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SYNTHESIS OF SIX-MEMBERED RING ANALOGUES OF PROSTAGLANDIN $F_{1\alpha}$

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Several isomeric prostaglandin $F_{1\alpha}$ analogues in which the cyclopentane moiety is replaced by a cyclohexane ring, have been prepared starting from the Diels-Alder adduct of 1,4-diacetoxy-1,3-butadiene and dimethyl fumarate.

Whereas a number of prostaglandin analogues with modified five-membered ring (heterocyclic analogues) have been described[2], only few reports[3] dealt with analogues containing a six-membered ring. We wish to report now the synthesis of 9a-homo-$PGF_{1\alpha}$ ethyl ester and 8,12-diiso-9a-homo-$PGF_{1\alpha}$ ethyl ester.
We reasoned that synthesis of the 1,4-dihydroxycyclohexane part of the analogues might be achieved *via* Diels-Alder reaction of a dienophile with a protected 1,4-dihydroxybutadiene. Due to the stereoselectivity of the Diels-Alder reaction, the configuration of the adduct will be determined by the stereochemistry of the starting materials. Reaction of a dienophile with *trans,trans*-1,4-diacetoxy-1,3-butadiene **1** - readily available from cyclo-octatetraene[4] - would lead therefore to the required 1,4-*cis* configuration of the hydroxy groups at the future C_9 and C_{11}. Reaction of **1** with dimethyl fumarate in refluxing xylene for 20 h afforded adduct **2**[5] (m.p.= 128-130°) in 94% yield. Heating **2** in methanol in the presence of p-TsOH for 20 h provided diol **3**[6] (m.p.= 158-159.5°), which was converted into the di-THP ether **4** with dihydropyran and p-TsOH in benzene at room temperature. Reduction of the ester groups in **4** was accomplished with $LiAlH_4$ in THF, affording **5** in 81% yield from **2**.
Protection of one of the hydroxymethyl groups by reaction with benzyl bromide and NaH in THF or DMF at 60-70° yielded monobenzylated product (67%) along with dibenzylated product **6** (6%) and starting material **5** (13%). The monobenzylated product consisted of a 1:2.5 mixture of the two isomers **7** and **8** which, after chromatographic separation, were used for the synthesis of 9a-homo-$PGF_{1\alpha}$ ethyl ester and 8,12-diiso-9a-homo-$PGF_{1\alpha}$ ethyl ester.
Moffatt oxidation[7] of **7** gave aldehyde **9** which upon Horner reaction with the anion of triethyl phosphonosorbate[8] in THF afforded the unsaturated ester **10** in 58% yield. Catalytic hydrogenation of **10** in ethyl acetate in the presence of 10% Pd/C gave reduction of the double bonds in the ring and the side chain. Subsequent hy-

drogenation of 11 over Pd/C under acidic conditions (ethyl acetate/acetic acid) led to removal of the protecting benzyl group, affording alcohol 12. Moffatt oxidation of 12 gave aldehyde 13 which, after purification by column chromatography, was obtained in 48% yield from 10. Horner reaction of 13 with dimethyl 2-oxo-heptylphosphonate[9] in THF furnished enone 14. Removal of the THP groups in 14 under acidic conditions, followed by reduction of 15 with $Zn(BH_4)_2$ in DME[9], yielded a mixture of 9a-homo-$PGF_{1\alpha}$ethyl ester 16 and its C_{15}-epimer 17[10], which could be separated by column chromatography (TLC; SiO_2, ethyl acetate : 16 Rf= 0.20; 17 Rf= 0.30).

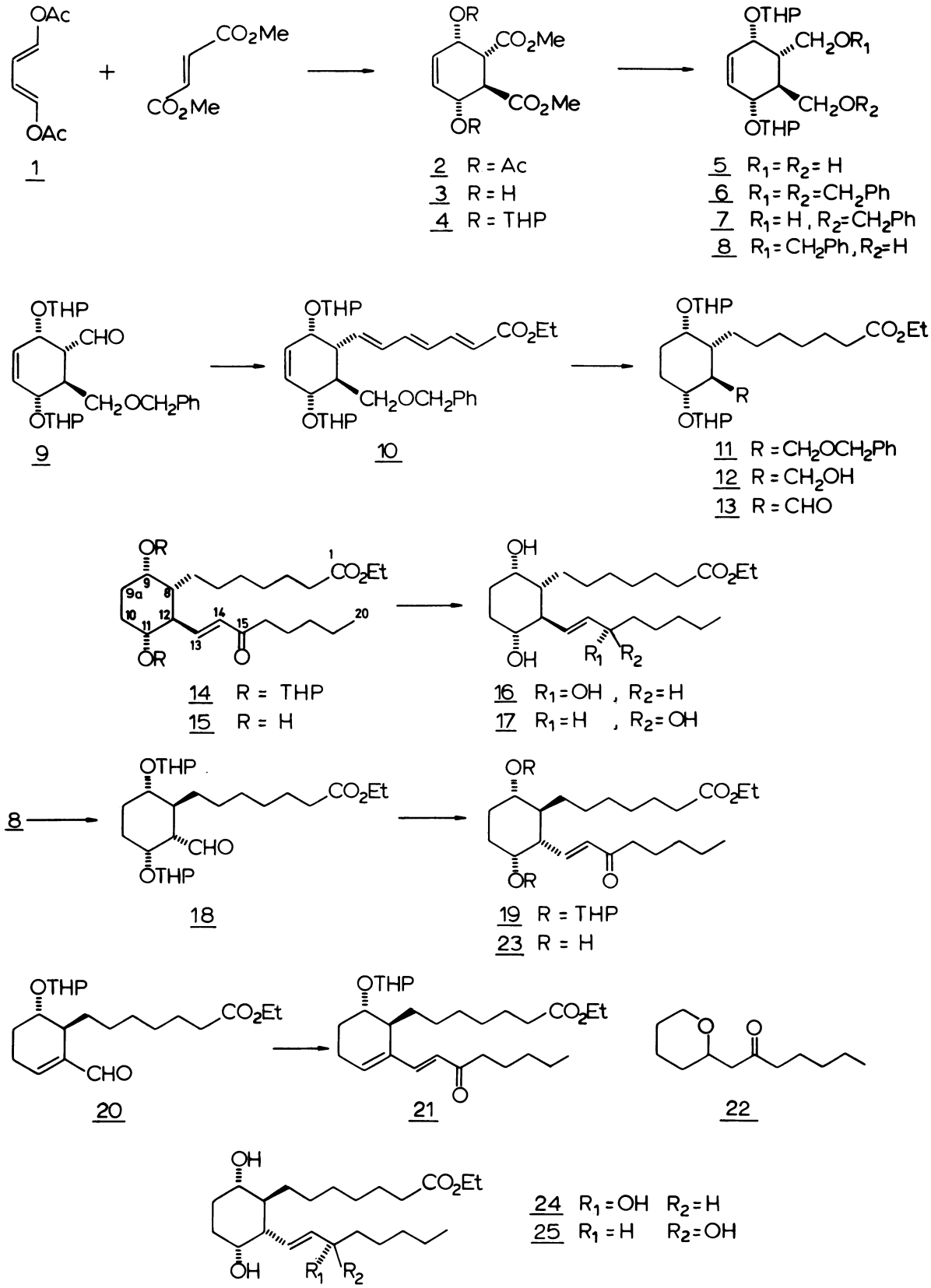
Isomer 8 could be converted into aldehyde 18 (50% overall yield) in a similar way as has been described for the conversion of 7 into 13. Horner reaction of 18 with excess dimethyl 2-oxoheptylphosphonate and NaH in THF, however, proceeded differently from the corresponding reaction of 13. Besides enone 19 two other compounds were isolated. These compounds (21 and 22) originate from elimination of a tetrahydropyranyloxy group in 18, leading to the formation of α,β-unsaturated aldehyde 20, which can react with the anion of dimethyl 2-oxo-heptylphosphonate to give dienone 21. The eliminated tetrahydropyranyloxy group contains a masked aldehyde function which also can react in a Horner reaction, yielding 2-(2-oxoheptyl)tetrahydropyran 22[11]. Aldehyde 20 could be isolated, along with enone 19, if only 1 equivalent of phosphonate anion was used, and the reaction was performed at room temperature instead of 65°.

Removal of the THP groups in 19 and subsequent reduction of 23, thus obtained, with $Zn(BH_4)_2$ in DME gave a mixture of 8,12-diiso-9a-homo-$PGF_{1\alpha}$ethyl ester 24 and its C_{15} epimer 25, which could be separated (TLC; SiO_2, ethyl acetate: 24 Rf=0.26; 25 Rf= 0.33).

The configuration of the analogues was established[12] at the stage of the dihydroxy-enone compounds 15 [IR ($CHCl_3$): 3500 (OH), 1680 and 1620 (enone) cm^{-1}; NMR ($CDCl_3$): δ= 6.18 (d) C_{14}-H; δ= 6.53 (dd, $J_{13,14}$= 16, $J_{12,13}$= 9Hz) C_{13}-H] and 23 [NMR ($CDCl_3$): δ= 6.08 (d) C_{14}-H; δ= 6.86 (dd, $J_{13,14}$= 16, $J_{12,13}$= 9Hz), C_{13}-H]. The NMR spectrum of 15 displayed, for the protons at C_9 and C_{11}, a broad signal (H_{ax}) at δ= 3.99 and a narrow signal (H_{eq}) at δ= 3.38. Assuming a diequatorial position of the side chains at C_8 and C_{12}, the relative configuration can be resolved by irradiating C_{12}-H.

Thus irradiation at δ= 2.10 changed the double doublet of C_{13}-H into a doublet and caused sharpening of the broad signal at δ= 3.99, whereas the narrow signal was unaffected. From these results it can be concluded that C_{11}-H occupies an axial position, indicating a *trans* relationship for the substituents at C_{11} and C_{12}. Enone 23 exhibited a broad signal at δ= 3.80 (H_{ax}) and a narrow signal at δ= 3.41 (H_{eq}) for the protons at C_9 and C_{11}. Irradiation at δ= 2.03 (C_{12}-H) caused sharpening of the narrow signal at δ= 3.41, whereas the broad signal at δ= 3.80 was unaffected now. This implies a *cis* relationship for the substituents at C_{11} and C_{12}.

The screening of the *in vivo* and *in vitro* biological activities of the four 9a-homo-PGF_1 stereoisomers showed the relative configurations at C_8, C_{12} and C_{15} to


OAc
OAc
1
CO2Me
CO2Me
OR
CO2Me
CO2Me
OR
2 R = Ac
3 R = H
4 R = THP
OTHP
CH2OR1
CH2OR2
OTHP
5 R1 = R2 = H
6 R1 = R2 = CH2Ph
7 R1 = H, R2 = CH2Ph
8 R1 = CH2Ph, R2 = H
OTHP
CHO
CH2OCH2Ph
OTHP
9
OTHP
CO2Et
CH2OCH2Ph
OTHP
10
OTHP
CO2Et
R
OTHP
11 R = CH2OCH2Ph
12 R = CH2OH
13 R = CHO
OR
1
CO2Et
9a
9
8
10
11
12
14
15
20
13
OR
O
14 R = THP
15 R = H
OH
CO2Et
OH
R1
R2
16 R1 = OH, R2 = H
17 R1 = H, R2 = OH
8
OTHP
CO2Et
CHO
OTHP
18
OR
CO2Et
OR
O
19 R = THP
23 R = H
OTHP
CO2Et
CHO
20
OTHP
CO2Et
O
21
O
O
22
OH
CO2Et
OH
R1
R2
24 R1 = OH R2 = H
25 R1 = H R2 = OH

be important for the potency. The isomer with "natural" relative configuration (16) appeared to possess the highest potency. Details will be published elsewhere[13].

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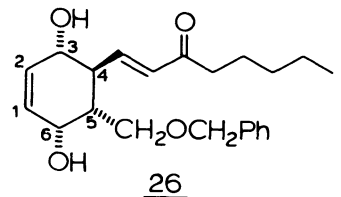
10. The more polar isomer (TLC; silica gel) was tentatively assigned the α-configuration at C_{15} by analogy with the chromatographic behaviour of the esters of the natural prostaglandins.
11. This compound was also obtained in a separate experiment from 2-hydroxytetrahydropyran.
12a. The elimination of the tetrahydropyranyloxy group in 18 is in support of the assigned C_{12}-C_{13} cis configuration; see N. Finch, J.J. Fitt and I.H.S. Hsu, J.Org.Chem., 40, 206 (1975).
b. Additional evidence for the relative configuration of the analogues was also obtained in an early stage of the synthesis by converting alcohol 8 into the enone 26.



26

C_3-H δ = 3.97 $J_{3,4}$ = 9 Hz

C_6-H δ = 4.28 $J_{5,6}$ = 3.5 Hz

The observed coupling constants $J_{3,4}$ and $J_{5,6}$ were typical of trans and cis vicinal protons, respectively.

13. D.W.R. Hall and K.D. Jaitly, to be published.

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