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SYNTHESIS OF PROSTACYCLIN ANALOGUES VIA KNOEVENAGEL CONDENSATION

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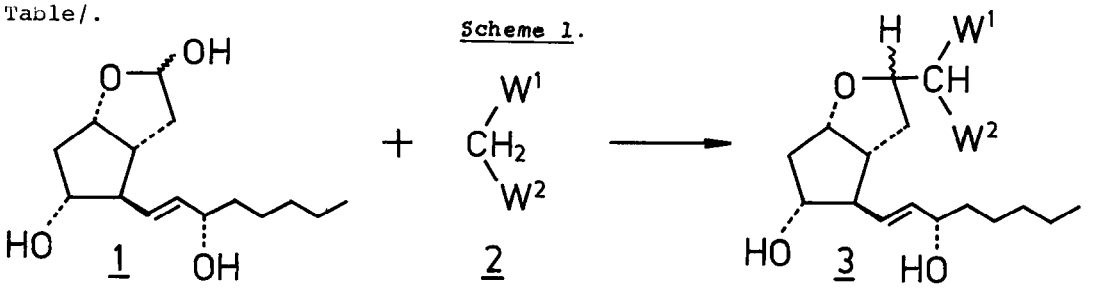
Abstract: A novel, simple procedure is described for the synthesis of prostacyclin analogues starting from the hemiacetal 1 and active methylene compounds.

In the last decade widespread interest has developed in the construction of specially substituted tetrahydrofuran rings[1], due to their occurence in various natural products with different biological activities. One of these interesting compounds is prostacyclin /PGI_2/, which exhibits highly potent antiaggregatory and vasodilating properties[2]. Since prostacyclin contains 3-alkylidene -2-oxabicyclo/3.3.0/octane structural unit, the preparation of similar systems have become an important task in the field of prostaglandins. The syntheses published until now usually follow two common strategies, namely the cyclization of $PGF_{2\alpha}$ or its analogues[3], and the reaction of the hemiacetal 1 with appropriate phosphonates or phosphoranes[4].

In this communication we report a new approach leading to 3-alkyl-2-oxabicyclo/3.3.0/octane systems. Our procedure makes advantage of the well-known Knoevenagel condensation[5]. The reaction of hemiacetal 1 with active methylene compounds 2 in the presence of catalyst leads to 3 in 76-92 % yields /Scheme 1. Table/.

Scheme 1.



1 2 3

The versatility of the procedure is apparent from the Table, as a great variety of active methylene compounds provide the reaction in excellent yields. The reaction can be performed with malonic acid and aceto acetic acid derivatives as well as with β-oxo-sulfones and aliphatic nitro compounds. Another advantage of the procedure is its simplicity, that is it can be carried out without any technical difficulty even on a scale of 100 mmoles.

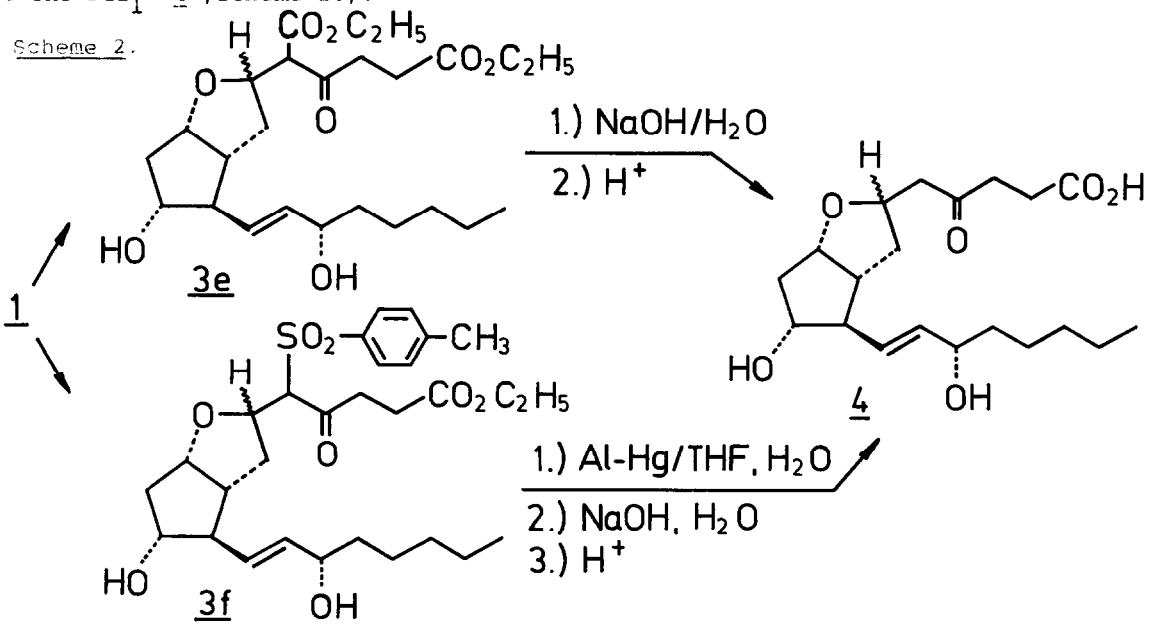
Table

	W^1	W^2	procedure[a]	yield[b,c] %
a.	CH_3CO	CH_3CO	B	80
b.	CH_3CO	CO_2Et	A	85
c.	CO_2Et	CO_2Et	B	80
d.	CO_2Et	CN	A	92
e.	CO_2Et	$C/O/CH_2CH_2CO_2Et$[7]	A	88
f.	$p\text{-}CH_3C_6H_4SO_2$	$C/O/CH_2CH_2CO_2Et$[8]	A	90
g.	NO_2	H	B	85
h.	NO_2	CH_3	C	89
i.	NO_2	C_2H_5	A	76
j.	NO_2	$/CH_2/_3CO_2CH_3$[9]	A	78

a/ A: 3-5 equiv of 2 in benzene in the presence of 0.5-1 equiv of piperidine and 0.1-2 equiv of acetic acid with continuous removal of water. B: Great excess of condensating agent without solvent in the presence of 1.1 equiv of piperidine at room temperature. C: 1 equiv of piperidine, 10 equiv of 2 at room temperature. b/ Isolated yields. c/ The products were identified by IR, ^1H and ^{13}C NMR spectra.[10]

In the reaction, however, all four possible isomers of 3 can be detected by TLC or HPLC analysis. Despite this disadvantage, the Knoevenagel reaction was applied succesfully as a key step in two independent syntheses of the known 4-oxo PGI_1[6] 4 /Scheme 2./.

Scheme 2.



In the first approach 1 was condensed with diethyl 3-oxo adipate[7] /2e/, in the second with methyl 5-p-tosyl levulinate[8] /2f/ under the conditions given in the Table. Hydrolysis of 3e led directly to 4 in 95 % yield /4 equiv of NaOH in water-methanol 1:1, 25 °C, 4 h/. The sulfone 3f was transformed to 4 in a two step sequence: reductive cleavage[10] /50-60 mg/ml THF-H_2O 10:1, 10 equiv of Al-Hg, 50-60 °C, 3h/ and ester hydrolysis furnished 4-oxo-PGI_1 in 79 % everall yield.

Our efforts to transform 3f to 4-oxo PGI_2 were unsuccesful[11]. The problem, however, can be solved through the analogous sulfoxide[12].

Hydrolysis of 5-nitro PGI_1 methyl ester[13] /3j/ was accomplished with 3 equiv of NaOH in methanol-water 1:1 at room temperature overnight, then acidification with 1 N HCl furnished 5-nitro PGI_1 as colourless oil in almost quantitative yield. 5-Nitro PGI_1 sodium salt exhibits extremely strong vasodilating activity without any antiaggregatory properties[14].

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References and Notes

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8. The compound 2f was prepared from succinic anhydride and p-tosyl-methyl magnesium bromide /see F.G. Baddar, L.S. El-Assal, A. Hanashi, J. Chem.Soc., 1955, 456/, followed by esterification with diazomethane in 65-70 % yield. Oil; R_f /hexane-ethyl acetate 1:1/:0.27; ^1H NMR /$CDCl_3$/ δ/ppm/: 7.75 /2H,d, J=8Hz, Ar-H_o/, 7.38 /2H,d, J=8Hz,Ar-H_m/, 4.16 /2H,s,SO_2CH_2/, 3.65 /3H,s,OCH_3/ 3.02 /2H,t,J_v=6Hz,$CH_2C/O/CH_2$/, 2.58 /2H,t,J_v=6Hz,CH_2CO_2/, 2.44 /3H,s,$ArCH_3$/.
9. The compound 2j was prepared from 5-bromo valeric acid methyl ester with $NaNO_2$ in DMF at -10°C in the presence of benzyltributylammonium bromide, or see: S.Africa patent, 6.705.789; CA. 70 77365 /1969/.

10. H.O.House, J.K. Larson, J. Org. Chem., 1968, 33, 61; E.J. Corey, M. Chaykovsky, J. Am. Chem. Soc., 1965, 87, 1345.

11. Methods tried for the transformation: thermal elimination, hydrolysis with base; bromination at C-5, reductive removal of the tosyl group, then base induced elimination; for a review see P.D. Magnus, Tetrahedron, 1977, 33, 2019.

12. G. Galambos, V. Simonidesz, J. Ivanics, K. Horváth, G. Kovács, Tetrahedron Lett., submitted for publication.

13. Oil; R_f: 0.24, 0.27, 0.32, 0.35 /for the four isomers, ethyl acetate/, ^1H NMR/$CDCl_3$/ δ/ppm/: 5.6 /2H,m,CH=CH/, 4.35, 4,45 /1H,m,C-5-H/, 4.3-4.6 /2H,m,C-6-H,C-9-H/, 3.75 /1H,m,C-11-H/, 4.07 /1H,m,C-15-H/, 3.62 /3H,s,OCH_3/ ^{13}C NMR/$CDCl_3$/ δ/ppm/: 173.19, 136.23, 135,68, 131.92, 131.68, 91.68, 91.44, 82.40, 81.12, 78,21, 76.21, 72.93, 57.46, 55.70, 51.57, 46.96, 46.72, 40.58 39.62, 37.13, 34.46, 33.30, 32.88, 31.67, 29.66, 25.05, 22.50, 20.98, 13.88

14. The acid was treated with 1 equiv of NaOMe in methanol; the compound showed an identical pattern to PGI_2 sodium salt on cat haemodynamic test, it was 1.5 times stronger than PGI_2 sodium salt. More detailed pharmacological data will be presented in due course.

15. Physical data of mixtures of isomers. Abrevations:IR:IR/film/ ν /cm^{-1}/; ^1H NMR; ^1H NMR/$CDCl_3$/ δ/ppm/.

3a: R_f:0.43/ethyl acetate/ IR:1700, 1720 C=O; ^1H NMR: 5.45-5.65/m,2H,CH=CH/ 3.9-4.6/m,4H,CH-O/, 2.17, 2.23/s,6H,CH_3CO/

3b: R_f:0.55/10ethyl acetate-1 methanol/; IR:1720, 1740 C=O; ^1H NMR: 5.4-5.7 /m,2H,CH=CH/ 3.9-4.7/m,4H,O-CH/ 4.08, 4.03/qq,4H,OCH_2, J=14,6H_2/ 2.12, 2.17/s,3H,$OCCH_3$

3c: R_f:0.56/ethyl acetate/; IR: 1740 C=O;1070 C-O-C/; ^1H NMR: 5.4-5.7/m,2H CH=CH/; 3.5-4.5/m,5H,CH-o, $CHCOOC_2H_5$/; 4.2, 4.3/qq,4H,J=14,0Hz,OCH_2/

3d: R_f:0.45/ethyl acetate/; IR: 2290 CN; 1750 C=O/ ^1H NMR: 5.4-5.7/m,2H, CH=CH/ 4.1,4.2/qq,2H,J=14.2Hz,OCH_2/; 3.9-4.7/m,4H,CHO/

3e: R_f:0.35/ethyl acetate/; IR:1730, 1740 C=O/; ^1H NMR: 5.4-5.7/m,2H,CH=CH/ 4.12, 4.21/qq,J=14.0Hz, 4H,OCH_2/; 2.88, 2.50/tt,4H,C/O/$CH_2CH_2CO_2C_2H_5$/

3f: R_f:0.48/1ethyl acetate-1acetone/; IR:1725, 1735 C=O; 1150, 1320 SO_2/ UV/ethanol/:λ_{max}:230nm logε:1.110; ^1H NMR: 7.2-7.8/m,4H,aromatic/;5.4-5.7 /m,2H,CH=CH/; 3.37/s,3H,OCH_3/3.8-42/m,5H,CHO,$CHSO_2$/; 2.8-3.2/m,2H, C/O/CH_2/

3g: R_f:0.39/ethyl acetate/ IR:1560,1380 NO_2; ^1H NMR: 5.5-5.7/m,2H,CH=CH/ 3.8-4.8/m,4H,CH-O/; 4.4-4.5/m,2H,CH_2NO_2/

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