Bioorganic & Medicinal Chemistry Letters, Vol.2, No.5, pp. 445-448, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

SYNTHESIS OF POTENT 6-OXO AND 9-FLUORO-PGE$_1$-DERIVATIVES AND THEIR BIOLOGICAL PROPERTIES

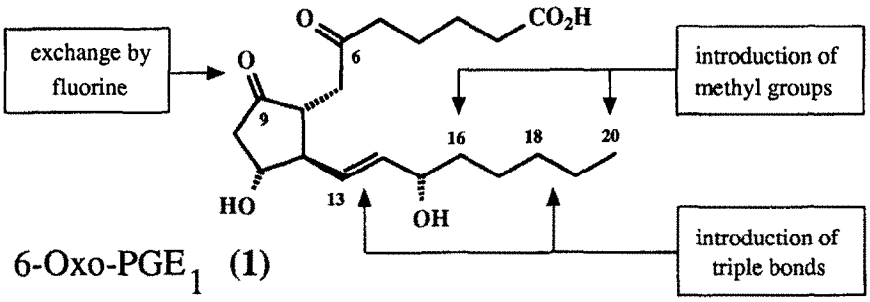
U. Klar*, A. Pletsch, W. Skuballa, H. Vorbrüggen
Research Laboratories of Schering AG,
Müllerstr. 170-178, W-1000 Berlin 65, FRG

(*Received* 17 *February* 1992)

SUMMARY: The synthesis of the biologically potent 6-oxo-PGE$_1$ analog **18** and its 9-fluoro-derivative **21** as well as their biological data are presented.

INTRODUCTION: 6-Oxo-PGE$_1$ (1) is formed species-dependent from prostacyclin (PGI$_2$) by oxidative cleavage of the 6,9α-epoxy ring in PGI$_2$ by the action of 9-hydroxydehydrogenase (9-PGDH)[1]. In mammalians 9-PGDH activity is present in platelets, lung, and kidney and there are several indications that 6-oxo-PGE$_1$ can be released from intact organs[2]. 6-Oxo-PGE$_1$ inhibits platelet aggregation with 1/4 the potency of PGI$_2$[3] and is thus much more active than PGE$_1$ or PGD$_2$. It shows higher potency, however, compared to PGI$_2$, e.g., in the vasodilation of renal arteries and as a fibrinolytic agent ex vivo (rat, rabbit)[4]. Although the chemical stability is much higher compared to PGI$_2$, 6-oxo-PGE$_1$ is inactivated very rapidly by 15-PGDH and other, as yet not identified enzymes. Due to the pronounced biological actions of natural 6-oxo-PGE$_1$, we became interested in the synthesis of 6-oxo-PGE$_1$-mimetics with improved metabolic stability.

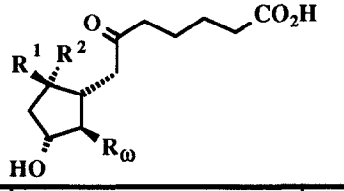
CONCEPT AND RESULTS: To improve the metabolic stability, we concentrated our attempts on the modification of the ω-chain and the carbonyl unit at position 9 as indicated below.

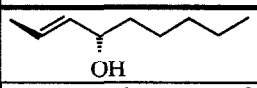
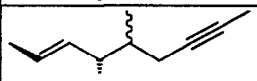
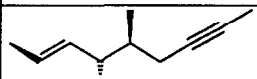
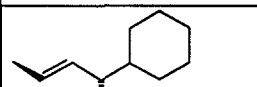
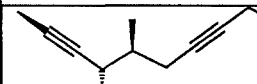


6-Oxo-PGE$_1$ (1)

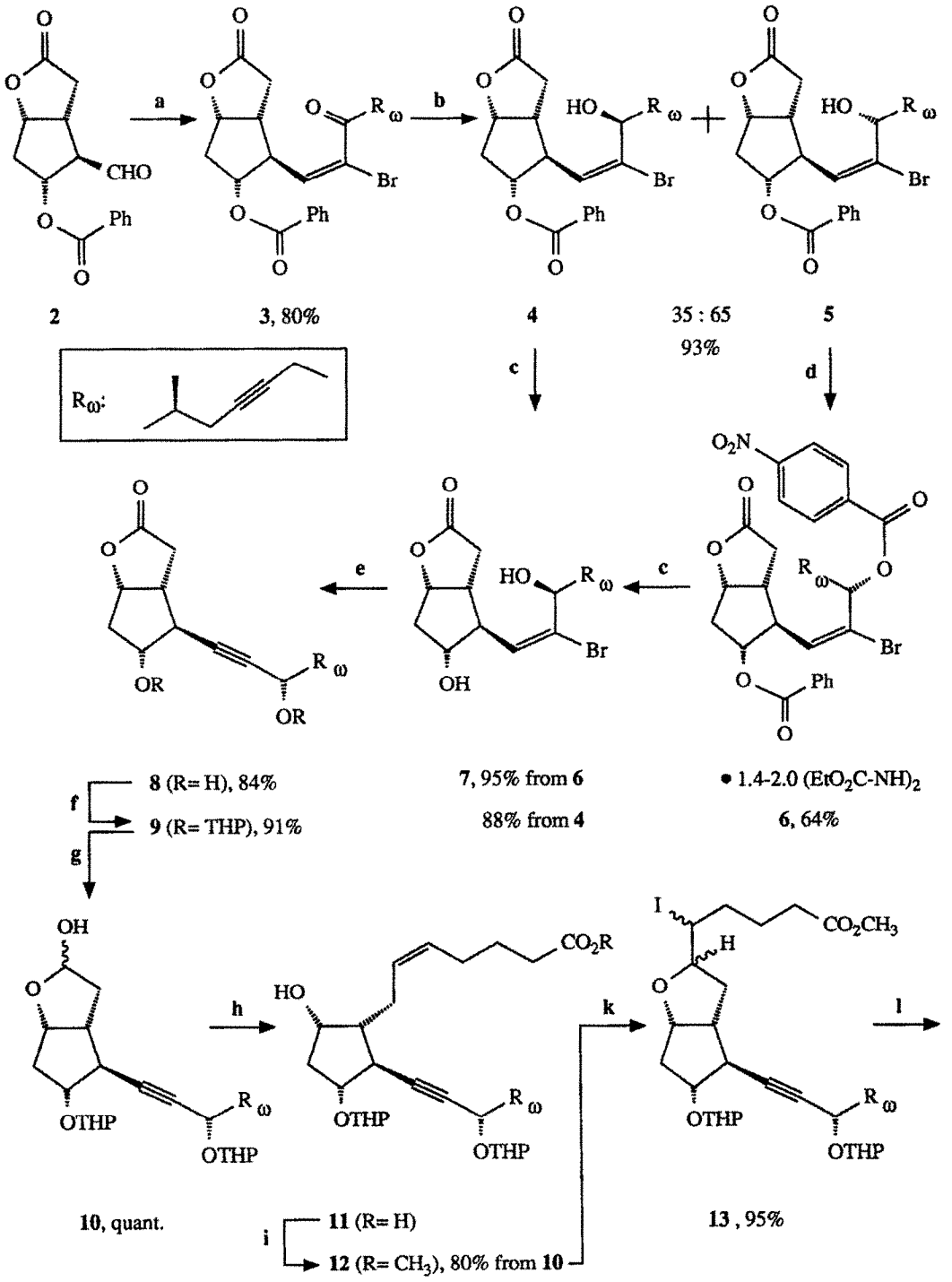
Based on prior results with the potent carbacyclin analogs Iloprost and Cicaprost[5], we modified the ω-side chain by introduction of a methyl group in position 16 and a triple bond in position 18 resulting in potent 6-oxo-PGE$_1$ analogs (entries 1 and 2 in *Table 1*), showing similar affinities to the PGI$_2$- as well as to the PGE$_2$-receptor. An additional triple bond at position 13 and a methyl group in position 20 further enhanced the antiaggregatory activity 10-fold (entry 6). As shown by entry 5, it is also possible to obtain a PGD$_2$-quality by introducing a 15-cyclohexyl moiety[6]. The exchange of the 9-carbonyl-oxygen atom by a fluorine atom lead to a hundred-fold loss in antiaggregatory activity.

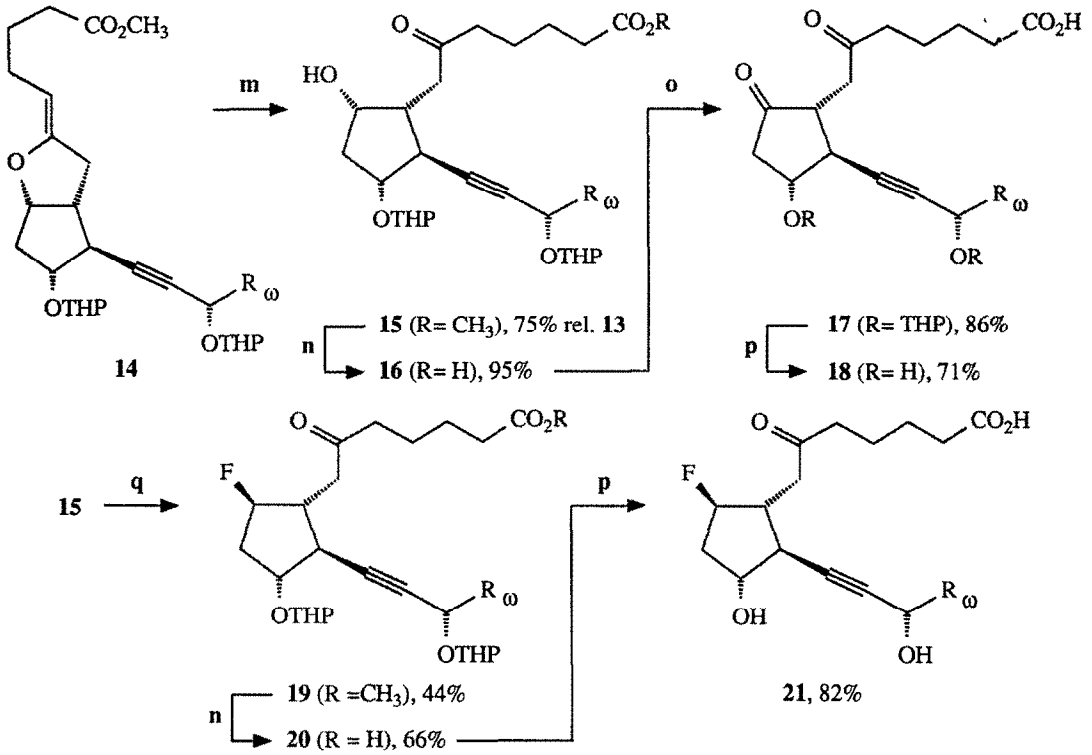
Table 1:



Entry	-R_ω	R^1R^2	Biological activities [7] of 6-Oxo-PGE_1-Derivatives: receptor affinities (np: not parallel, nc: no competition) K_F PGI_2	K_F PGE_2	K_F PGD_2	inhibition of blood platelet aggregation induced by ADP (IC_{50}) $\cdot 10^{-9}$M
ref.		=O	129	7.1		7.0
1		=O	60	140	600	1.6
2		=O	40 np	40		1.0
3		F H	200 np			100
4		H F	n.c.			1000
5		=O	58	n.c.	70	3.0
6		=O	5	7.5		0.09
7		F H	32 np	700		20

SYNTHESIS: Starting from optically active Corey-lactone **2**, the lower side chain was introduced by in situ bromination of deprotonated dimethyl-3S-methyl-2-oxo-5-octynylphosphonate with NBS and subsequent Wittig-Horner reaction, resulting stereoselectively in only one α,β-unsaturated ketone (**3**) which was assigned the E-configuration based on the chemical shift (δ= 6.97 ppm, $CDCl_3$) of the olefinic proton in the ^{1}H-NMR spectrum. The reduction of the carbonyl group with different reagents always gave a mixture of diastereoisomers under a variety of conditions, in which the desired alcohol **4** was the minor component[8]. Fortunately, the undesired diastereoisomer **5** could be converted to **6** by a Mitsunobu reaction with 4-nitrobenzoic acid[9] followed by subsequent saponification to **7** in satisfactory yield. Compound **6** was isolated after chromatography on silica gel as a crystalline adduct containing 1.4 to 2.0 equivalents hydrazoester. After deprotection of **4** and **6**, the diol **7** was obtained in 65% overall yield starting from ketone **3**. Introduction of the 13,14-triple-bond (PG-numbering) by CsOAc/18-crown-6 in toluene[10], followed by protection of the 11,15-hydroxyl functions as THP-ethers and reduction of the lactone led to **10**, in which the α-side chain was introduced by a Wittig-reaction. Iodine-induced cyclisation and subsequent elimination of HI gave the protected prostacyclin analog **14**. Hydrolysis of the enol ether moiety in methylene chloride with silica gel produced the key intermediate **15**. Saponification of the methyl ester, oxidation at position 9 followed by deprotection of both hydroxyl groups led to the 6-oxo-PGE_1-analog **18**, whereas treatment of **15** with (diethylamino)sulfur trifluoride (DAST), saponification of the methyl ester and deprotection of both hydroxyl groups gave the 9-fluoro-derivative **21**. Compounds with other ω-chains (entries 1 to 5, *Table 1)* were synthesized analogously using the corresponding phosphonates.


a
b
CHO
Ph
Br
HO
2
3, 80%
4
35 : 65
93%
5
Rω:
c
d
O_2N
e
OR
OH
• 1.4-2.0 (EtO_2C-NH_2)
7, 95% from 6
88% from 4
6, 64%
f
8 (R= H), 84%
9 (R= THP), 91%
g
OTHP
h
CO_2R
CO_2CH_3
I
H
k
l
10, quant.
i
11 (R= H)
12 (R= CH_3), 80% from 10
13 , 95%



a: NaH, dimethyl-3S-methyl-2-oxo-5-octynylphosphonate, NBS, DME, 3°C, 1.5h, argon; SiO_2; **b:** $NaBH_4$, MeOH, -40°C, 1h, argon; SiO_2; **c:** K_2CO_3, MeOH, rt, 22h, argon; SiO_2; **d:** Ph_3P, 4-O_2N-C_6H_4-CO_2H, DEAD, toluene, rt, 15min, argon; SiO_2; **e:** CsOAc, 18-crown-6, toluene, rt, 9h, argon; SiO_2; **f:** dihydropyrane, cat. p-TsOH, CH_2Cl_2, rt, 0.5h, argon; SiO_2; **g:** DIBAL, toluene, -70°C, argon; **h:** carboxybutyltriphenylphosphonium bromide, Li-HMDS, THF, 50°C, 2h, argon; **i:** CH_2N_2, CH_2Cl_2, ether, 3°C, 1h; SiO_2; **k:** I_2, $NaHCO_3$, H_2O, ether, 3°C, 2h; SiO_2; **l:** DBU, benzene, 65°C, 3h, argon; **m:** SiO_2, CH_2Cl_2, rt, 16h; SiO_2; **n:** 10% KOH or 5% LiOH, MeOH, rt, 0.5h; SiO_2; **o:** Jones-oxidation, acetone, -30°C, 1.5h, argon, SiO_2; **p:** HOAc, H_2O, THF, rt, 16h; SiO_2; **q:** DAST, toluene, pyridine, -70°C → 0°C, 6h; SiO_2.

REFERENCES AND NOTES:

1) Wong, P.Y-K., Lee, W.H., Chao, P.H-W., Reiss, R.F., McGiff, J.C. *J. Biol. Chem.* **1980**, *225*, 9021.
2) For reviews see: a) Hoult, J.R.S., Moore P.K. *TIPS* **1986**, 197. b) Wong, P.Y.-K., Pieroni, J.P., McGiff, J.C. *Atheroscler. Rev.* **1985**, *13*, 1. c) Lewis, R., Schölkens, B.A., Beck, G. *Prostaglandins Leukotriens Med.* **1984**, *16*, 303. d) Moore, P.K., Griffiths, R.J. *Prostaglandins* **1983**, *26*, 509.
3) Miyamori, I., Morise, E., Yasuhra, S., Takeda, Y., Koshida, H., Takeda, R. *Br. J. Clin. Pharmacol.* **1985**, *20*, 681.
4) a) Hussaini, I., Moore, P.K. *Br. J. Pharmacol.* **1985**, *86*, 813P. b) Korbut, R., Byrska-Danek, A., Gryglewski, R.J. *Thromb. Haemostasis* **1983**, *50*, 893.
5) a) Skuballa, W., Schillinger, E., Stürzebecher, C.-St., Vorbrüggen, H. *J. Med. Chem.* **1986**, *29*, 313. b) for a review of the synthesis and pharmacological action of Iloprost, see: Prostacyclin and Its Stable Analogue Iloprost, Eds.: Gryglewski, R.J., Stock, G. Springer Verlag 1987
6) Thierauch, K.-H., Stürzebecher, C.-St., Schillinger, E., Rehwinkel, H., Radüchel, B., Skuballa, W., Vorbrüggen, H. *Prostaglandins* **1988**, *35*, 855.
7) We are indebted to Drs. K.-H. Thierauch and C.-St. Stürzebecher for the biological data.
8) The configuration of **4** and **8** was assigned on the basis of their higher biological activity compared to their 15-epimers.
9) Martin, St.F., Dodge, J.A. *Tetrahedron Lett.* **1991**, *32*, 3017.
10) Klar, U. to be published.