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12-METHYLPROSTAGLANDINS

TOTAL SYNTHESIS OF 12-Methyl$PGF_{2\alpha}$ and 12-MethylPGE_2

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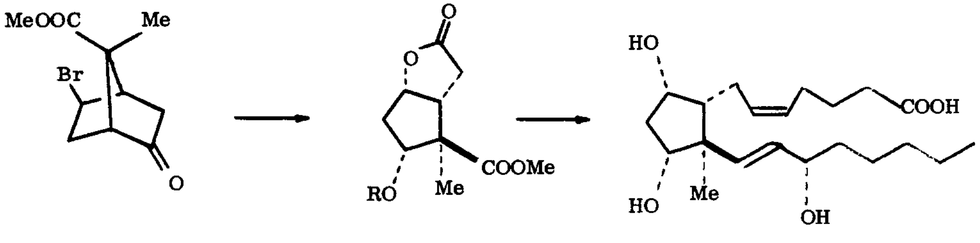
We recently reported a total synthesis of sesquifenchene[2] from the key bicyclo[2.2.1]heptanone derivative 3 and suggested at that time the possibility of utilizing 3 and derivatives thereof for construction of 12-methylprostaglandins[3] via a Corey-like intermediate(Scheme I). We now wish to report the results of this investigation which have led to the synthesis of 12-methyl$PGF_{2\alpha}$ and 12-methylPGE_2(2).

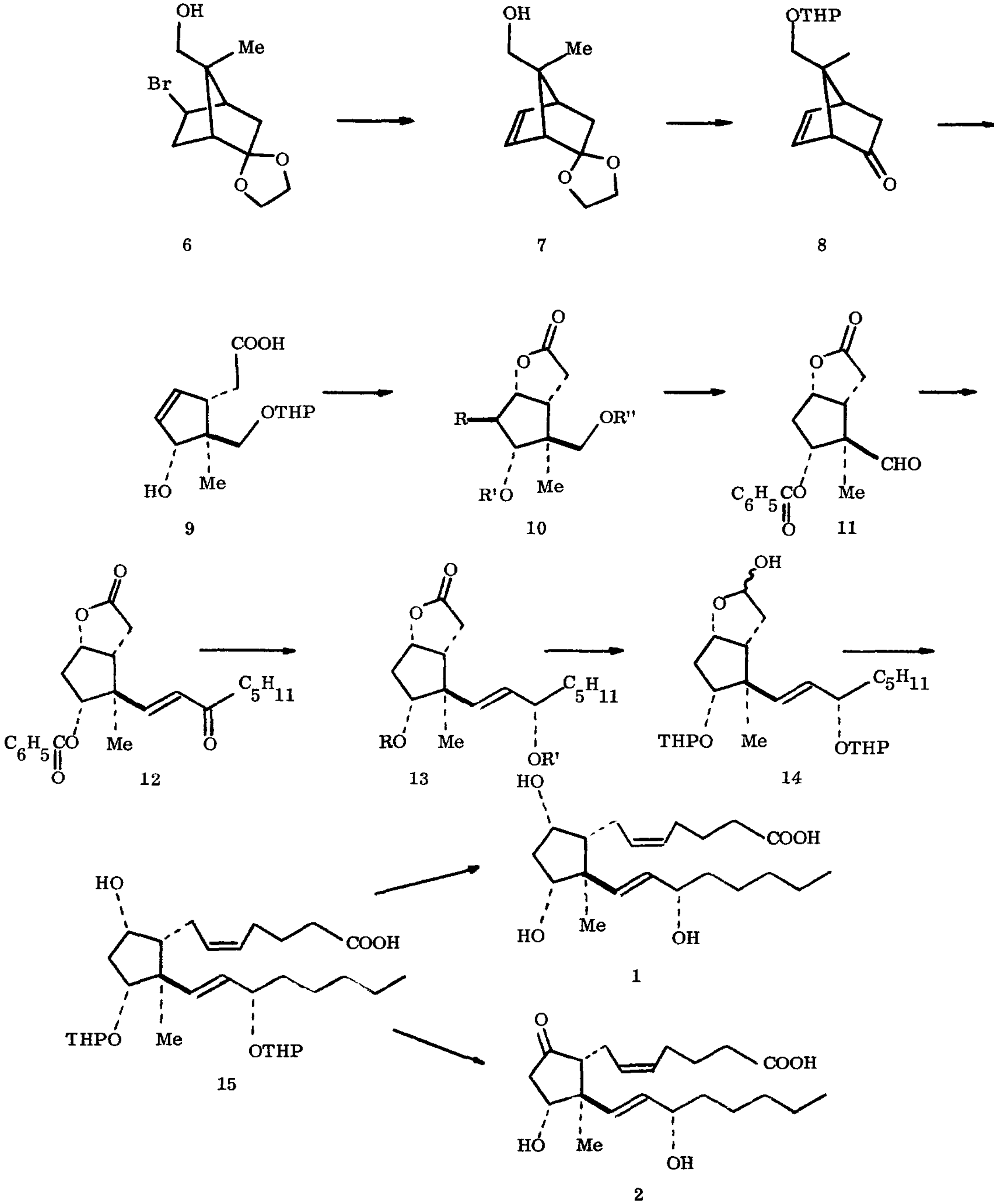


3

12-Methyl$PGF_{2\alpha}$(1)

Scheme I

Ketalization of 3 followed by reduction with lithium aluminum hydride gave bromide 6(mp 93-94°) in 90 % overall yield.[4] Dehydrobromination with 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing benzene afforded 7 in 95 % yield. Conversion of 7 to the ketone 8 via deketalization(30 % glacial acetic acid/90°/2.5 hr) and tetrahydropyranylation(dihydropyran/CH_2Cl_2/TsOH), followed by Baeyer-Villiger oxidation[5,6] employing hydrogen peroxide(7 equiv) and sodium hydroxide(4 equiv) in aqueous methanol(1:1) at 5° for 16 hr gave the hydroxy acid 9 in 80 % overall yield from 7. Neutralization of 9 in water containing 1.2 equiv of sodium hydroxide at 0° followed by neutralization with carbon dioxide and treatment with 2.5 equiv of aqueous


OH
Me
Br
O
O
6
OH
Me
O
O
7
OTHP
O
8
COOH
OTHP
HO
Me
9
O
O
R
OR"
R'O
Me
10
O
O
CHO
C_6H_5CO
O
Me
11
O
O
C_5H_{11}
C_6H_5CO
O
Me
O
12
O
O
C_5H_{11}
RO
Me
OR'
13
OH
O
C_5H_{11}
THPO
Me
OTHP
14
HO
COOH
HO
Me
OH
1
HO
COOH
THPO
Me
OTHP
15
O
COOH
HO
Me
OH
2

potassium triiodide solution at 5° for 30 hr produced the iodo lactone 10(R = I, R' = H, R'' = THP)[carbonyl absorption($CHCl_3$) at 5.61 μ] in 82 % yield. Deiodination using tributyltin hydride[7] in benzene at 50°(initiation with azobisisobutyronitrile) produced the hydroxy tetrahydropyranyl derivative 10(R = R' = H, R'' = THP)[95 %] which was benzoylated using benzoyl chloride in pyridine and hydrolyzed[methanol/p-toluenesulfonic acid] in quantitative yield to alcohol 10(R = R'' = H, R' = C_6H_5CO-). Oxidation using Collins reagent[8] in methylene chloride at 0° produced the stable aldehyde 11 in 90 % yield.

Condensation of aldehyde 11 with the sodio derivative of dimethyl 2-oxoheptylphosphonate[9] in diemthoxyethane at 45° for 16 hr afforded stereospecifically the the trans-enone lactone 12 in 63 % yield after chromatography. Treatment of the enone 12 with sodium borohydride(2 equiv) in ethanol at -20° gave in near quantitative yield a mixture of the 15α-hydroxy lactone 13(R = C_6H_5CO-, R' = H) and the 15β epimer (ratio ca. 1:1). The epimers were cleanly separated by preparative thin layer chromatography on 0.25 mm silica gel plates[two elutions with 15 % methyl ethyl ketone in benzene]. By analogy to the tlc behavior of similar natural prostaglandin intermediates(where p-phenylbenzoate rather than benzoate was used[10]) the less polar isomer has been tentatively assigned the natural 15S configuration in 13(R = C_6H_5CO-, R' = H).

(±)-12-Methylprostaglandin $F_{2\alpha}$(1) was obtained from the 15α-hydroxy intermediate 13(R = C_6H_5CO-, R' = H) in the following manner. Debenzoylation with an equimolar amount of potassium carbonate in methanol followed by bistetrahydropyranylation using dihydropyran in methylene chloride containing p-toluenesulfonic acid gave 13(R = R' = THP). Reduction with diisobutylaluminum hydride(2.0 equiv) in toluene at -78° afforded hemiacetal 14 which was without purification condensed with the Wittig reagent derived from 5-triphenylphosphoniopentanoic acid and sodio methylsulfinylcarbanide in dimethyl sulfoxide[11] giving hydroxy acid 15 in 70 % overall yield from 12. Acid hydrolysis of 15 gave (±)-12-methyl $PGF_{2\alpha}$(1) in 90 % yield which was homogeneous by tlc in several solvent systems.

Oxidation of 15 by dichromate/sulfuric acid(two phase)[12] and cleavage [acetic acid-water(2:1)/40°/3 hr] of the tetrahydropyranyl protecting groups afforded in 65 % yield pure (±)-12-methyl PGE_2(2).[13]

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References

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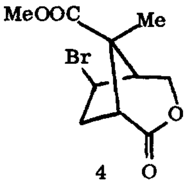

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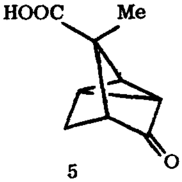

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