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SYNTHESIS OF 6,9-HOMO-PROSTACYCLIN
A STABLE PROSTACYCLIN ANALOG[1]

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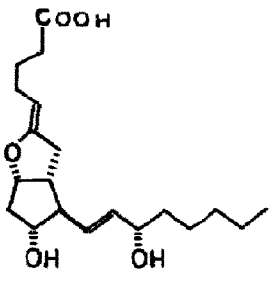
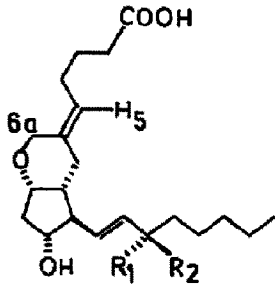
Abstract: A stable prostacyclin analog was synthesized starting from an intermediate of the Corey prostaglandin synthesis.

The extreme instability of the biologically important prostacyclin (PGI_2)[2] 1 limits its therapeutical usefulness. Therefore intensive synthetic efforts have been focused on modifying the reactive enolether system to prepare analogs with greater chemical and metabolic stability and comparable physiological activities to natural PGI_2 1[3].

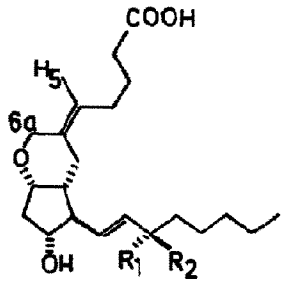
In this paper is described the synthesis of the stable prostacyclin-analogs 2 - 5, in which the labile enolether function of the tetrahydrofuran ring is transformed by ring enlargement and shift of the double bond to form the more stable allylic ether, as well as the synthesis of interesting 6-ring intermediates (11 and 12) which are versatile and interesting synthons for further prostacyclin-analogs.



1 Prostacyclin (PGI_2)



2 R_1 = OH R_2 = H
3 R_1 = H R_2 = OH



4 R_1 = OH R_2 = H
5 R_1 = H R_2 = OH

Starting from the readily available known lactone 6[4], reduction with diisobutylaluminiumhydride (-70°C), Wittig-reaction ($Ph_3P{=}CH_2$, DMSO, 25°C) and

acetylation (Ac_2O, pyridine, 25°C) gave the diacetate 7 (80% yield).

Functionalization of the double bond with N-bromosuccinimide in wet dimethylsulfoxide (20°C, 0,5 h)[5], followed by chromatographic separation, yielded 65% of the bromohydrin 8[6] and 20% of the more polar isomeric bromohydrin 9[6]. Transformation of 8 into the tetrahydropyranylether 10 (dihydropyran, pTsOH, CH_2Cl_2, 25°C) and subsequent cyclization with a 20% solution of KOH in ethanol at 60°C for 1 h resulted in the formation of the bicyclic alcohol 11[7] (84% yield from 8). Esterification of 11 (PhCOCl, pyridine), followed by removal of the tetrahydropyranylether (HOAc, H_2O, THF 65:35:10), Jones oxidation and cleavage of the benzylether (H_2, Pd/C, EtOH, HOAc) gave the ketone 12[8] (92% yield).

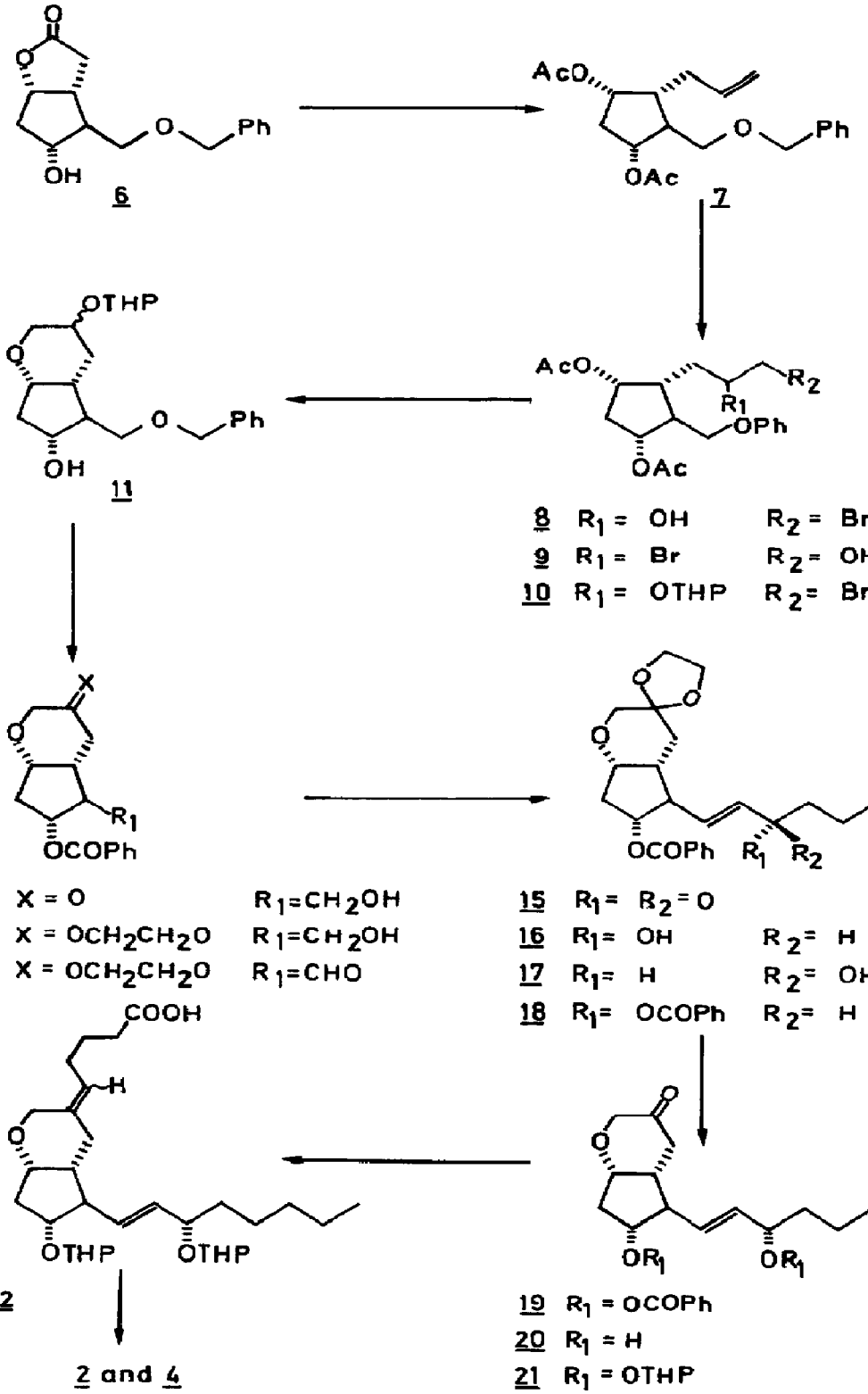
After ketalization ($HOCH_2CH_2OH$, C_6H_6, pTsOH) of 12 to 13, the introduction of the allylic alcohol side chain was achieved by standard methods: Collins oxidation of 13 yielded the aldehyde 14 which was immmdiately condensed with the sodium salt of dimethyl-2-oxoheptyl phosphonate (DME, -20°C) to afford the enone 15 (70% yield from 13). Reduction of 15 ($NaBH_4$, CH_3OH, -40°C) gave a 1:1 mixture of the allylic alcohols 16 and 17 which was separated chromatographically[9].

The allyl alcohol system in 16 was protected by benzoylation (PhCOCl, pyridine, yield: 100%) against the rather vigorous subsequent hydrolysis of the ketal function (70% HOAc, 100°C, 5 h) to afford the ketone 19 (yield 98%). Transesterification (K_2CO_3, CH_3OH) of 19, followed by tetrahydropyranylation, Wittig-reaction ($Ph_3P{=}CH{-}(CH_2)_3COONa$, DMSO, 45°C) and removal of the tetrahydropyranylethers gave, after chromatographic separation, the more polar Z-isomer 2[10] (mp. 58°C) and the E-isomer 4[10] (mp. 85°C) in a 2:1 ratio. 17 was analogously transformed into the 15-epi isomers 3 and 5.

The configurational assignment of the trisubstituted Δ^5 double bond as Z in 2 and 3 and as E in 4 and 5 is based on the difference in the chemical shift of the 6a-protons. Due to the steric interaction with the upper side chain the 6a-protons show a broad AB system (J = 12,5 Hz) in the Z-isomers 2 and 3 whereas the corresponding signals in 4 and 5 are magnetically practically equivalent. The olefinic proton H-5 in 2 and 3 (δ = 5.17 ppm, t, J = 7,5 Hz) as well as in 4 and 5 (δ = 5,42 ppm, t, J = 7,5 Hz) are also characteristic.

Whereas 2 showed some hypotensive activity in the rat, neither of 2 - 5 exhibited any antiaggregatory activity with human platelets[11].

Acknowledgment: The author thanks Prof. Dr. H. Vorbrüggen for stimulating discussions and Dr. A. Seeger for the interpretation of the NMR data.


6
7
11
8 R1 = OH R2 = Br
9 R1 = Br R2 = OH
10 R1 = OTHP R2 = Br
12 X = O R1=CH2OH
13 X = OCH2CH2O R1=CH2OH
14 X = OCH2CH2O R1=CHO
15 R1 = R2 = O
16 R1 = OH R2 = H
17 R1 = H R2 = OH
18 R1 = OCOPh R2 = H
19 R1 = OCOPh
20 R1 = H
21 R1 = OTHP
22
2 and 4

References and Notes

1) Prostaglandin Analogs 3. - For paper 2, see W. Skuballa, B. Radüchel, O. Loge, W. Elger, H. Vorbrüggen, J. Med. Chem. 21, 443 (1978).

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K.C. Nicolaou, W.E. Barnette, R.L. Magolda, J. Amer. Chem. Soc. 101, 766 (1979);
K. Kojama, K. Sakai, Tetrahedron Lett. 3743 (1978).

4) E.J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, T.K. Schaaf, J. Amer. Chem. Soc. 93, 1490 (1971).

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6) 8, oil; ir (neat) 3460, 1730, 1495, 1245, 1030 cm^{-1}; nmr ($CDCl_3$) δ 2.02 (3H, s), 2.08 (3H, s), 3.21-3.56 (2H, m), 5.58 (2H, m), 3.75 (1H, m), 4.53 (2H, s), 4.95-5.30 (2H, m), 7.32 (5H, s).
9, oil; ir (neat) 3650, 3450, 1730, 1494, 1242, 1030 cm^{-1}; nmr ($CDCl_3$) δ 2.02 (3H, s), 2.06 (3H, s), 3.58 (2H, t, J = 3.5 Hz), 3.74 (2H, dt, J = 5.5 + 1 Hz), 4.10 (1H, m), 4.53 (2H, s), 4.96-5.26 (2H, m), 7.33 (5H, s).

7) 11, oil; ir (neat) 3450, 1495, 1120, 1075, 1035 cm^{-1}; nmr ($CDCl_3$) δ 3.25-3.81 (8H, m), 4.42, 4.51 (2H, ABq, J = 5.8 Hz), 4.63 (1H, m), 7.31 (5H, s).

8) 12, oil; ir (neat), 1720, 1605, 1585, 1495, 1280, 1100 cm^{-1}; nmr ($CDCl_3$) δ 3.70 (2H, m), 3.86, 4.20 (2H, ABq, J = 18 Hz), 4.14 (1H, q, J = 6 Hz), 5.28 (1H, q, J = 7 Hz), 7.35-7.69 (3H, m), 8.00-8.12 (2H, m).

9) The less polar fraction on TLC was assigned the structure of the 15S-isomer 16 and the more polar one as the 15R based on the known chromatographic behavior of synthetic PG-intermediates, E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker, N.M. Weinshenker, J. Amer. Chem. Soc. 92, 398 (1970); E.J. Corey, N.M. Weinshenker, T.K. Schaaf, W. Huber, J. Amer. Chem. Soc. 91, 5675 (1969).

10) 2, mp. 58°C; ir (KBr) 3430, 2730, 1725, 1060 cm^{-1}; nmr ($CDCl_3$) δ 0.90 (3H, t, J = 5 Hz), 3.77, 4.48 (2H, ABq, J = 12.5 Hz), 3.78-4.17 (3H, m), 5.17 (1H, t, J = 7.5 Hz), 5.42-5.55 (2H, m).
4, mp. 85°C; ir (KBr) 3410, 2700, 1730, 1050 cm^{-1}; nmr ($CDCl_3$) δ 0.89 (3H, t, J = 5 Hz), 3.83-4.14 (5H, m), 5.42 (1H, t, J = 7.5 Hz), 5.50-5.57 (2H, m).

11) I am obliged to Dr. G. Mannesmann for the hypotensive and Prof. W. Losert for the platelet aggregation tests.

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