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SYNTHESIS OF STABLE PROSTACYCLIN ANALOGUES

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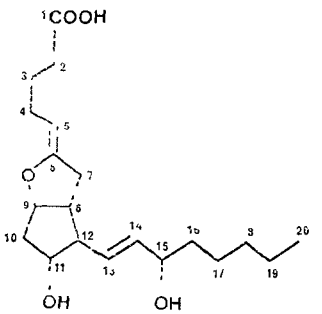
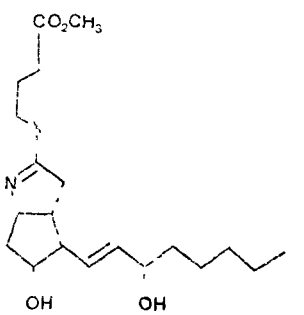
A synthesis for ß-hetero-imino-prostacyclins is described

The short chemical half-life under physiological conditions limits the potential clinical use of prostacyclin PGI_2[1] Therefore the preparation of orally active and chemically stable analogues of PGI_2 represents a desirable goal[2] In order to mimic the labile enol ether linkage of PGI_2 our research has focused upon ß-hetero-imino-prostacyclins 1a-c[3]



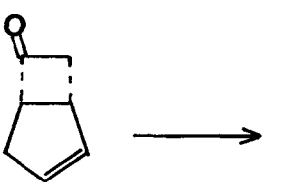
PGI_2



1a (X= O)
1b (X= S)
1c (X= NH)

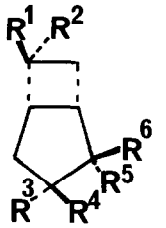
We wish to report a synthesis of ß-thia-imino-prostacyclins, which allows a variety of structural modifications for this pharmacological interesting class of compounds [4]

The readily available bicyclo[3 2 0]hept-2-en-6-one 2, a general synthetic intermediate for natural prostaglandins[5] was utilized as starting material for our synthesis Using standard methodology ketone 2 was transformed to ketal 3 in 60 % overall yield[5] Treatment of ketal 3 with 2-lithio-dithiane (-50 °C, THF, 24hrs) furnished after acetylation (Ac_2O, Py, r t) the crystalline acetates 4 and 5 in 61 % yield (ratio 4 5, 20 80)



2

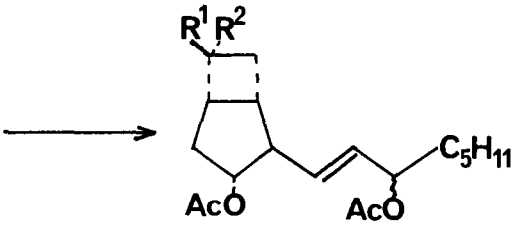
3



4 R^3=H R^4=  R^5=OAc R^6=H

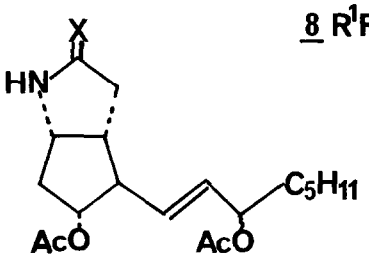
5 R^3=OAc R^4=H R^5=H R^6= 

6 R^3=OAc R^4=H R^5=H R^6=CHO



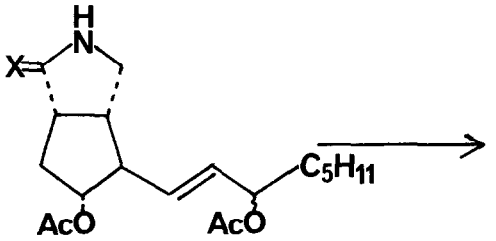
7

8 R^1R^2=O



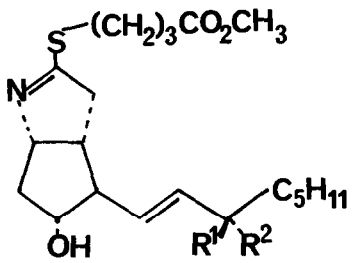
9 X=O

11 X=S



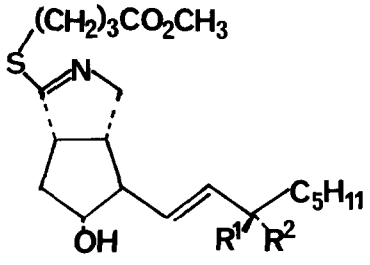
10 X=O

12 X=S



13 R^1=OH R^2=H

1b R^1=H R^2=OH



14a R^1=OH R^2=H

14b R^1=H R^2=OH

The acetates 4 (mp 130-131 °C) and 5 (mp 73-75 °C) could be easily separated by preferential crystallisation (petrolether 40°-80° C) of the minor isomer 4 Selective hydrolysis of the dithiane moiety in acetate 5 with mercuric oxide/ bortrifluorid-etherate (THF, H_2O, 50 °C, 30 min) to the corresponding aldehyde 6, Wadsworth-Emmons-Horner reaction (THF, r t) reduction of the resulting enone ($ZnBH_4$, diglyme, r t) and acetylation (Ac_2O, Py, r t) afforded ketal 7 in 43 % overall yield Exposure of 7 to 0 2 N sulfuric acid in acetonitrile/ water for 24 hrs yielded ketone 8 in 87 % Beckmann rearrangement of ketone 8 could not be accomplished by standard methods[6] However upon treatment of 8 with O-mesitylensulfonyl-hydroxylamine[7] (CH_2Cl_2, 0°C, 30min) the crystalline lactam 9 was obtained in 55 % yield, along with 15 % of the isomeric lactam 10 The ratio of lactams 9 to 10 was easily determined by 270 MHz ^{1}H-NMR(-CONHC<u>H</u>- in 9 = 4 12 and-C<u>H</u>CONH- in 10 = 2 95) The mixture of lactams 9 and 10 was heated for 6 hrs at 80 °C in toluene with 10 equiv of P_4S_{10} x 4Py to afford thiolactams 11 and 12 in 80 % yield after filtration over silica gel Alkylation of thiolactams 11 and 12 with ethyl γ-bromobutyrate (1 equiv NaH, DME, 12 hrs.) followed by hydrolysis of the acetate groups (K_2CO_3, MeOH, r t , 4 hrs) produced compounds 13, 1b and 14a, 14b in a combined yield of 64 %. The isomeric compounds 13, 1b and 14a, 14b were separated easily by a single chromatography on Florisil (EE) The ß-thia-iminoprostacyclins 13 and 1b were thus obtained in a combined yield of 39 %

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References and Notes

*Author to whom correspondence should be addressed

**Dedicated to Prof Dr Klaus Weissermel on the occasion of his 60th birthday

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[8] Satısfactorı , NMR, IR and mass spectral data were obtaıned for each synthetıc ıntermedıate usıng chromatographıcally homogenous samples

NMR ($CDCl_3$) and IR data are gıven for

(5) δ = 5.0 (m, 1H,-C<u>H</u>-OAc), 4 15 (d, 1H, -S-C<u>H</u>-S-), 3 85 (bs, 4H, -O-(C<u>H</u>$_2$)$_2$-O-)
IR(KBr) cm^{-1} 1730 (C=O Ester)

(<u>11</u>)δ = 6 8 (s, 1H, N<u>H</u>), 5,5(m, 2H, -C<u>H</u>=C<u>H</u>-), 4,81 (dd, 1H, -C<u>H</u>--OAc), 4 95 (m, 1H, -CH=CH-C<u>H</u>-OAc), 4 3 (m, 1H, -CSNH-C<u>H</u>-), 2 85 and 2 52 (m, 3H, -NHCS-C<u>H</u>$_2$ and -C<u>H</u>-), 2 4-2 3 (m, 1H, -C<u>H</u>-CH-CH-), 2 0 (2s, 6H, -COC<u>H</u>$_3$), 0 95 (t, 3H, -C<u>H</u>$_3$)
IR(KBr) cm^{-1} 3140 (NH), 1725 (C=O Ester), 1525 (S = C-N)
mp 94-97 °C

(<u>12</u>)δ = 6 75 (S, 1H, N<u>H</u>), 5,5 (m, 2H, -C<u>H</u> = C<u>H</u>-), 4 90 (m, 1H, -CH=CH-C<u>H</u>-OAc), 4 81 (dd, 1H, -C<u>H</u>-OAc), 3 68 and 3 22 (dd bzw t, 2H, -CSNH-C<u>H</u>$_2$), 3.15 (m, 1H, -C<u>H</u>CSNHCH$_2$-), 2 52 (m, 1H, -C<u>H</u>-), 2 4 - 2 3 (m, 1H, -C<u>H</u>-CH=CH-), 2 0 (2s, 6H, -COCH$_3$), 0 98 (t, 3H, -C<u>H</u>$_3$)
IR(CCl_4) cm^{-1} 3135 (NH), 1730 (C=O Ester), 1525 (S = C-N)

(<u>1b</u>)δ = 5 5 (m, 2H, -C<u>H</u> = CH-), 4 1 (dd, 1H, -CH=CH-C<u>H</u>(OH)-CH$_2$-), 4 0-3 7 (m, 2H, -C=N-C<u>H</u>- and -C<u>H</u>OH), 3 65 (s, 3H, -CO_2C<u>H</u>$_3$), 3 1 (t, 2H, -N=C-S-C<u>H</u>$_2$-), 0 88(t, 3H, -C<u>H</u>$_3$)
IR(fılm) cm^{-1} 3500 (OH), 1735 (C=O Ester)

(Receıved ın Germany 29 Aprıl 1982)