Tetrahedron Letters No. 34, pp 2945 - 2948, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 10,10-DIMETHYLPROSTAGLANDINS[1]

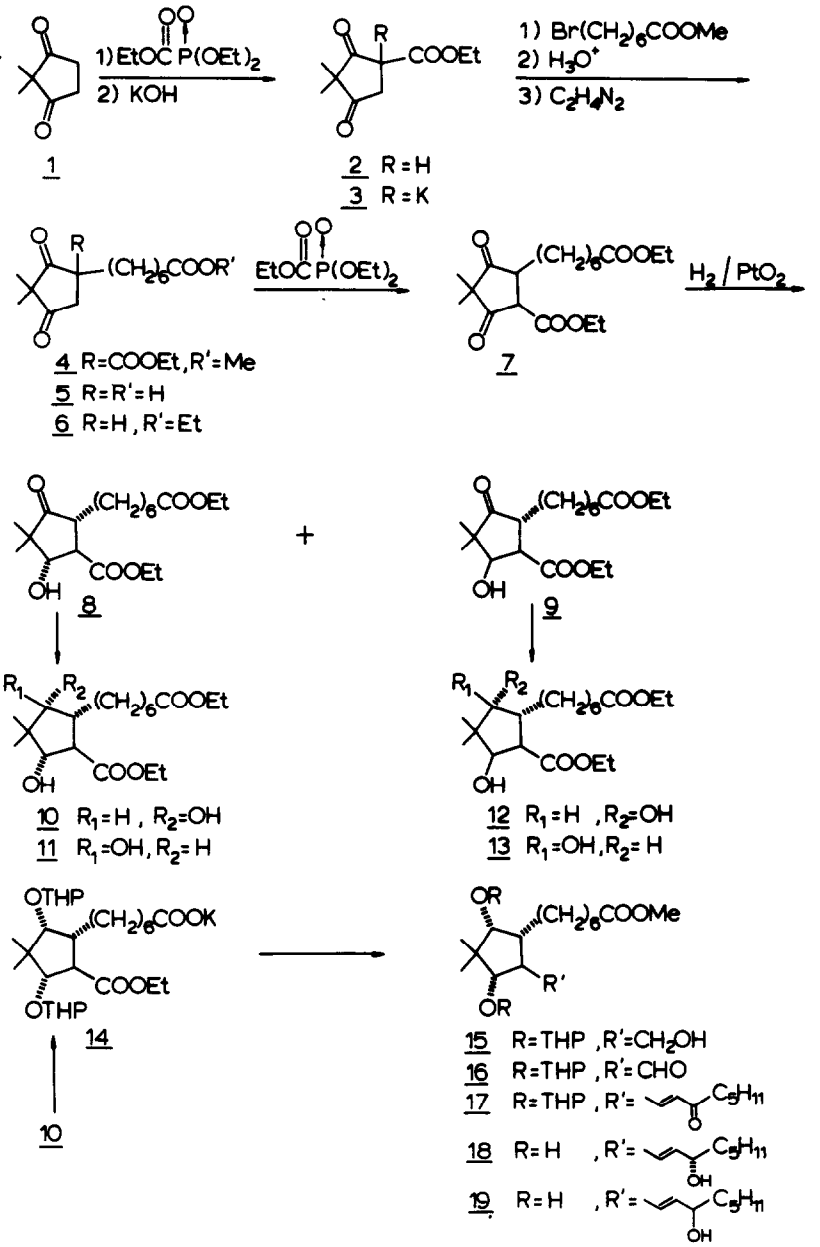
O.G. Plantema, H. de Koning* and H.O. Huisman
Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

(Received in UK 1 July 1975; accepted for publication 10 July 1975)

We wish to report the total synthesis of the 10,10-dimethyl-$PGF_{1\alpha}$, $PGF_{1\beta}$ and 11-epi-$PGF_{1\beta}$ methylesters and their C_{15}-epimers, by a route in which all isomers are obtained from a common intermediate.

Reaction of 2,2-dimethyl-1,3-cyclopentanedione 1[2] with ethyl diethoxyphosphinylformate[3] and NaH afforded β-keto ester 2 [bp. 69-71°/0.05 mm; ir 1750, 1725, 1660 and 1620; m/e 198 (M)][4]. Treatment with KOH in aqueous ethanol[5] produced potassium salt 3 [ir 1730, 1650]. Reaction of 3 with methyl 7-bromoheptanoate in dry DMSO provided diester 4 [ir 1740, 1725; nmr 3.30 (d,J = 19, ring CHCO), 2.70 (d,J = 19, ring CHCO)] besides some O-alkylated product [ir 1740, 1710 and 1620; nmr 3.26 (s, C = CCH_2CO)]. Treatment of 4 with boiling 10% sulfuric acid for 16 h gave carboxylic acid 5 [mp. 45-46°; ir 3600-2500, 1760 and 1720; nmr 9.0 (s, COOH), 2.25 (t, J = 7, CH_2COOH, 1.13 (s, CH_3), 1.10 (s, CH_3)], which was converted to ethyl ester 6 [bp. 140-144°/0.01 mm; ir 1755, 1720; m/e 282 (M)] with diazoethane. Reaction of 6 with ethyl diethoxyphosphinylformate and NaH yielded β-keto ester 7 [30% from 1; bp. 160-164°/0.01 mm; ir 1740, 1720, 1660 and 1620; m/e 354 (M)].

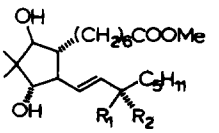
Catalytic hydrogenation of 7 over PtO_2 in ethanol produced a mixture of alcohols 8 and 9, separable by column chromatography. These compounds are assumed to possess a relative trans configuration at C_8[6] and C_{12} because of the easily enolisable β-keto ester[7] in 7. The relative configuration at C_{11} and C_{12} was confirmed by ir dilution experiments[8,9]: only 9 showed a concentration-independent behaviour in the OH-region. Reduction of 8 with sodium borohydride in ethanol gave 10 and 11, while 12 and 13[10] were obtained from 9. The diols


1) EtOC P(OEt)2
2) KOH
COOEt
1) Br(CH2)6COOMe
2) H3O+
3) C2H4N2
1
2 R=H
3 R=K
(CH2)6COOR'
EtOC P(OEt)2
(CH2)6COOEt
COOEt
H2 / PtO2
4 R=COOEt, R'=Me
5 R=R'=H
6 R=H, R'=Et
7
OH
8
9
R1 R2
10 R1=H, R2=OH
11 R1=OH, R2=H
12 R1=H, R2=OH
13 R1=OH, R2=H
OTHP
COOK
14
OR
COOMe
R'
15 R=THP, R'=CH2OH
16 R=THP, R'=CHO
17 R=THP, R'=
18 R=H, R'=
19 R=H, R'=
C5H11

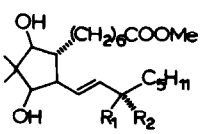
could be separated by column chromatography. Reaction of both cis-1,3-diols 10 and 13 with p-nitrobenzaldehyde and a catalytic amount of p-toluenesulfonic acid, forming cyclic benzylidene derivatives, established the C_9-C_{11} configuration [11,12].

Conversion of diol 10 to the bis-tetrahydropyranyl ether followed by selective hydrolysis[13] of the less hindered ester function with one equivalent of potassium hydroxide in aqueous ethanol gave the mono ester 14. Reduction of the ester function in 14 with lithium borohydride in diglyme at 100° and subsequent methylation of the carboxylate with methyl iodide in HMPT[14] afforded alcohol 15 [ir 3500, 1720; nmr 3.64 (s, $COOCH_3$), 2.28 (t, J = 7, CH_2COOMe)]. Moffatt oxidation of 15 with 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-p-toluenesulfonate[9] gave aldehyde 16. The remaining steps in the synthesis were completed by established procedures[15]. Reaction with the sodium derivative of dimethyl 2-oxoheptylphosphonate and subsequent reduction of the resulting enone 17 [ir 1720, 1690, 1660 and 1620; nmr 6.75 (m, H_{13}), 6.13 (m, H_{14})] with zinc borohydride, followed by hydrolysis of the tetrahydropyranyl ethers with acetic acid in aqueous tetrahydrofuran gave a mixture of C_{15}-epimers 18 [14% from 10; R_f = 0.31 (SiO_2, ethyl acetate); m/e 380 (M-18)] and 19 [14% from 10; R_f = 0.43; m/e 380] which were separated by column chromatography. Compound 18 is assumed to possess "natural" stereochemistry at C_{15} by analogy with the chromatographic behaviour of esters of the natural prostaglandins.

The C_{11} and C_9, C_{11} epimeric prostaglandins were prepared via the same route starting from 11 and 13: 20 [13% from 11; R_f = 0.26; m/e 380], 21 [13% from 11; R_f = 0.37; m/e 380], 22 [8% from 13; R_f = 0.32; mp. 71-72°; m/e 380], 23 [7% from 13; R_f = 0.37; mp. 90-91°; m/e 380] [10].



20 R_1=H, R_2=OH
21 R_1=OH, R_2=H



22 R_1=H, R_2=OH
23 R_1=OH, R_2=H

REFERENCES:

1. Taken in part from the forthcoming thesis of O.G. Plantema.
2. W.C. Agosta, A.B. Smith, J.Org.Chem., 35, 3856 (1970).
3. I. Shahak, Tetrahedron Lett., 2201 (1966).
4. All compounds are racemic. Satisfactory elemental analysis were obtained. ^{1}H-NMR spectra (chemical shifts are reported in ppm on the δ-scale) were obtained on a Varian HA 100 spectrometer in deutero chloroform containing tetramethylsilane as internal reference. IR spectra (cm^{-1}) were obtained in chloroform. Mass spectra were obtained with an AEI MS-9 spectrometer.
5. R. Mayer in "Neuere Methoden der Präparativen Organischen Chemie", Bnd.II, Ed. W. Foerst, Verlag Chemie, Weinheim, 1960, p. 69.
6. Prostaglandin numbering.
7. K. Kojima, K. Sakai, Tetrahedron Lett., 3337 (1972).
8. J. Castells, J. Palau, J.Chem.Soc., 4938 (1964).
9. N. Finch, L. Della Vecchia, J.J. Fitt, R. Stephani, I. Vlattas, J.Org. Chem., 38, 4412 (1973).
10. ^{1}H- and ^{13}C-NMR Spectra of 8-13 and 18-23 were consistent with the assigned structures and will be published elsewhere.
11. P.F. Beal, J.C. Babcock, F.H. Lincoln in "Prostaglandins, Proceedings of the 2nd Nobel Symposium", Stockholm 1966, Ed.S. Bergström and B. Samuelsson, Almqvist and Wiksell, Stockholm, 1967.
12. D. van Haver, D. Tavernier, M. Anteunis, M. Vandewalle, Tetrahedron, 30, 105 (1974).
13. K. Kojima, K. Sakai, Tetrahedron Lett., 3333 (1972).
14. J.E. Shaw, D.C. Kunerth, J.J. Sherry, Tetrahedron Lett., 689 (1973).
15. E.J. Corey, N.M. Weinshenker, T.K. Schaaf, W. Huber, J.Amer.Chem.Soc., 91, 5675 (1969).