APPLICATION OF CARBONYL UMPOLUNG TO PROSTAGLANDIN SYNTHESIS II[1]. SYNTHESIS OF THE INTERMEDIATES OF (±)-11-DEOXYPROSTAGLANDINS $F_{1\alpha}$ AND $F_{2\alpha}$, AND PROSTAGLANDIN $F_{2\alpha}$

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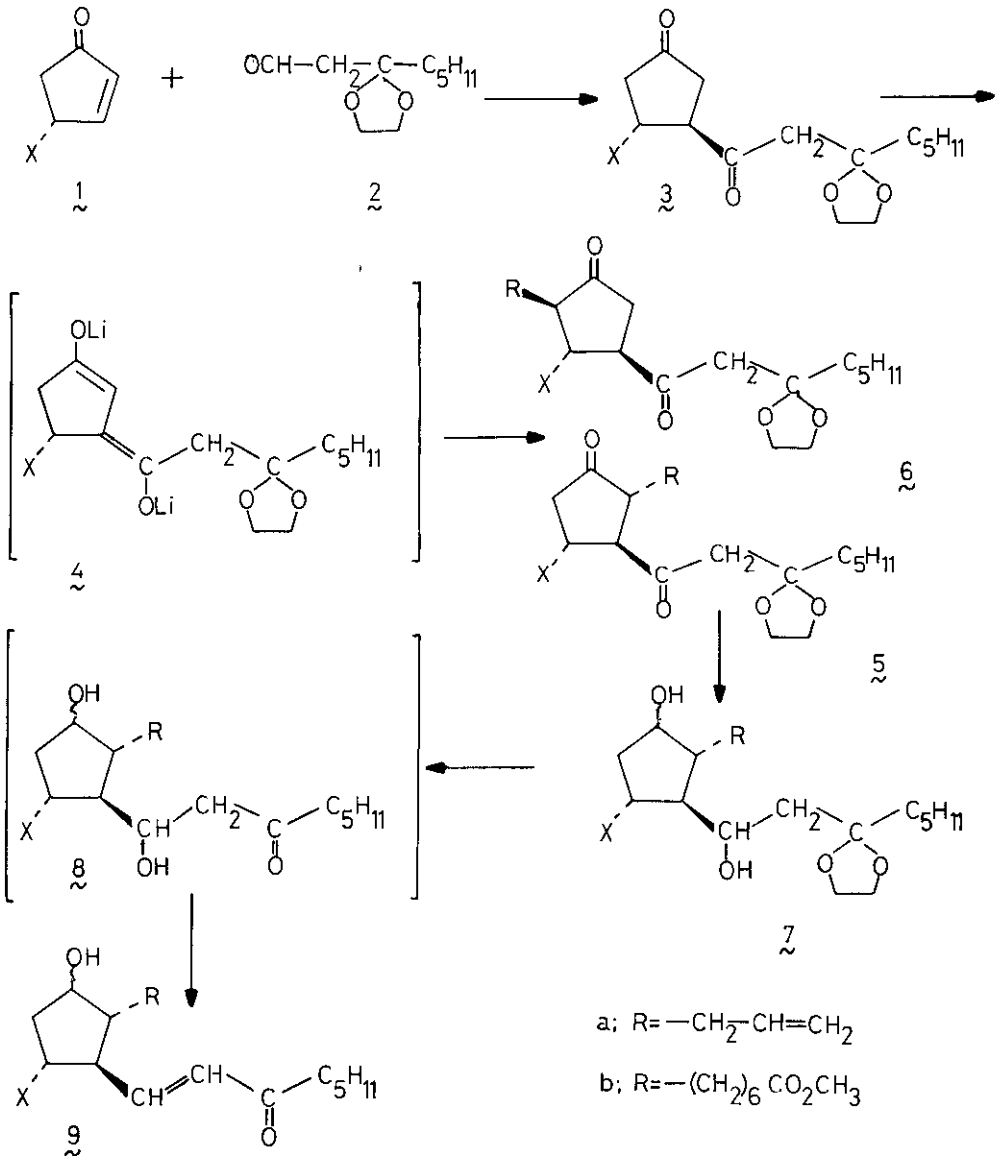
Abstract - The intermediates of prostaglandins have been synthesized from 2-cyclopenten-1-one derivatives by a novel thiazolium ion-catalysed acylation.

We have previously described the application of the conjugate addition of acyl carbanion equivalent to α,β-unsaturated ester for the synthesis of 11-deoxy prostaglandin intermediates[1]. The result was encouraging enough for exploring the possibility of employing this reaction for the synthesis of prostaglandins too.

Now we wish to report a new synthesis of prostaglandin intermediates in which the nucleophilic addition of acyl carbanion equivalent to 2-cyclopenten-1-one derivative plays a central role.

Conjugate addition reaction of aldehyde (2)[2] [b.p. 96°/10 mm; δ 0.9 (3H, t, J=7 Hz), 2.6 (2H, d, J=3 Hz), 4.0 (4H, s), 9.6 (1H, t, J=3 Hz)], easily obtained from methyl 3-oxo-octanoate[3] via the corresponding ethylene ketal[4] with diisobutylaluminium hydride (toluene, -70°), to 2-cyclopentenone (1; X=H) catalyzed by 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride[5] (0.025 equiv) (70°, 24 hr, 0.1 equiv triethylamine) yielded the cyclopentanone derivative (3; X=H) [30 %; b.p. 155°/0.1 mm; ν_{max} 1740, 1710, δ 0.9 (3H, t, J=7 Hz), 2.85 (2H, d, J=3 Hz), 3.95 (4H, s)][6].

Treatment of this cyclopentanone with fresly prepared lithium diethylamide[7] in benzene - hexamethylphosporic triamide (6 equiv, 20°, 2 hr) led to the intermediate conjugated dianion (4; X=H)[8] which underwent clean α-alkylation with allyl bromide (3 equiv, 20°, 3 hr) to afford a mixture of 5a (X=H) [35 %, ν_{max}



1735, 1710, δ 0.9 (3H, t, J=7 Hz), 2.9 (2H, s), 3.95 (4H, s), 4.9-6 (3H, m) and (6a; X=H) [10 %; ν_{max} 1745, 1710, δ 0.85 (3H, t, J=7 Hz), 2.85 (2H, s), 3.85 (4H, s), 5.05-5.8 (3H, m)].

This mixture was separated by chromatography and the major product (5a; X=H) was reduced by sodium borohydride (3 equiv, methanol) to give the alcohol (7a; X=H) as a mixture of diastereomers. Acid treatment of the latter to regenerate the carbonyl group yielded the hydroxy ketone (8a; X=H) which on

standing in acidic solution (p-TSA, acetone 20°C, 0.5 hr) afforded, after chromatography the intermediate of (±)-11-deoxy-prostaglandin $F_{2\alpha}$ (9a; X=H) [40 %; ν_{max} 3420, 1670, 1610, δ 0.85 (3H, t, J= 7 Hz), 4.85-5.6 (3H, m), 6.1 (1H, m), 6.7 (1H, m)]. The intermediate of (±)-11-deoxy-prostaglandin $F_{1\alpha}$ (9b; X=H) was also prepared by this procedure. Alkylation of the dianon (4; X=H) with methyl 7-bromo-heptanoate (3 equiv, 20°, 4 hr) and reduction of the resulting cyclopentanone derivative (5b; X=H) [25 %; ν_{max} 1735, 1710, δ 0.9 (3H, t, J=7 Hz), 2.7 (2H, m), 3.6 (3H, s), 3.95 (4H, m)] with sodium borohydride (4 equiv, methanol) followed by acid promoted hydrolysis and elimination afforded, after chromatography (±)-11-deoxy-15-dehydroprostaglandin $F_{1\alpha}$ (9b; X=H)[9] [25 % (based on 5b used); ν_{max} 3340, 1735, 1670, 1610, 0.9 (3H, t, J=7 Hz), 1.5-2.1 (7H, m), 3.6 (3H, s), 4.1 (1H, m), 4.3 (1H, m), 6.1 (1H, m), 6.4 (1H, m)].

Finally the application of this methodology to the intermediate of (±)-prostaglandin $F_{2\alpha}$ (9a; X=OH) was carried out. Addition of the aldehyde (2) to the cyclopentenone (1:X=O-t-Bu)[10] was achieved using the above chiazolium salt (80°, 36 hr, 1 equiv Et_3N) to give the cyclopentanone (3:X=O-t-Bu) [42 %, ν_{max} 1730, 1700, δ 0.9 (3H, t, J=7 Hz), 2.9 (2H, m), 3.9 (4H, m), 4.30 (1H, q, J=6 Hz) which was regiospecifically alkylated with allyl bromide via the corresponding lithio-derivative (4a:X=O-t-Bu) (6 equiv lithium diethylamide, benzene-hexamethylphosporic triamide, 20°, 4 hr). Sequential treatment of the product (5a:X=O-t-Bu). [35 %; ν_{max} 1735, 1700, 1635, δ 0.9 (3H, t, J=7 Hz), 2.9 (2H, m), 3.9 (4H, m), 4.3 (1H, t, J=6 Hz), 4.6-5.9 (3H, m)], with sodium borohydride (3 equiv, ethanol) to reduce the carbonyl groups and p-toluene-sulphonic acid to regenerate the carbonyl group and eliminate the elements of water provided the enone (9a:X=O-t-Bu) [40 %; ν_{max} 3400, 1670, 1615, δ 0.9 (3H, t, J=7 Hz), 4.85-5.6 (3H, m), 6.15 (1H, m), 6.8 (1H, m)].

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References and Notes

1. For part I see, L. Novák, G. Baán, J. Marosfalvi and Cs. Szántay, Tetrahedron Letters, 1978, 487.
2. All new compounds described herein were obtained as chromatographically homogeneous sample, and had mass spectral data and elemental analyses consistent with tehir assigned structure.
3. L. Weiler, J. Amer. Chem. Soc., 93, 6702 (1970).
4. This compound had b.p. 96°/0.2 mm, and exhibited the following spectral data, NMR; 0.9 (3H, t, J27 Hz), 2.5 (2H, d, J=3 Hz), 3.6 (3H, s), 4.0 (4H, s).
5. H. Stetter, Angew. Chem., 88, 695 (1976) and references cited therein.
   B.-Th. Grobel and D. Seebach, Synthesis, 1977, 357.
   H. Stetter and H. Kuhlmann, Chem. Ber., 109, 2890 (1976).
   H. Stetter and G. Dämbkes, Synthesis, 1977, 403.
6. Alternatively, 3 (X=H) could be obtained by reacting 2 with 1 (X=H) in the presence of KCN (1 equiv, 25°, 48 hr, DMF, yield 25 %).
7. T. Cuvigny, J. F. Le Borgne, M. Larcheveque and H. Normant, Synthesis, 1976, 237.
8. This compound exhibited the following NMR data: δ 0.9 (3H, t, J=7 Hz), 1.15-1.55 (8H, m), 2-2.15 (4H, m), 2.85 (2H, s), 3.80 (4H, s), 7.05 (1H, s). Our attempts to prepare the corresponding trimethylsilyl ether have not yet been succesful.
9. M. P. L. Caton, E. C. J. Coffee and G. L. Watkins, Tetrahedron Letters, 1972, 773.
10. This compound was prepared according to the method reported by Haubenstock et al, and Stork and Isobe;
    a) H. Haubenstock, P. G. Mennitt and P. E. Butler, J. Org. Chem., 35, 3208 (1970).
    b) G. Stork and M. Isobe, J. Amer. Chem. Soc., 97, 6260 (1975).
    Spectral data of 1 (X=O-t-Bu) are as follows: δ 1.2 (9H, s), 2.05 (1H, dd), 2.55 (1H, dd), 4.72 (1H, m), 6.0 (1H, dd), 7.3 (1H, dd).

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