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Synthetic Studies on Prostanoids II[1] Stereospecific Total Synthesis of Prostaglandin $F_{1\alpha}$

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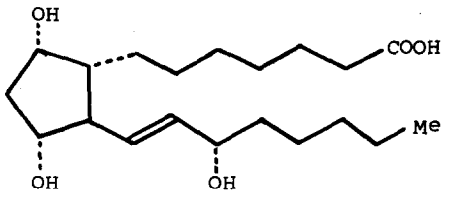
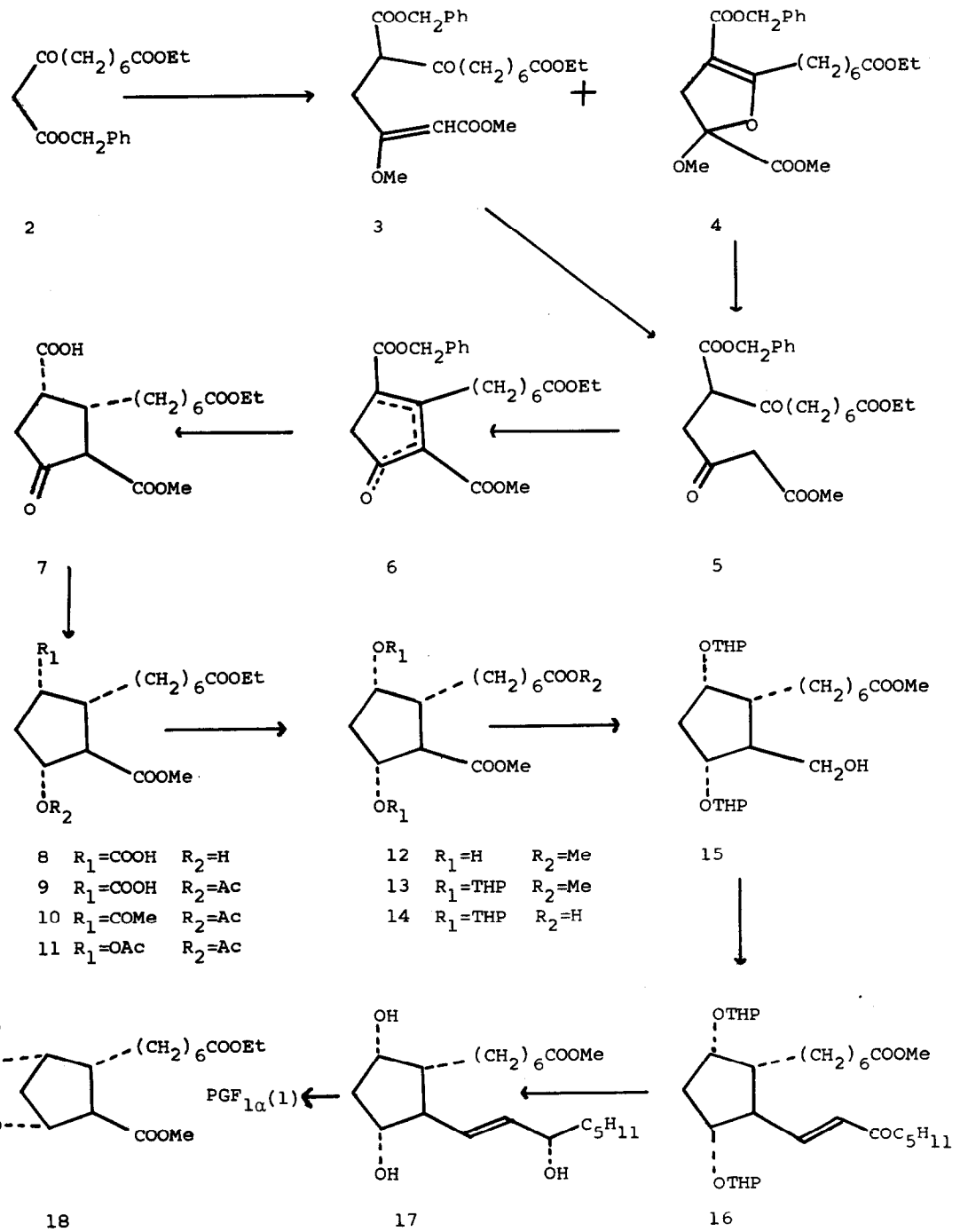
Prostaglandins (PGs) are naturally occurring oxygenated C_{20} fatty acids, which show diverse biological properties with high potency. Synthesis of natural PGs[2] has been studied extensively in recent years. We now wish to report a new highly stereospecific total synthesis of $PGF_{1\alpha}$(1), which proceeds in good to excellent yield at each step. Four asymetric centers on the cyclopentane ring required for the synthesis of $PGF_{1\alpha}$ was introduced stereospecifically by the catalytic reduction of the enone (6) with palladium on charcoal (6 ⟶ 7: the formation of three asymetric centers), followed by sodium borohydride reduction (7 ⟶ 8: the formation of additional one asymetric center).



$PGF_{1\alpha}$(1)

Sodium salt of 2[3] was alkylated with methyl γ-bromo-β-methoxycrotonate[4] to give a triester (3): ir*; 1741, 1712, 1630, and the ether (4): ir; 1738, 1700, 1645, nmr*; 6.70 (3H, s, OCH_3). Both 3 and 4 was treated with trifluoroacetic acid in chloroform yielding a triketone (5): ir; 1745, 1730, nmr; 6.30 (3H, s, $COOCH_3$). The conversion of 5 into the enone (6)[5]: ir; 1735, 1630, was effected smoothly with potassium bicarbonate in methanol. Catalytic reduction, coupled with hydrogenolysis of 6 with 10% palladium on charcoal yielded in excellent yield a desired trans-cis trisubstituted


CO(CH2)6COOEt
COOCH2Ph
2
COOCH2Ph
CO(CH2)6COOEt
CHCOOMe
OMe
3
COOCH2Ph
(CH2)6COOEt
O
OMe
COOMe
4
COOCH2Ph
CO(CH2)6COOEt
COOMe
O
5
COOCH2Ph
(CH2)6COOEt
COOMe
O
6
COOH
(CH2)6COOEt
COOMe
O
7
R1
(CH2)6COOEt
COOMe
OR2
8 R1=COOH R2=H
9 R1=COOH R2=Ac
10 R1=COMe R2=Ac
11 R1=OAc R2=Ac
OR1
(CH2)6COOR2
COOMe
OR1
12 R1=H R2=Me
13 R1=THP R2=Me
14 R1=THP R2=H
OTHP
(CH2)6COOMe
CH2OH
OTHP
15
OTHP
(CH2)6COOMe
COC5H11
OTHP
16
OH
(CH2)6COOMe
C5H11
OH
OH
17
O
(CH2)6COOEt
O
COOMe
PGF1α(1)
18

cyclopentanone (7)[6]: ir; 1750, 1740, 1700. Yield from 2 to 7 is 35%. Sodium borohydride reduction of 7 gave, through steric approach control, an α-hydroxy ester (8)[6]: ir; 3480, 3250. The cis relationship between the carboxyl and the hydroxyl function was proved by the conversion of 8 into a lactone (18): ir; 1795, with p-toluenesulphonic acid in refluxing benzene. Acetylation of 8 with acetic anhydride in pyridine afforded an acetate (9): nmr; 7.95 (3H, s, OAc). The acetate (9) was then treated with oxalyl chloride, followed by dimethyl copper lithium[7] in ether at -78° to yield, without isomerization of acetyl function, a methyl ketone (10): ir; 1745, 1700, nmr; 7.85 (3H, s, $COCH_3$) 7.95 (3H, s, OAc). Baeyer-Villiger oxidation of 10 with trifluoroperacetic acid and disodium hydrogen phosphate in methylene chloride gave diacetate (11): nmr; 7.98 (3H, s, OAc), 7.91 (3H, s, OAc). Transesterification of 11 with potassium carbonate in anhydrous methanol yielded a diol (12): ir; 3450, 1735, nmr; 6.30 (3H, s, $COOCH_3$), 6.34 (3H, s, $COOCH_3$). Treatment of 12 with dihydropyran in the presence of picric acid afforded a dipyranyl (13): ir; 1020. Selective hydrolysis of the ester function in 13 with 5% potassium carbonate in 70% aqueous methanol yielded a monomethyl ester (14): nmr; 6.32 (3H, s, $COOCH_3$). Potassium salt of 14 was then reduced with lithium borohydride in refluxing tetrahydrofuran, followed by methylation with diazomethane to give an alcohol (15): ir; 3440, 1740. Collins oxidation[8] of 15, followed by Wittig reaction with 1-tributyl-phosphoranylidene-2-heptanone in ether gave the enone (16): ir; 1740, 1695, 1670, 1632. Sodium borohydride reduction of 16 in methanol, followed by depyranylation with acetic acid-water-tetrahydrofuran (5:2.5:1) yielded a mixture of triols (15α and β), which was separated with column chromatography over acid washed silicagel to give $PGF_{1\alpha}$ methyl ester (17): mp 75-7° (lit. mp 70-73°)[2d], ir ($CHCl_3$); 3400, 1730, mass spectrum; M^+-H_2O:m/e=352, and 15-iso-$PGF_{1\alpha}$ methyl ester in almost equal amount. Hydrolysis of 17 yielded a crystalline $PGF_{1\alpha}$ (1): mp 78-9.5° (lit. mp 81°)[2c] identical in its ir,

nmr, mass spectrum and tlc behavior with natural $PGF_{1\alpha}$. Overall yield of 1 from 7 is 6.7%. The synthesis of natural $PGF_{1\alpha}$ using the optically active 7 is now under investigation.

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References

*) ir (cm^{-1}) spectrum was taken of neat liquids and nmr(τ) spectrum was taken in $CDCl_3$ solution containing tetramethylsilane as internal standard unless otherwise stated.

1) Part I: K. Sakai et al.; Tetrahedron Letters 1287 (1972)

2) Prostaglandins: a) Analls of New York Acad. of Sciences 180 24 (1971) Synthesis of $PGF_{1\alpha}$: b) E.J. Corey, R. Noyori, T.K. Schaaf; J. Am. Chem. Soc. 92 2586 (1970) and references cited therein. c) E.J. Corey, N.H. Anderson, R.M. Carlson, J. Paust, E. Vedejs, I. Vlattas, R.E.K. Winter; J. Am. Chem. Soc. 90 3245 (1968). d) G. Just, C. Simonovitch, F.H. Lincoln, W.P. Schneider, U. Axen, G.B. Spero, J.E. Pike; J. Am. Chem. Soc. 91 5364 (1969). e) J. Katsube, H. Shimomura, M. Matsui; Agr. Biol. Chem. 35 1828 (1971) and references stated therein.

3) 2 was synthesised from benzyl acetoacetate and 7-ethoxycarbonylheptanoyl chloride by the similar method reported in Org. Synth. 42 41 (1962)

4) R.B. Reid, W.R. Ruby; J. Am. Chem. Soc. 73 1054 (1951)

5) 6 consists of a mixture of double bond isomers.

6) Stereochemical assignment of 7 and 8 will be discussed in detail in the following paper.

7) G.H. Posner, C.E. Witten; Tetrahedron Letters 4647 (1970)

8) J.C. Collins, W.W. Hess, F.J. Franck; Tetrahedron Letters 3363 (1968)