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SYNTHESIS OF PROSTACYCLIN ANALOGS STABILIZED BY ACCEPTOR SUBSTITUENTS AT THE 5-POSITION

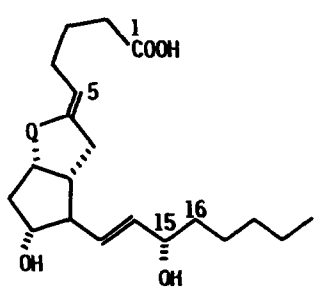
Werner Skuballa, Bernd Radüchel and Helmut Vorbrüggen

Research Laboratories of Schering AG,
D-1000 Berlin 65,
Federal Republic of Germany

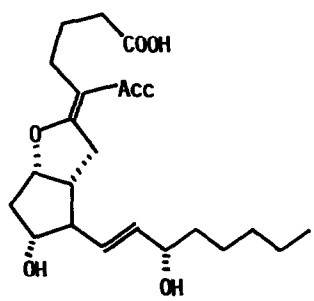
Abstract - The chemically labile natural prostacyclin (PGI_2) 1 can be stabilized by introduction of an electron withdrawing 5-substituent like cyano, formyl, carboxy or alkoxycarbonyl resulting e.g. in 5-cyano-16-methyl-prostacyclin (nileprost) 6, a potent ulcer healing agent.

Prostacyclin (PGI_2) 1, which is primarily synthesized by endothelial cells in the vessel wall is the most powerful natural inhibitor of ADP induced aggregation of human platelets as well as a potent vasodilator and cytoprotective agent[1]. Due to the inherent chemical instability of the reactive cyclic enol ether system in natural prostacyclin, intensive efforts have been made by several groups to prepare chemically stable and biologically potent prostacyclin analogs[2].

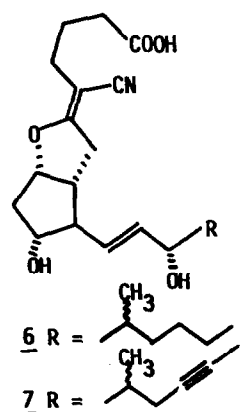
Our present work was stimulated by some earlier studies on the reaction of dihydropyran with chlorosulfonylisocyanate and subsequent elimination of HCl and SO_3 by triethylamine to afford the stable 3-cyano-dihydropyran[3]. In this communication we describe the synthesis of prostacyclin analogs 2 - 7, in which the labile enolether function is stabilized by the introduction of electron-withdrawing groups at the 5-position. To impede the metabolic inactivation caused by the 15-hydroxy-dehydrogenase a methyl group is introduced at C-16 resulting in the structure of 5-cyano-16-methyl-prostacyclin (nileprost)[4] 6.



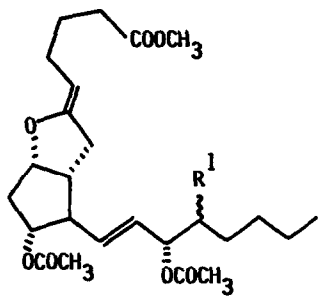
1 prostacyclin (PGI_2)



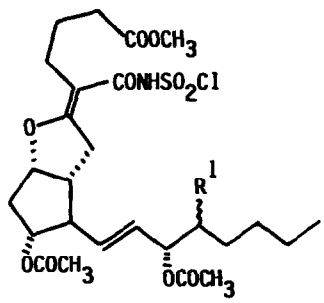
2 Acc = CN
3 Acc = $COOCH_3$
4 Acc = COOH
5 Acc = CHO



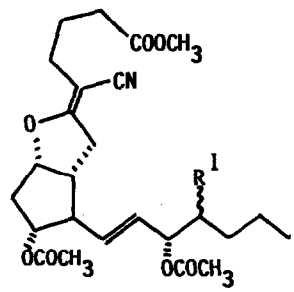
6 R =
7 R =



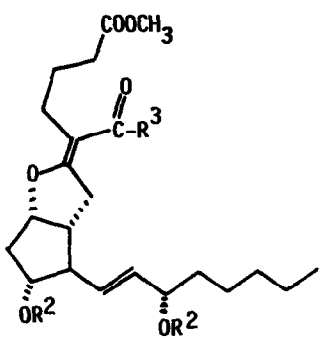
8a $R^1 = H$
8b $R^1 = CH_3$



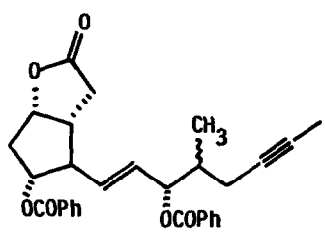
9a $R^1 = H$
9b $R^1 = CH_3$



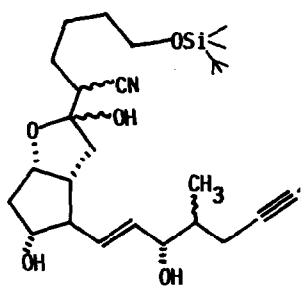
10a $R^1 = H$
10b $R^1 = CH_3$



11 $R^3 = OH$, $R^2 = COCH_3$
12 $R^3 = OCH_3$, $R^2 = H$
13 $R^3 = H$, $R^2 = COCH_3$



14



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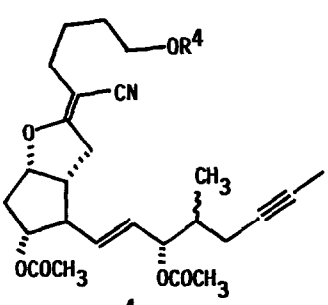
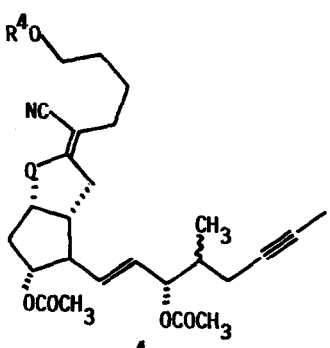
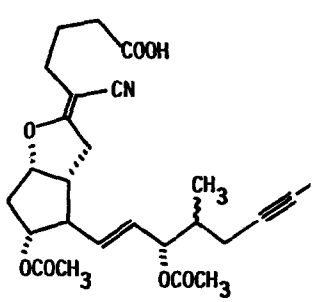


16 $R^4 = Si\!\!<$
17 $R^4 = H$



18 $R^4 = Si\!\!<$
19 $R^4 = H$



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The starting prostacyclin derivatives 8a and 8b were prepared from the corresponding prostaglandin $F_{2\alpha}$ derivatives[5] using standard methodology[6]. Reaction of the protected prostacyclin derivatives 8a and 8b in ether with chlorosulfonylisocyanate afforded the intermediate N-chlorosulfonylamides 9a, 9b, which gave without isolation on treatment with triethylamine in dichloromethane at 0°C[3] or solvolysis with N,N-dimethylformamide at -65° - 20°C[7] the protected 5-cyanoprostacyclins 10a and 10b in up to 83% yield as well as ca. 5% of the corresponding 5Z-configurated isomer[8], readily removed by chromatography. After saponification (NaOH, MeOH, H_2O, 20°C) and subsequent acidification with citric acid the free 5E-configurated 5-cyanoprostacyclin analogs 2 and 6 were obtained[9].

The synthesis of 5-carboxyprostacyclin 4[10] was achieved by hydrolysis (H_2O, $NaHCO_3$, 0°C) of the intermediate N-chlorosulfonylamide 9a to give 11 and subsequent saponification (KOH, MeOH, H_2O, 20°C). Esterification of 4 (CH_2N_2, CH_2Cl_2, 0°C) followed by selective hydrolysis (LiOH, CH_3OH, H_2O, THF, 24°C, 22 h) of the 1-methyl ester in 12 afforded 5-carbomethoxy-prostacyclin[11] 3 in 40% yield. Finally, we treated the diacetyl-prostacyclin-methyl ester 8a with chloromethylendimethylammonium chloride[12] (THF, -30°C, 15 min; 0°C, 2.5 h) to give after deprotection (NaOH, H_2O, CH_3OH) the 5-formylprostacyclin[13] 5 in 30% yield.

Whereas the prostacyclin analogs stabilized by a 5-carbomethoxy, 5-carboxy or 5-formyl group were nearly biologically inactive, the 5-cyanoprostacyclins 2 and 6 (nileprost) were weak vasodilators and inhibitors of platelet aggregation, but especially 6 (nileprost) showed in animal studies potent gastric antisecretory and cytoprotective activity and is presently evaluated in clinical trials as a new antiulcer drug[4].

Due to some difficulties with the synthesis of analogs with a triple bond in the lower side chain and to avoid labile intermediates like 8 we looked for an alternative synthetic route to 5-cyanoprostacyclin analogs.

Condensation of the γ-lacton 14[14] with the tert.-butyldimethylsilyl ether of 5-cyano-1-pentanol[15] (4 equiv. LDA, HMPA in THF at -78°C then 4 equiv. 14) furnished 50% of a diastereomeric mixture of the cyano alcohols 15 and 35% of the starting material 14. Acid-catalyzed dehydration ($BF_3 \cdot Et_2O$, 24°C, Et_2O, 1 h) of 15 followed by esterification (Ac_2O, pyridine) afforded an easily separable ca. 1 : 1 mixture of the desired 5E-configurated isomer 16 (39% yield) and the more polar 5Z-configurated isomer 18 (33% yield)[16]. The silyl ether in 16 was removed (NBu_4F, THF, 25°C) to give the free alcohol 17, which was oxidized with pyridinium dichromate (DMF, 24°C, 29 h) to afford the acid 20 (65% yield). Subsequent hydrolysis (K_2CO_3, CH_3OH, 25°C) gave the 5-cyanoprostacyclin analog 7 (70% yield)[17].

The 5E-configurated hydroxy-olefin 19, which was obtained from 18 with NBu_4F, could be isomerisized with $SnCl_4$ (CH_2Cl_2, 25°C, 22 h) to give an easily separable 4 : 1 mixture of 17 and 19.

7 showed about the same potency as PGE_1 and was about 50 x more active than 6 (nileprost) as an inhibitor of ADP-induced aggregation of human platelets.

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REFERENCES AND NOTES

* Dedicated to Professor Dr. Rudolf Wiechert on the occasion of his 60th birthday.

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8) The configurational assignment of the 5-double bond is based on the chemical shift of the protons at C-7. Due to the magnetic anisotropy of the CN group these protons appear at a lower field in the Z-isomers 10a and 10b when compared with the E-isomers. In the UV spectra of the E-isomers a hypsochromic shift of 3-4 nm is observed (see loc. cit. 9). (The NMR spectra were measured in $CHCl_3$).

9) 6: ir (neat): 3400, 2960, 2930, 2870, 2205, 2730, 2650, 1710, 1650 cm^{-1}.
NMR δ 0.80 and 0.84 (3H,d,J=7 Hz,16-CH_3), 0.83 (3H,t,J=7 Hz,H-20), 2.78 (1H,dd,J=18 + 3 Hz,H-7α), 2.90 (1H,dd,J=18 + 8 Hz,H-7ß), 3.82-3.95 (2H,M,H-11ß,H-15ß), 4.85 (1H,dt,J= 2 + 6.5 Hz,H-9ß), 5.44 and 5.64 (2H,ddd,J=15 + 9 + 3 Hz and dt,J = 15 + 7.5 Hz,H-13,H-14)
UV: λ_{max} = 236 nm (ε = 16000 in CH_3OH).
6-(Z-isomer): ir (neat): 3400, 2960, 2930, 2870, 2205, 2640, 2450, 1715, 1650 cm^{-1}.
NMR δ 0.78 and 0.83 (3H,two d,J=7 Hz,16-CH_3), 0.82 (3H,t,J=7 Hz,H-20), 2.61 (1H,d,J=-18 Hz,H-7α), 2.72 (1H,dd,J=18 + 8 Hz,H-7ß), 3.86-3.96 (2H,m,H-11ß,H-15ß), 4.89 (1H,dt, J=2 + 6.5 Hz,H-9ß), 5.49 and 5.62 (2H,dd,J = 15 + 8 Hz and dt, J=15 + 6.5 Hz,H-13,H-14).
UV: λ_{max} = 240 nm (ε = 15400 in CH_3OH).

10) 4: ir (neat): 3400, 2960-2860, 1685, 1615 cm^{-1}. NMR δ 0.86 (3H,t,J=7 Hz,H-20), 3.6-3.95 (2H,m,H-11 and H-15), 4.74 (1H,m,H-9), 5.47 (2H,m,H-13 and H-14).
UV: λ_{max} = 248 nm (ε = 8650 in CH_3OH).

11) 3: ir (neat): 3400, 2960-2858, 1739, 1700, 1240 cm^{-1}. NMR δ 0.87 (3H,t,J=7 Hz,H-20), 3.60 (3H,s,-CO_2CH_3), 3.69-3.99 (2H,m,H-11 and H-15), 4.77 (1H,m,H-9), 5.47 (2H,m,H-13 and H-14).
UV: λ_{max} = 248 nm (ε = 13600 in CH_3OH).

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13) 5: ir (neat): 3360, 2930-2860, 1710, 1615 cm^{-1}. NMR δ 0.87 (3H,t,J=7 Hz,H-20), 3.7 - 3.98 (2H,m,H-11 and H-15), 4.89 (1H,m,H-9), 5.46 (2H,m,H-13 and H-14).

14) 14 was obtained from the optically active Corey aldehyde by Wittig-Horner reaction, followed by reduction with $NaBH_4$ and benzoylation using standard methology, see: E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, N. H. Weinshenker, J. Am. Chem. Soc. 92, 397 (1970); E. W. Yankee, U. Axen, G. L. Bundy, J. Am. Chem. Soc. 96, 5865 (1974); W. Skuballa, H. Vorbrüggen, Angew. Chem. Int. Ed. Engl. 20, 1046 (1981).

15) prepared from 1,5-pentandiol by selective silylation, followed by tosylation and treatment with sodium cyanide in DMSO.

16) 16: ir (neat) 2960-2860, 2200, 1735, 1650, 1240 cm^{-1}. NMR δ 0.0 (6H,s,Si(CH_3)$_2$), 0.84 (9H,s,Si-C(CH_3)$_3$), 1.72 (3H,m,H-20), 1.92 and 2.01 (each 3H,s,11-OAc,15-OAc), 4.75-5.2 (3H,m,H-9,H-11,H-15), 5.51 (2H,m,H-13,H-14).
UV: λ_{max} = 235 nm (ε = 19700 in CH_3OH).
18: ir (neat) 2960-2980, 2200, 1735, 1645, 1235 cm^{-1}. NMR δ 0.0 (6H,s,Si(CH_3)$_2$), 0.82 (9H,s,Si-C(CH_3)$_3$), 1.71 (3H,m,H-20), 1.92 and 2.0 (each 3H,s,11-OAc,15-OAc), 4.7-5.15 (3H,m,H-9,H-11,H-15), 5.5 (2H,m,H-13,H-14).
UV: λ_{max} = 239 nm (ε = 14500 in CH_3OH);(see also loc. cit. 8).

17) 7: ir (neat) 3400, 2960-2860, 2200, 1710 cm^{-1}. NMR δ 0.88 (3H,d,J=6 Hz,16-CH_3), 1.74 (3H,m,H-20), 3.62-3.92 (2H,m,H-11,H-15), 4.91 (1H,m,H- 9), 5.48 (2H,m,H-13,H-14).
UV: λ_{max} = 236 nm (ε = 14100 in CH_3OH)

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