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SYNTHESIS OF A 9,11-BIS-DESOXY-PROSTAGLANDIN

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In a previous Communication we reported a synthesis of dl-11-desoxy-$PGF_{2\alpha}$ and dl-11-desoxy-PGE_2[1], using the known iodo-lactone (1)[2] which was efficiently converted into the bicyclic olefin (2)[1]. Pursuing our effort aimed at the preparation of modified prostaglandins[3], we now wish to report the synthesis of the dl-9,11-bis-desoxy-prostaglandin (8).

This synthesis benefited greatly from the specific and high yielding conversion of the ethylenic lactone (2) into the acid (3a) with a wide variety of catalysts. In particular, hydrogenation of (2) with Raney nickel in methanol solution provoked simultaneous reduction of the double bond and hydrogenolysis of the alkyl oxygen bond of the lactone group, thus affording the acid (3a) [ν_{max} 3350, 1710 cm^{-1}; n.m.r. 7.23 (5 aromatic H), 10.63 ppm (CO_2H, exchanged with D_2O)][4].

An hydrogenation experiment of (2) performed with 10% palladium on carbon in dimethoxyethane solution in the presence of a catalytic amount of perchloric acid led additionally to the hydrogenolysis of the benzyl ether, providing the hydroxy acid (3b) in one step [ν_{max} 3450, 1710 cm^{-1}]. Treatment of (3a) with diazomethane in ether solution provided the corresponding methyl ester (3c) [ν_{max} 1735 cm^{-1}; n.m.r. 3.63 (CO_2Me), 7.33 ppm (5 aromatic H)]. Cleavage of the benzyl ether was effected by stirring (3c) in an hydrogen atmosphere with 10% palladium on carbon, giving the hydroxy-ester (3d) [ν_{max} 3400, 1735 cm^{-1}; n.m.r. 3.66 (CO_2Me)], in 45% overall yield from (2). Oxidation of the alcohol (3d) with Collins' reagent[5] furnished the aldehyde (4) [ν_{max} 1730, 1710 cm^{-1}; n.m.r. 3.66 (CO_2Me), 9.63 ppm (CHO)].

Alkylation of (4) with the sodium salt of dimethyl 2-oxoheptylphosphonate[2] provided the expected enone (5) [λ_{max} 228 nm (log ε 4.2), ν_{max} 1735, 1675, 1625 cm^{-1}; n.m.r. 0.89 (Me), 3.56 (CO_2Me), 5.93 ppm (d, J 16 Hz, *trans* olefin at C-13)]. Zinc borohydride reduction of the carbonyl function at C-15 yielded a mixture of 15(R)- and 15(S)-isomeric alcohol separated by preparative TLC. The desired 15(S)-alcohol (6a) [ν_{max} 3400, 1735 cm^{-1}; n.m.r. 0.9 (Me), 3.6 (CO_2Me), 5.45 ppm (d, 2 vinyl H)] was reacted with dihydropyran to give the corresponding ether (6b) [ν_{max} 1735 cm^{-1}; n.m.r. 0.9 (Me), 3.33 (CO_2Me), 5.4 ppm (2 vinyl H)].

The concluding steps of the synthesis are shown in the scheme. Reaction of the ester moiety of (6b) with diisobutylaluminum hydride in toluene solution at -70°[6], provided the aldehyde (7) (73% yield). This was allowed to react with 5-triphenylphosphoniopentanoic acid disodium salt[2], thus giving the novel prostanoic acid as its 15-tetrahydropyranyl ether derivative [ν_{max} 3350, 1710 cm^{-1}; n.m.r. 0.86 (Me), 5.41 (4 vinyl H), 7.96 ppm (CO_2H)]. Ready hydrolysis of the ether protecting group by brief exposure to acid afforded the dl-9,11-bis-desoxy-prostaglandin (8) [colorless oil; ν_{max} 3350, 1710 cm^{-1}; n.m.r. 0.9 (Me), 5.43 (4 vinyl H), 7.73 ppm (CO_2H)].

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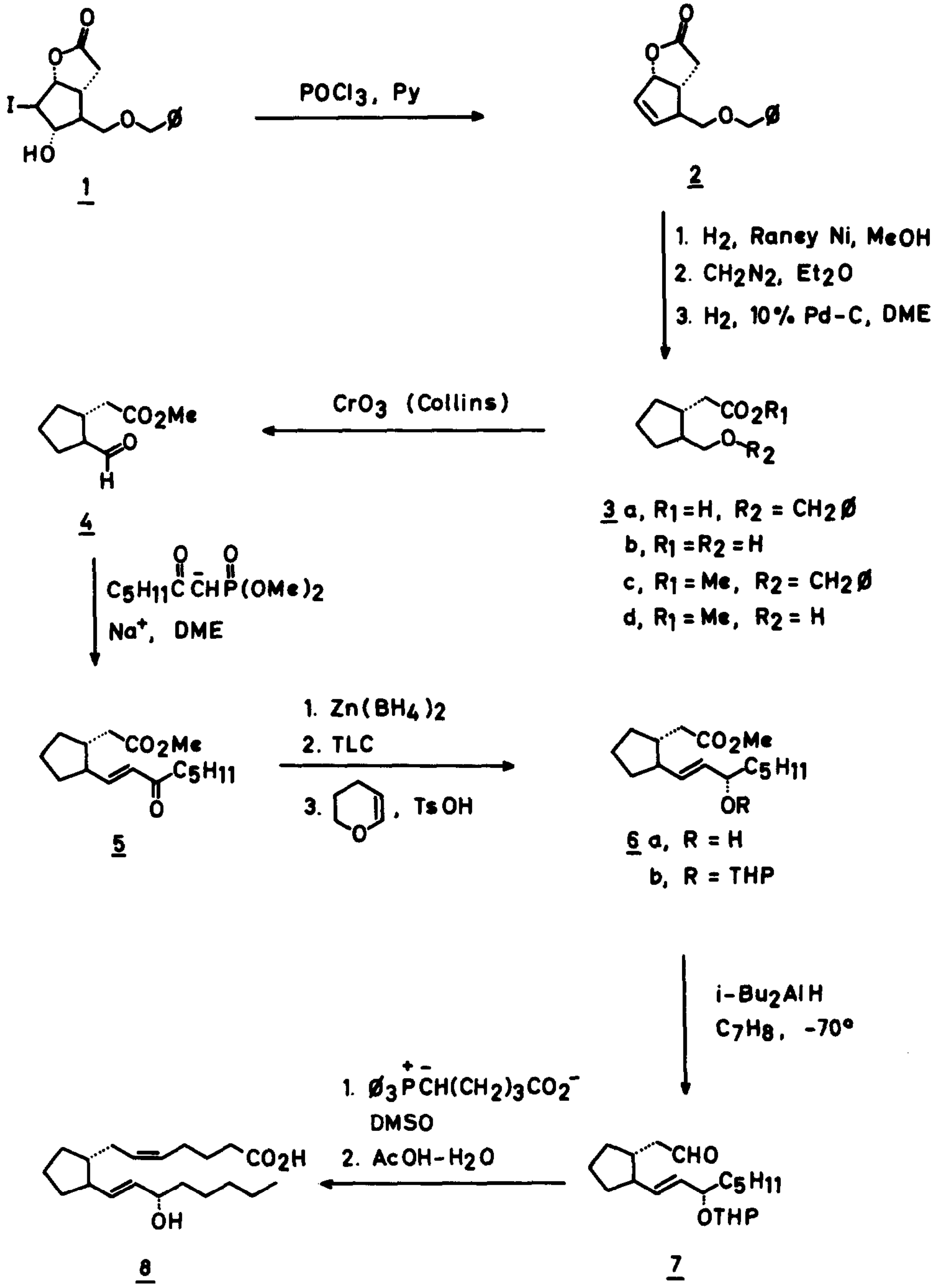
1
POCl3, Py
2
1. H2, Raney Ni, MeOH
2. CH2N2, Et2O
3. H2, 10% Pd-C, DME
CO2R1
O-R2
3 a, R1=H, R2 = CH2Ø
b, R1=R2=H
c, R1=Me, R2= CH2Ø
d, R1=Me, R2= H
CrO3 (Collins)
CO2Me
H
4
C5H11C(=O)C̄HP(=O)(OMe)2
Na+, DME
CO2Me
C5H11
5
1. Zn(BH4)2
2. TLC
3. , TsOH
CO2Me
C5H11
OR
6 a, R = H
b, R = THP
i-Bu2AlH
C7H8, -70°
CHO
C5H11
OTHP
7
1. Ø3P+C−H(CH2)3CO2−
DMSO
2. AcOH-H2O
CO2H
OH
8