CHEMISTRY LETTERS, pp. 141-144, 1978. Published by the Chemical Society of Japan

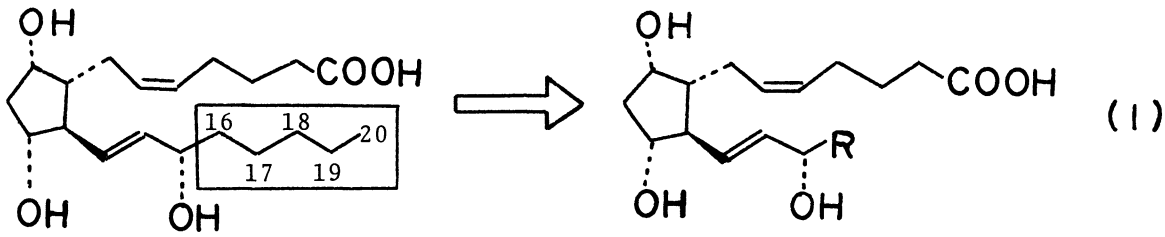
SYNTHESIS OF PROSTAGLANDIN ANALOGS I.
NOVEL AND EFFECTIVE INTERMEDIATES FOR MODIFICATION OF ω-CHAIN

Hirohisa WAKATSUKA, Yoshitaka KONISHI,
Seiji KORI, and Masaki HAYASHI*

Research Institute, Ono Pharmaceutical Co., Ltd.,
Shimamoto-cho, Mishima-gun, Osaka 618

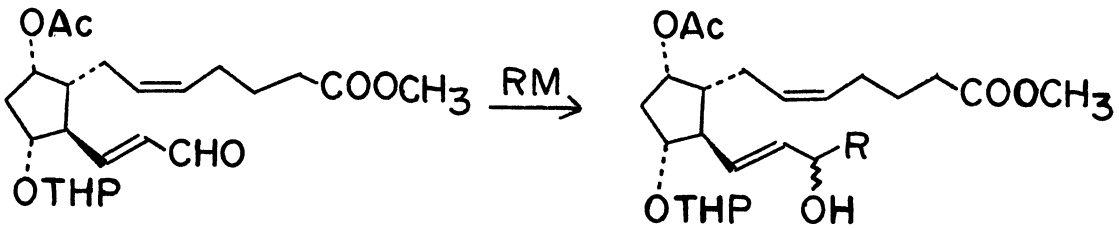
A simple and effective preparation of the useful intermediates for the synthesis of the prostaglandin (PG) analogs which are modified at ω-chain is reported.

The modification of ω-chain (C_{13}-C_{20}) of the natural prostaglandins (PGs) (eq.1) is increasingly important in the field of pharmacological study[1]. Outlined below (eq.2) is a new synthetic approach to PGs which is designed specifically for the preparation of these significant analogs. The synthetic intermediate 1 was selected for our study since a variety of PG analogs, which were modified at the ω-chain, were prepared simply by the reaction with nucleophilic reagents (e.g.



(1)

$PGF_{2\alpha}$ PG Analogs



(2)

1

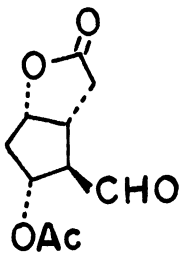
RMgX, RLi, etc.) (eq.2). We report herein the synthesis of this versatile aldehyde 1.

The Wittig reaction of the readily available (-)-β-acetoxyaldehyde 2[2] with the anion from triethyl phosphonoacetate[3] in THF for 1 h at room temperature afforded the α,β-unsaturated ester 3a (60% yield after column chromatography on silica gel): nmr (CCl_4) δ 6.77 (1H, dd), 5.87 (1H, d); ir (liquid film) ν 1775, 1735, 1710, 1650 cm^{-1}; homogeneous by tlc[4] (ethyl acetate-benzene 1:2, R_f 0.38). Exposure of 3a with potassium carbonate (1 equiv) in methanol followed by 1N-HCl (2 equiv) gave the alcohol 3b (90% yield): nmr ($CDCl_3$) δ 6.82 (1H, dd), 5.90 (1H, d); ir (liquid film) ν 1786-1690 (broad), 1650 cm^{-1}; homogeneous by tlc[4] (CH_2Cl_2-MeOH 19:1, R_f 0.38). The alcohol 3b upon treatment with dihydropyran in the presence of a trace of p-TsOH in CH_2Cl_2 followed by diisobutylaluminum hydride[5] (3 equiv) in toluene at -78°C for 20 min produced the allylic alcohol 4a quantitatively: nmr ($CDCl_3$) δ 5.80-5.30 (3H, m); ir (liquid film) ν 1440, 1120 cm^{-1}; homogeneous by tlc[4] (CH_2Cl_2-MeOH 19:1, R_f 0.24). The lactol 4a was condensed with 4-carboxy-n-butylidene-triphenylphosphorane[2] in dimethyl sulfoxide for 2 h at 25°C to afford the unstable carboxylic acid 5a. Since the inter- or intra-molecular migration of the tetrahydropyranyl functions (self-catalyst) in 5a gives rise to a rather complex mixture, the crude 5a should be immediately esterified by diazomethane to 5b (73% yield from 4a): nmr ($CDCl_3$) δ 5.75-5.20 (4H, m), 4.67 (1H, m); ir (liquid film) ν 3420, 1740 cm^{-1}; homogeneous by tlc[4] (ethyl acetate-cyclohexane 2:1, R_f 0.31). Oxidation of 5b with manganese dioxide (40 equiv) in CH_2Cl_2-n-hexane (1:2) at 0°C for 1 h yielded 6a (80% yield after chromatography on silica gel): nmr ($CDCl_3$) δ 9.54 (1H, d), 6.82-6.79 (1H, m), 6.20-6.18 (1H, m); ir (liquid film) ν 1735, 1688, 1632 cm^{-1}; homogeneous by tlc[4] (ethyl acetate-benzene 1:2, R_f 0.27). The 9-keto aldehyde 7a was also produced as a by-product (ca. 3%), which was transformed to the PGE_2 type compounds[6]. Acetylation of 6a with Ac_2O (10 equiv) and pyridine (10 equiv) at room temperature for 16 h furnished the desired product 1 quantitatively: nmr ($CDCl_3$) δ 9.56 (1H, d), 6.82-6.79 (1H, m), 6.26-6.23 (1H, m); ir (liquid film) ν 1737, 1687, 1636 cm^{-1}; homogeneous by tlc[4] (ethyl acetate-benzene 1:2, R_f 0.50). Thus, the aldehyde 1 was synthesized from (-)-β-acetoxy aldehyde 2 in 32% overall yield through eight steps.

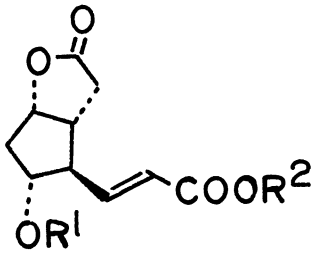
The 9,11-dihydroxy aldehyde was prepared as follows. Reduction of 3a with diisobutylaluminum hydride (6 equiv) in toluene at -50°C gave 4b (66% yield): nmr (DMSO-d_6) δ 5.65-5.30 (3H, m); ir (KBr tablet) ν 3360 cm^{-1}; mp 132°C.

Condensation of 4b with 4-carboxy-n-butylidene-triphenylphosphorane in dimethyl sulfoxide at 25°C for 2 h produced 5c (70% yield after column chromatography on silica gel): nmr ($CDCl_3$-DMSO-d_6) δ 5.90-4.80 (8H, m); ir (liquid film) ν 1710 cm^{-1}; homogeneous by tlc[4] (CH_2Cl_2-MeOH 4:1, R_f 0.30). The allylic alcohol 5c was oxidized with manganese dioxide (50 equiv) in acetone at room temperature for 16 h to form 6b (57% yield after chromatography on silica gel): nmr ($CDCl_3$-DMSO-d_6) δ 9.52 (1H, d), 6.82 (1H, d), 6.17 (1H, dd); ir (liquid film) ν 1720-1680 (broad) cm^{-1}; homogeneous by tlc[4] (ethyl acetate-formic acid 400:5, R_f 0.25). PGF_2 analogs were obtained directly by reaction of 6b with the various alkyl lithium reagents.[6] The esterification of 6b produced 6c which was further converted to 6d (Ac_2O-pyridine).

The aldehydes 1, 6a, 6b, 6c, 7a prepared as above, and 7b prepared by treatment of 7a with 65% aqueous acetic acid are useful synthetic intermediates for the preparation of a variety of PG analogs, some of which are exemplified by the accompanying communication.[6]

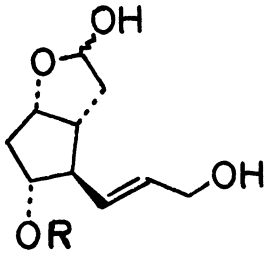


2



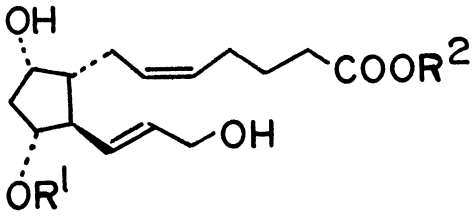
3a R^1=Ac, R^2=Et

3b R^1=H, R^2=Me



4a R=THP

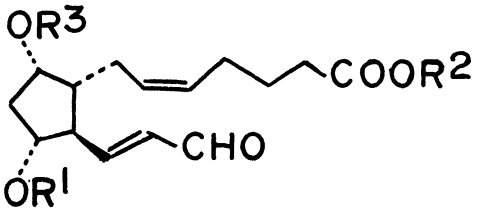
4b R=H

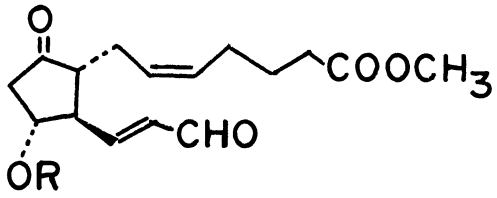


5a R^1=THP, R^2=H

5b R^1=THP, R^2=Me

5c R^1=H, R^2=H





6a R^1=THP, R^2=CH_3, R^3=H

6b R^1=H, R^2=H, R^3=H

6c R^1=H, R^2=CH_3, R^3=H

6d R^1=Ac, R^2=CH_3, R^3=Ac

7a R=THP

7b R=H

Acknowledgment. The authors wish to express their thanks to Dr. Hisashi Yamamoto of University of Hawaii for his valuable suggestions.

References and Notes

1. (a) M. Hayashi, H. Miyake, T. Tanouchi, S. Iguchi, Y. Iguchi, and F. Tanouchi, J. Org. Chem., 38, 1250 (1973); (b) B. J. Magerlein, D. W. Duclarme, W. E. Magee, W. L. Miller, A. Robert, and J. R. Weeks, Prostaglandins, 4, 143 (1973); (c) H. Miyake, S. Iguchi, S. Kori, and M. Hayashi, Chem. Lett., 1976, 211; (d) A. P. Labhsetwar, Prostaglandins, 2, 375 (1972); (e) B. J. Magerlein and W. L. Miller, Prostaglandins, 9, 527 (1975); (f) W. L. Miller, J. R. Weeks, J. W. Lauderdale, and K. T. Kirton, Prostaglandins, 9, 9 (1975); (g) J. R. Jonson, B. S. Meddlediich, and D. M. Desiderio, Science, 157, 1093 (1975).
2. E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, J. Am. Chem. Soc., 92, 397 (1970).
3. W. S. Wadsworth, Jr. and W. D. Emmons, J. Am. Chem. Soc., 83, 1733 (1961).
4. The plate used for TLC analysis is Kieselgel 60F_{254} (E. Merck).
5. L. I. Zakharkin and I. M. Khorlina, Tetrahedron Lett., 1962, 619.
6. H. Miyake, T. Tanouchi, T. Yamato, T. Okada, Y. Konishi, H. Wakatsuka, S. Kori, and M. Hayashi, an accompanying communication.

(Received November 10, 1977)