under the condition of removal of THP group gave the rearranged diol 15 [pmr ($CDCl_3$) δ 5.45 (1H, dd. J=16 amd 7 Hz, -C<u>H</u>=CH-C-OH) and 5.71 ppm (1H, d, J=16 Hz, -CH=C<u>H</u>-C-OH); mass m/e 266 (M^+)].

5) This diol 13 was used for the next Wittig reaction without further purification. All other new compounds reproted herein were purified by column chromatography on SiO_2.

6) E. W. Yankee, C. H. Lin and J. Fried, J. Chem. Soc., Chem. Commun., 1972, 1120.

7) (a) J. C. Collins, W. W. Hess and F. J. Frank, Tetrahedron Lett., 1968, 3363.

(b) R. Ratcliffe and R. Rodehorst, J. Org. Chem., 35, 4000 (1970).

(Received August 26, 1977)