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TOTAL SYNTHESIS OF A 9-DESOXY-PROSTAGLANDIN

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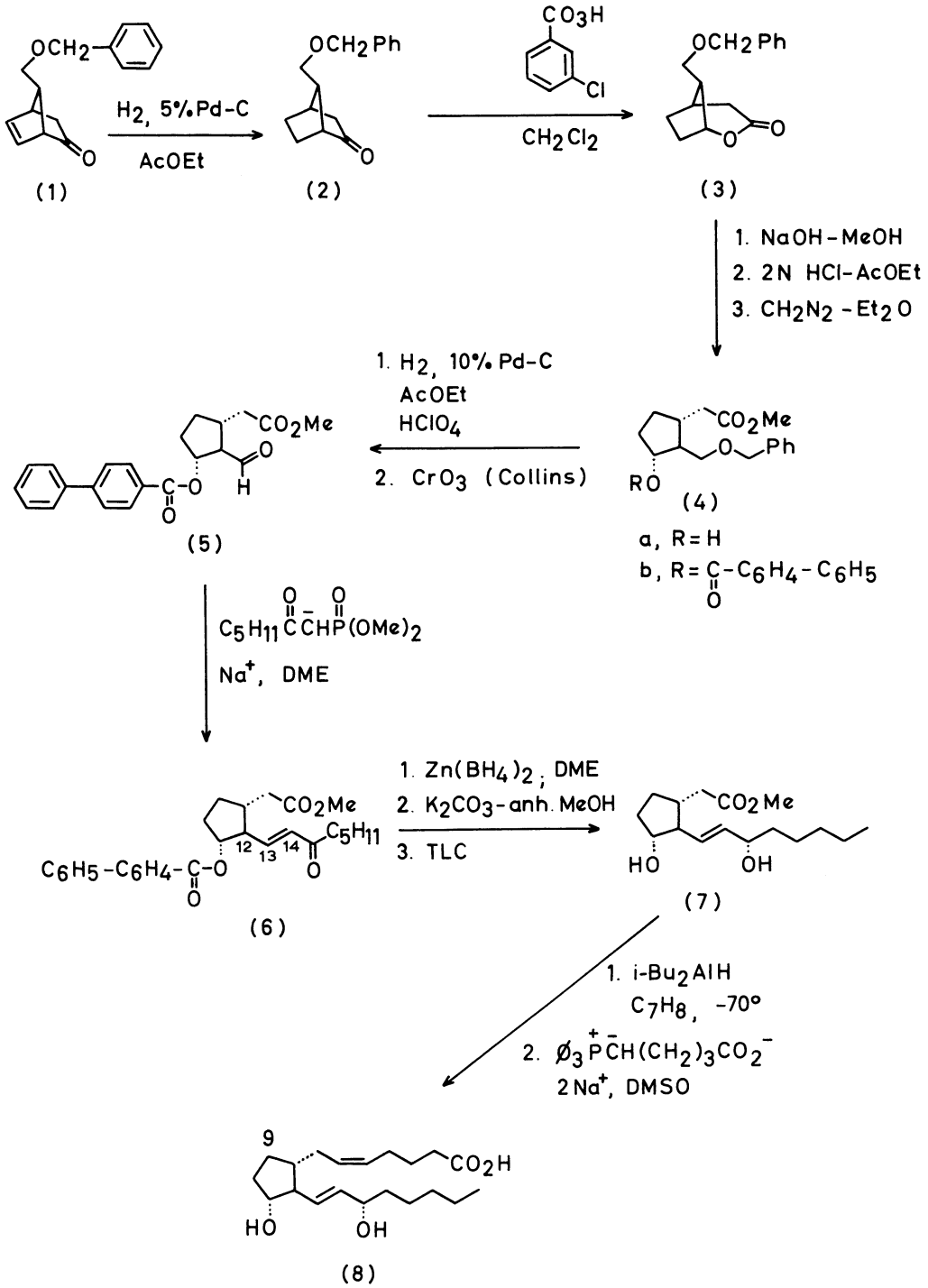
The unsaturated ketone (1) is reduced catalytically into the saturated keto-derivative (2). Further transformations allow to open the bicyclic intermediate (2) into the tri-substituted cyclopentane derivative (4). This is then converted by classical methods into the 9-desoxy-prostaglandin(8).

Previously, we have described the synthesis of 11-desoxy[2] and 9,11-bis-desoxy[3] prostaglandins. The recent publication mentioning the preparation of a 9-desoxy-dihydro-prostaglandin[4] prompts us to report our work on the stereospecific synthesis of the 9-desoxy-prostaglandin (8).

Catalytic hydrogenation of the bicyclic ketone (1)[5] with 5 % Pd-C affords the saturated ketone (2) [ν_{max} 1735 cm^{-1} ; δ 3.38 (CH_2-O-), 4.5 (CH_2-Ph), 7.3 p.p.m. (aromatic H][6], (70 %). Baeyer-Villiger oxidation of (2) with m-chloroperbenzoic acid provides the corresponding lactone (3) (95 %). Opening of the ε-lactone (3)with methanolic sodium hydroxide, followed by careful neutralization and esterification with diazomethane, give the alcohol-ester (4a) [ν_{max} 3400 and 1725 cm^{-1} ; δ 3.65 p.p.m. (CO_2Me)], in 75 % overall yield from (3). Esterification of the hydroxyl of (4a) with p-phenyl-benzoyl chloride furnishes the corresponding di-ester (4b) (95 %) [ν_{max} 1725, 1715, and 1610 cm^{-1}].

Hydrolysis of the benzyl ether group of (4b) with 10 % Pd-C, in an hydrogen atmosphere in ethyl acetate solution in the presence of a catalytic amount of $HClO_4$, affords the corresponding alcohol (95 %), which is oxidised with Collins' reagent[7] to provide the aldehyde (5). This is immediately alkylated with the sodium salt of dimethyl 2-oxoheptylphosphonate to provide the enone di-ester (6) with its u.v. at λ_{max} 274 nm (ε 24,000) and its typical n.m.r. signals at δ 3.63 (CO_2Me), 7.8 (d, $J_{13,14}$ 16 Hz), 6.8 and 6.9 p.p.m. (dd, $J_{12,13}$ 7 Hz, $J_{14,13}$ 16 Hz)(70 %). Zinc borohydride reduction of the carbonyl group at C-15 yields a mixture of isomeric-alcohols 15(R)- and 15(S),


OCH2Ph
H2, 5%Pd-C
AcOEt
(1)
(2)
CO3H
Cl
CH2Cl2
(3)
1. NaOH-MeOH
2. 2N HCl-AcOEt
3. CH2N2 -Et2O
1. H2, 10% Pd-C
AcOEt
HClO4
2. CrO3 (Collins)
CO2Me
RO
(4)
a, R=H
b, R=C-C6H4-C6H5
(5)
C5H11C(=O)CHP(OMe)2
Na+, DME
1. Zn(BH4)2; DME
2. K2CO3-anh. MeOH
3. TLC
C6H5-C6H4-C-O
12 13 14
C5H11
(6)
HO
OH
(7)
1. i-Bu2AlH
C7H8, -70°
2. Ø3P+CH(CH2)3CO2-
2Na+, DMSO
9
CO2H
(8)

separated by preparative t.l.c., after selective hydrolysis of the biphenylbenzoate with anydrous methanolic potassium carbonate.

The desired 11,15-diol (7) is then submitted to the usual sequence of reactions.[3,5] Reduction of the ester group of (7) with di-isobutylaluminium hydride, provides the corresponding aldehyde,[3,8] which is immediately reacted with 5-triphenylphosphoniopentanoic acid di-sodium salt[5], to afford the (±)-9-desoxy-prostaglandin (8).

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