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SYNTHESIS OF DIFLUOROMETHYLENE-PROSTAGLANDINS

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Although a number of modified prostaglandins have been described, so far no mention has been made of the use of dihalocarbene chemistry in the prostanoid field. Pursuring our effort aimed at the preparation of novel prostaglandins,[2] we wish to report the stereospecific synthesis of five difluoromethylene-prostaglandins.

Treatment of the acetoxy-aldehyde (1)[3] with methanolic potassium carbonate afforded exclusively the conjugated aldehyde (2) [λ_{max} 230 nm (log ε 3.77); ν_{max} 1780, 1680, 1620 cm^{-1}][4]. Alkylation of (2) with the sodium salt of dimethyl-2-oxo-heptylphosphonate[3] provided the crystalline dienone (3) [λ_{max} 274 nm (log ε 4.25); ν_{max} 1770, 1690 cm^{-1}]. Addition of difluorocarbene, generated by pyrolysis of the sodium salt of chlorodifluoroacetic acid,[5] to (3) afforded a mixture of the α-difluoromethylene derivative (4) (26%) [λ_{max} 238 nm (log ε 4.17); ν_{max} 1760, 1660, 1640 cm^{-1}] and the isomeric β-adduct (5) (38%) [λ_{max} 238 nm (log ε 4.17); ν_{max} 1760, 1690, 1625 cm^{-1}], separated by preparative TLC. The β-configuration of the difluoromethylene bridge in the tricyclic compound (5) is supported by the nuclear magnetic resonance of the 8β-proton which appears as a doublet (J 8 Hz) at 3.33 ppm, attributed to long range coupling with a fluorine of the difluorocyclopropyl grouping. This coupling is absent in the α-difluorocyclopropyl isomer (4).

The noteworthy feature of this reaction is that although regiospecific, the difluorocarbene addition to (3) is not stereoselective, thus leading to both cycloadducts (4) and (5). This gave access to several new prostaglandins, namely those exhibiting the "natural" trans stereochemistry at C-8 and C-12, their isomeric cis counterparts, as well as a "retro" prostaglandin presenting the 8β,12α-configuration.

The synthetic intermediates (4) and (5) were then submitted to a sequence of reactions similar to that described previously[3] (see Chart), yielding (6a) and (8a) respectively.

The 15α-tetrahydropyranyl ether derivative (6a) [oil; ν_{max} 3350, 1710 cm^{-1}] was then briefly exposed to aqueous acetic acid, thus affording dl-11α,12α-difluoromethylene 11-

desoxy-$PGF_{2\alpha}$ (6b) [colorless oil; ν_{max} 3350, 1710, 960 cm^{-1}; nmr 0.89 (Me), 4.26 (CO_2H,OH), 5.5 ppm (4 vinylic H)], while Jones' oxidation[6] of (6a) followed by brief exposure to acid gave dl-11α,12α-difluoromethylene 11-desoxy-PGE_2 (7) [colorless oil; ν_{max} 3350, 1745, 1710 cm^{-1}; nmr 0.89 (Me), 4.64 (CO_2H, OH), 5.5 ppm (m, 4 vinylic H)].

In order to get a good separation of the desired 15(S)-compound (8a) from its 15 (R)-isomer by TLC, the acid function at C-1 was esterified with diazomethane. Mild acid treatment of the 15α-ether derivative (8a) [ν_{max} 3400, 1730 cm^{-1}; nmr 0.89 (Me), 2.05 (CO_2Me), 5.4 ppm (m, 4 vinylic H)] furnished dl-11β,12β-difluoromethylene 12-iso-11-desoxy-$PGF_{2\alpha}$ methyl ester (8b) [colorless liquid; ν_{max} 3350, 1710 cm^{-1}; nmr 0.89 (Me), 5.5 ppm (4 vinylic H)]. Oxidation of (8a) followed by acid hydrolysis of (9a) yielded dl-11β,12β-difluoromethylene 12-iso-11-desoxy-PGE_2 methyl ester (9b) [colorless oil; ν_{max} 3350, 1745, 1720 cm^{-1}; nmr 0.89 (Me), 2.05 (CO_2Me), 5.57 ppm (4 vinylic H)]. Additionally, treatment of (9b) with 2 equiv of sodium methoxide in methanol solution for 10 min at room temperature afforded the slightly more polar dl-11β,12β-difluoromethylene 8β,12α-(retro)-11-desoxy-PGE_2 methyl ester (10a) [oil; ν_{max} 3350, 1745, 1730 cm^{-1}; nmr 0.88 (Me), 2.05 (CO_2Me), 5.33 ppm (4 vinylic H)]. Avoiding the esterification step, the intermediate (5) was also converted, in low yield, into the free acid (10b) [colorless oil; ν_{max} 3350, 1740, 1710 cm^{-1}; nmr 0.87 (Me), 4.33 (CO_2H,OH) 5.33 ppm (vinylic H)], thus completing the total synthesis of these novel bicyclic prostaglandins.

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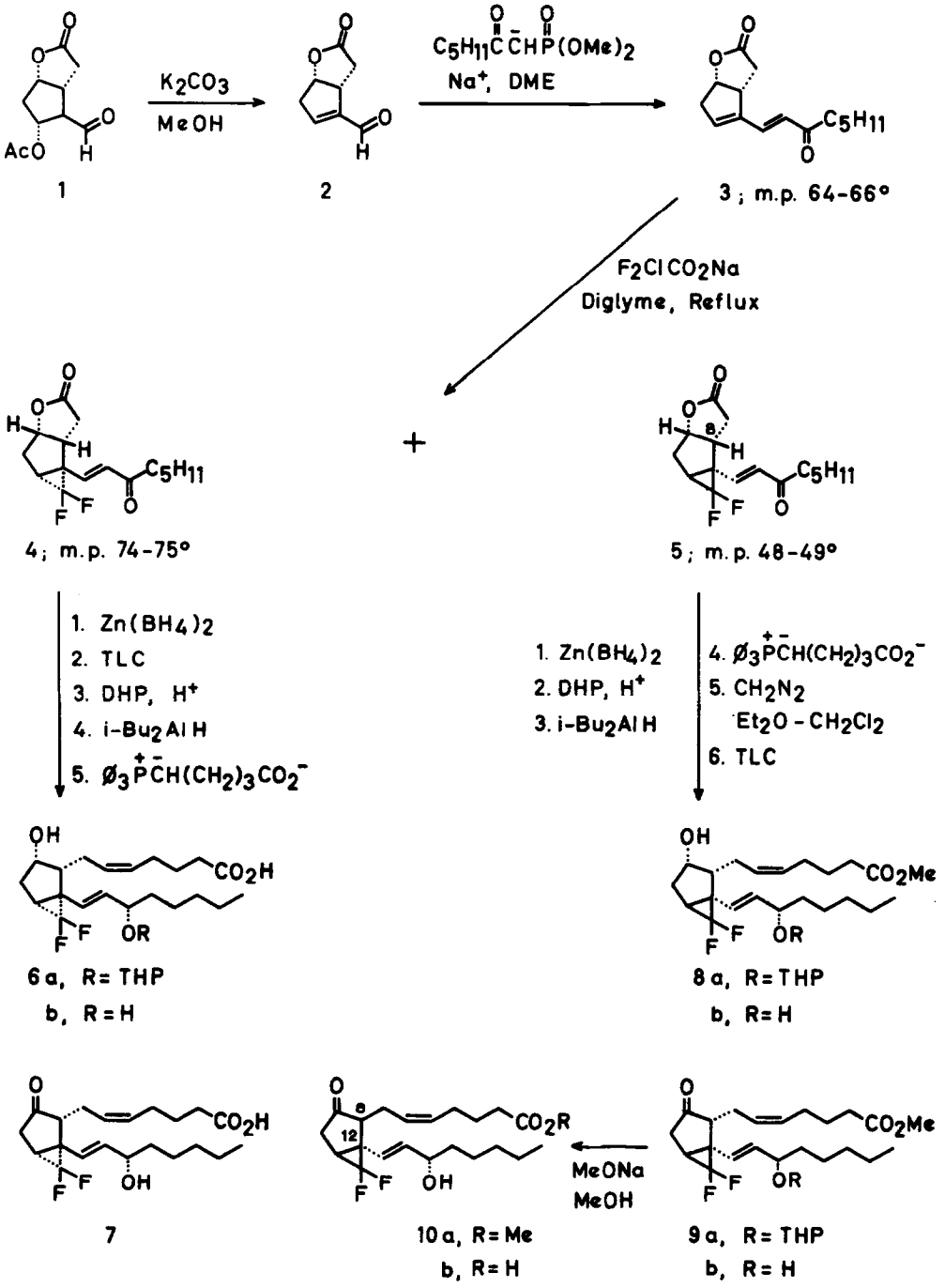
K2CO3
MeOH
C5H11C(=O)CHP(=O)(OMe)2
Na+, DME
1
2
3 ; m.p. 64-66°
F2ClCO2Na
Diglyme, Reflux
4 ; m.p. 74-75°
5 ; m.p. 48-49°
1. Zn(BH4)2
2. TLC
3. DHP, H+
4. i-Bu2AlH
5. Ø3P+CH(CH2)3CO2-
1. Zn(BH4)2
2. DHP, H+
3. i-Bu2AlH
4. Ø3P+CH(CH2)3CO2-
5. CH2N2
Et2O - CH2Cl2
6. TLC
6a, R=THP
b, R=H
8a, R=THP
b, R=H
7
10a, R=Me
b, R=H
MeONa
MeOH
9a, R=THP
b, R=H