CHEMISTRY LETTERS, pp. 145-148, 1978. Published by the Chemical Society of Japan

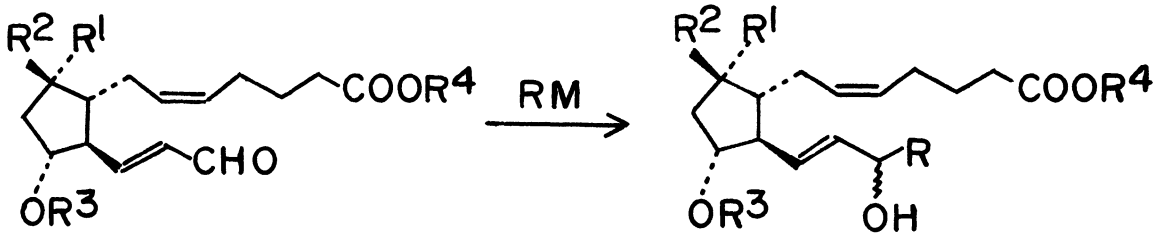
SYNTHESIS OF PROSTAGLANDIN ANALOGS II.
THE MODIFICATION OF ω-CHAIN

Hajimu MIYAKE, Tadao TANOUCHI, Takashi YAMATO,
Takanori OKADA, Yoshitaka KONISHI, Hirohisa WAKATSUKA,
Seiji KORI, and Masaki HAYASHI*

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

Many kinds of prostaglandin analogs, which are modified at the ω-chain and also unavailable by other methods, are synthesized simply by the reaction of the versatile aldehydes 1a, 1b, 1c, and 1d with nucleophilic reagents.

In the preceding communication we have disclosed a short and efficient route to a key intermediate of prostaglandin (PG) analogs. We report herein the synthesis of the different analogs some of which are unavailable by other procedures.



1 2

a) R^1=OAc, R^2=H, R^3=THP, R^4=CH_3

b) R^1=OAc, R^2=R^3=H, R^4=CH_3

c) R^1=OAc, R^2=H, R^3=Ac, R^4=CH_3

d) R^1, R^2=O, R^3=H, R^4=CH_3

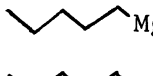
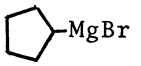
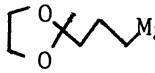
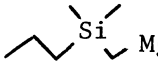
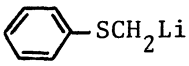
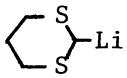
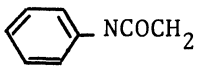
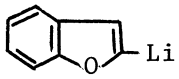
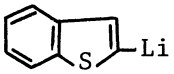
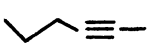
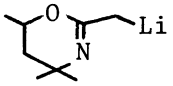
e) R^1=OH, R^2=R^3=H, R^4=CH_3

f) R^1=OH, R^2=R^3=R^4=H

As the vinylaldehyde 1 contains not only an aldehyde unit but also an ester function in the same molecule, the reaction conditions must be carefully controlled

in order to avoid the side-reactions. The Grignard reagents or alkyllithium reagents were suitable for obtaining good result. In general, treatment of 1 with Grignard reagents at 0°C or alkyllithium reagents at -78°C were found to be the best reaction conditions. The C_{15}-epimer was separated easily by chromatography on silica gel. The products were identified by nmr and ir spectra and also by tlc behavior. Results are shown in Table I.

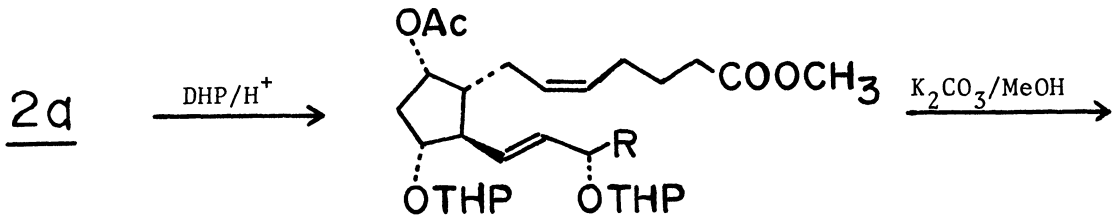
Table I

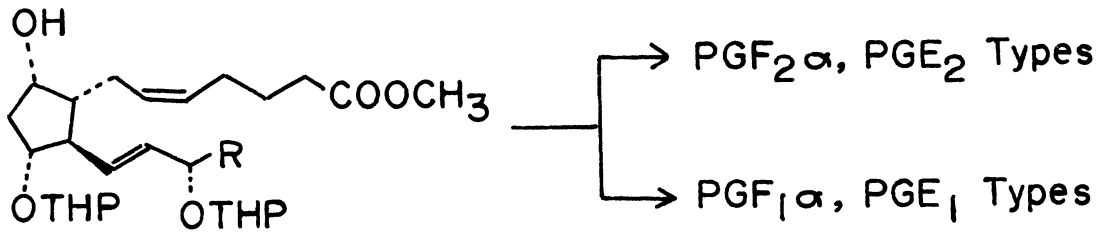
entry	RM (Ref)	solvent	Temp.(°C)	Product 2(%)
1		Et_2O	0	a(90)
		Et_2O	0	b(80)
		THF/HMPA	-78	f(81)
2		Et_2O	0	a(45)
3	 (5)	Benzene	20	a(78)
4	 (6)	THF	0	b(40)[12]
5	 (7)	THF/Et_2O	0	d(46)[13]
		THF/Et_2O	0	e(50)[13]
6	 (8)	THF	-78	a(80)
7	 (9)	THF	-78	a(48)
8	 (10)	Et_2O	-78	a(63)
9	 (11)	THF	-40	c(80)[12]
10	 (11)	THF	-40	c(80)[12]
11	 (1)	THF	-78	c(85)[12]
		THF	-78	e(70)[12]
12	 (2)	THF/HMPA	-78	e(40)

The following procedure (entry 11 of Table I) is representative. To a solution of the vinylaldehyde 1c (5 mmol) in dry THF (20 ml) was added at -78°C a solution of lithio-1-pentyne[1] (6 mmol) in dry THF under nitrogen atmosphere. After being stirred at -78°C for 1h, the mixture was poured into saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel using benzene-ethyl acetate (5:1) as eluant to afford $C_{15}\alpha$-2c (35% yield), $C_{15}\beta$-2c (31% yield), and a mixed fraction (19% yield)[2]. Spectra of $C_{15}\alpha$- and $C_{15}\beta$-2c are undistinguishable. Nmr: ($CDCl_3$) δ 5.92-5.60 (2H, m), 5.60-5.26 (2H, m), 5.26-4.60 (3H, m), 4.35-3.80 (1H, m), 3.70 (3H, s), 2.10 (3H, s), 2.05 (3H, s), 0.99 (3H, t); ir (liquid film) ν 3430, 2220, 1735 cm^{-1}. However, their R_f values on tlc (benzene-ethyl acetate 2:1) are different. Those of $C_{15}\alpha$- and $C_{15}\beta$-2c are 0.56 and 0.65[3], respectively.

In the Grignard reaction of the vinylaldehyde whose C_{11}-hydroxy function was not protected, the $C_{15}\alpha$-PG was obtained fairly selectively. The ratios of $C_{15}\alpha/C_{15}\beta$ were 7/3 and 6/1 in 2b (entry 1) and 2d (entry 5), respectively, although that of 2a (entry 1) was 1/1. This exceptionally high selectivity might probably be due to the steric effect of the oxygen-metal bond at C_{11}. The mechanistic detail of this selectivity will be published in due course.

Although all of the vinylaldehyde 1d, 1e and 1f could be converted to 2d, 2e and 2f, respectively, 1a was found to be the best for the preparation of PG analogs since only 1 equiv of alkyl anion was required and the product might be transformed into the various kinds of PG analogs ($F_{2\alpha}$, E_2, $F_{1\alpha}$ and E_1)[4], as shown in the following scheme.





Acknowledgment. The authors wish to thank Dr. Hisashi Yamamoto of University of Hawaii for important and stimulating discussions.

References and Notes

1. R. K. Boeckman, Jr. and R. Michalak, J. Am. Chem. Soc., 96, 1623 (1974).
2. Another special procedure, entry 12 of Table I, was followed. The vinylaldehyde 1f (1 mmol) upon treatment with the lithio salt of 2,4,4,6-tetramethyl-5,6-dihydro-1,3(4H)-oxazine [4.3 mmol, A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, and I. R. Pofitzer, J. Am. Chem. Soc., 91, 764 (1969)] in THF-HMPA (10:1, 20 ml) at -78°C for 1 h followed by esterification with diazomethane gave 2e (40% yield) after chromatography on silica gel.
3. Configurational assignment of $C_{15}\alpha$- and $C_{15}\beta$-2c was carried out easily by comparing the biological activities of their final products as $C_{15}\beta$-compound had little biological activities. In general, $C_{15}\alpha$-compound is more polar than $C_{15}\beta$-compound.
4. E. J. Corey, R. Noyori, and T. K. Schaaf, J. Am. Chem. Soc., 92, 2586 (1970).
5. G. Rosseels, J. Matteazzi, G. Wouters, P. Bruckner, and M. Prost, Synthesis, 1970, 302.
6. (a) C. Feugeas, Bull. Soc. Chim. France, 1963, 2568; (b) G. Büchi and H. Wüest, J. Org. Chem., 34, 1122 (1969).
7. R. J. Fessenden and M. D. Coon, J. Med. Chem., 8, 604 (1965).
8. E. J. Corey and D. Seebach, J. Org. Chem., 31, 4097 (1966).
9. E. J. Corey and D. Crouse, J. Org. Chem., 33, 298 (1968).
10. R. L. Gay and C. R. Houser, J. Am. Chem. Soc., 89, 1647 (1967).
11. W. E. Parham and B. G. Gadsby, J. Org. Chem., 25, 234 (1960).
12. The products are unstable in acidic condition.
13. The products are unstable in both acidic and basic conditions.

(Received November 10, 1977)