Tetrahedron Letters No. 41, pp 3933 - 3936.

0040-4039/79/1008-3933$02.00/0

# PROSTAGLANDIN ANALOGS MODIFIED AT THE 10 AND 11 POSITIONS

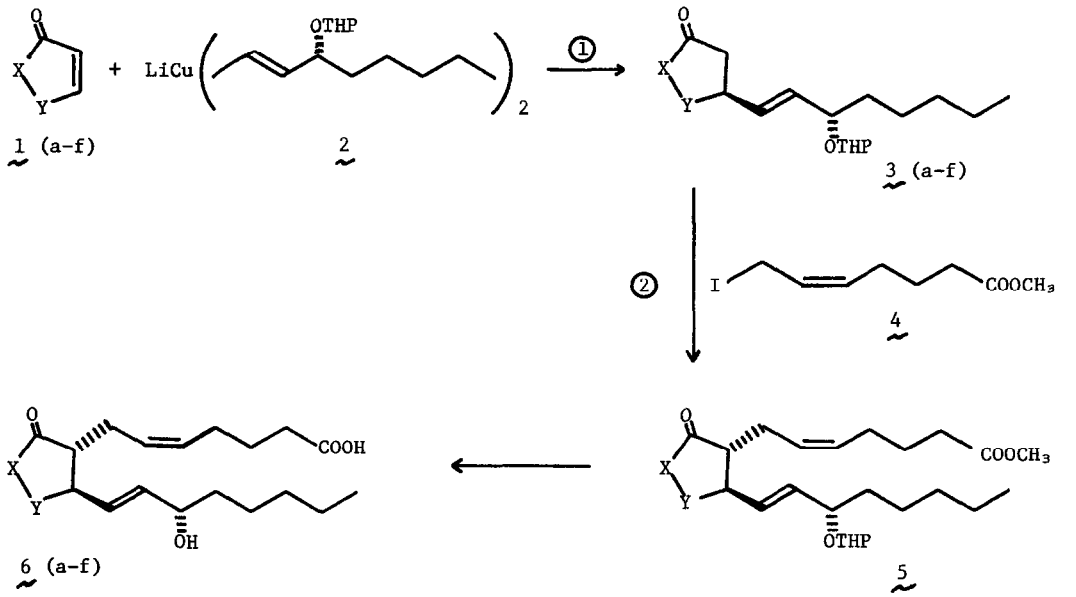
André G. Pernet*
Abbott Laboratories, 5400 Côte de Liesse, Montreal, Que., Canada
Hiromasa Nakamoto, Naoyasu Ishizuka, Masakazu Aburatani,
Kazuaki Nakahashi, Keiji Sakamoto and Tadashi Takeuchi
Fuji Chemical Industries Ltd., 530 Chokeiji, Takaoka-Shi, Toyama 933, Japan

Summary: A simplified methodology for the building of prostaglandins substituted at the 10 and 11 positions is presented.

During our search for a general chemical approach which would yield PG analogs modified in the ring, we realized that modifications at the 10 position would drastically simplify the synthetic process. The general scheme adopted is shown in figure I. When X is a heteroatom or a substituted carbon, the respective starting lactone (1 a-b) or cyclopentenone (1 c-f) can be alkylated directly in two steps with the complete side-chains.[1] Therefore, each new analog can be prepared in four steps starting from a simple cyclopentenone and the readily available side-chains. Illustrative examples of analogues made are shown in Table I.

In a typical experiment a 0.2 M solution of ring moiety precursor 1 in ether was added to a 0.2 M solution of the cuprate 2 in ether at -78°C (prepared as described by Sih et al[1] with n-$Bu_3P$ as a ligand for CuI), the mixture was stirred at -78°C for 30 min, then warmed slowly to -15°C; HCl (1 N) was added and the mixture rapidly extracted and washed twice with water. The residual syrup was freed from n-$Bu_3P$ and vinyl by-products by column chromatography (wakogel C-200, ethyl acetate-hexane 7:1) to afford pure 3 (step 1). The ketone 3 was added to a 0.2 M solution of lithium diisopropylamide in THF at -78°C, stirred for one hour, then the iodide 4[2] was added and stirred for one additional hour at -30°C, -15°C. Work up with 0.5 N HCl and ether afforded the protected PG 5 (step 2). Deblocking of the hydroxy group was effected in methanol containing a trace of p-toluenesulfonic acid at 0∿3°C for 6 hours, followed by the action of pancreatic lipase in McIlvaine buffer to afford the acid 6.[3]

FIGURE I

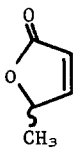
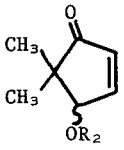
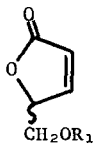
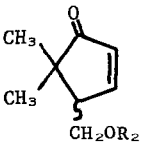
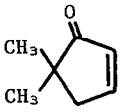
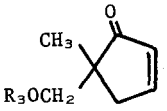



X is a heteroatom or substituted carbon

Y is a substituted carbon

Most of the analogs prepared were racemic mixtures. However, the method also allows for the preparation of optically pure analogs. When 3-(S)-trans-1-iodo-1-octen-3-ol (S)-2[4] was used, the two diastereomeric forms of 3c could be separated by column chromatography (Merck 7734, chloroform-methanol 99:1) when the hydroxy function at 15 was free. The synthesis was then continued with the pure isomers to afford nat-11-deoxy-10,10-dimethyl $PGE_2$, nat 6c,[5] $[\alpha]^{25}_D = -19.8^o$ (C 1.84 in $CHCl_3$) and 8,12-diepi-11-deoxy-10,10-dimethyl $PGE_2$, diepi 6c, $[\alpha]^{20}_D = +29^o$ (C 2 in $CHCl_3$). A small amount (less than 3%) of the cis isomer 12-epi 6c, $[\alpha]^{25}_D = +51.8^o$ (C 1 in $CHCl_3$), was isolated during the chromatographic separation. When allowed to equilibrate in 1 N NaOH/methanol (1:4) for 19 hours, 12-epi 6c epimerized to a final value of $[\alpha]^{25}_D = +37.8^o$. The same rotation was obtained after equilibration of the trans isomer diepi 6c. The configurations were assigned assuming that the trans isomer is thermodynamically more stable. Relative concentrations calculated from the rotation values are cis/trans = 38.6/61.4.

TABLE I

| Starting ketone | | Yield % step 1 | Yield % step 2 | | | Yield % step 1 | Yield % step 2 |
|---|---|---|---|---|---|---|---|
| 1a |  | 57 | 75 | 1d[8] |  | 77 | 8 |
| 1b[6] |  | 22 | 54 | 1e[8] |  | 84 | 44 |
| 1c[7] |  | 84 | 56 | 1f[8] |  | 63 | 62 |

$R_1$=THP; $R_2$=Ac; $R_3$=$SiPh_2Bu(t)$ in 1, 3, 5 and $R_1$=$R_2$=$R_3$=H in 6.

The approach presented offers optimal efficiency for modifying the ring, since three moieties of approximately equal weight are linked in two steps. Changes in the side-chains can be equally readily introduced.

Although 10,10-dimethyl PGs[9,10] have been reported to be inactive in stimulating uterus smooth muscle, we found analogs 6 (a,c,d,e,f) to be highly potent as gastric secretion inhibitors in dogs and as antihypertensives in rats and dogs.[11]

Acknowledgment

We thank professor S. Hanessian for useful discussions and for letting us know of the utility of t-butyldiphenylsilyl chloride prior to publication, as well as for generous supplies of the reagent. We are also indebted to Dr. D.L. Garmaise for his constant support.

## References


1) For previous examples of conjugate addition see:
K.F. Bernady, J.F. Paletto and M.J. Weiss, Tetrahedron Lett., 10, 765 (1975).
C.J. Sih, R.G. Salomon, P. Price, R. Sood and G. Peruzzoti, J. Am. Chem. Soc., 97, 857 (1975).
J.W. Patterson Jr. and J.H. Fried, J. Org. Chem., 39, 2506 (1974).
T. Tanaka, S. Kurozoni, T. Toru, M. Kobayashi, S. Miura and S. Ishimoto, Tetrahedron Lett., 1535 (1975).

2) E.J. Corey and H.S. Sachdev, J. Am. Chem. Soc., 95, 8484 (1973).

3) The silyl protective groups were deblocked with n-$Bu_4NF$ in THF as described by E.J. Corey and A. Wenkateswarly, J. Am. Chem. Soc., 94, 6190 (1972).

4) A.F. Kluge, K.G. Untch and J.H. Fried, J. Am. Chem. Soc., 94, 7827 (1972).

5) The structures were tentatively assigned on the difference of biological activity as precedented in reference 2. Nat 6c was found to be at least 10 times as potent as diepi 6c in reducing blood pressure in SHR rats when given I.V. in a single dose.

6) J. Font, Anales de Fisica y Chemica, 477 (1966).

7) W.C. Agosta, A.B. Smith III, J. Am. Chem. Soc., 93, 5513 (1971).

8) T. Matsumoto, H. Shirhama, A. Ichihara, H. Shin, S. Kagawa, F. Sakan, S. Nishida, S. Matsumoto, K. Saito and H. Hashimoto, Bull. Soc. Chim. Japan, 45, 1140 (1972).

9) O.G. Plantema, H. De Koning and H.O. Huisman, Tetrahedron Lett., 4595 (1975).

10) A. Hamon, E. Lacoume, G. Pasquet and W.R. Pilgram Tetrahedron Lett., 211 (1976).

11) To be published in full elsewhere.


(Received in USA 9 April 1979)