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APPLICATION OF CARBONYL UMPOLUNG TO PROSTAGLANDIN SYNTHESIS I. SYNTHESIS OF 11-DEOXY PROSTAGLANDIN INTERMEDIATES.

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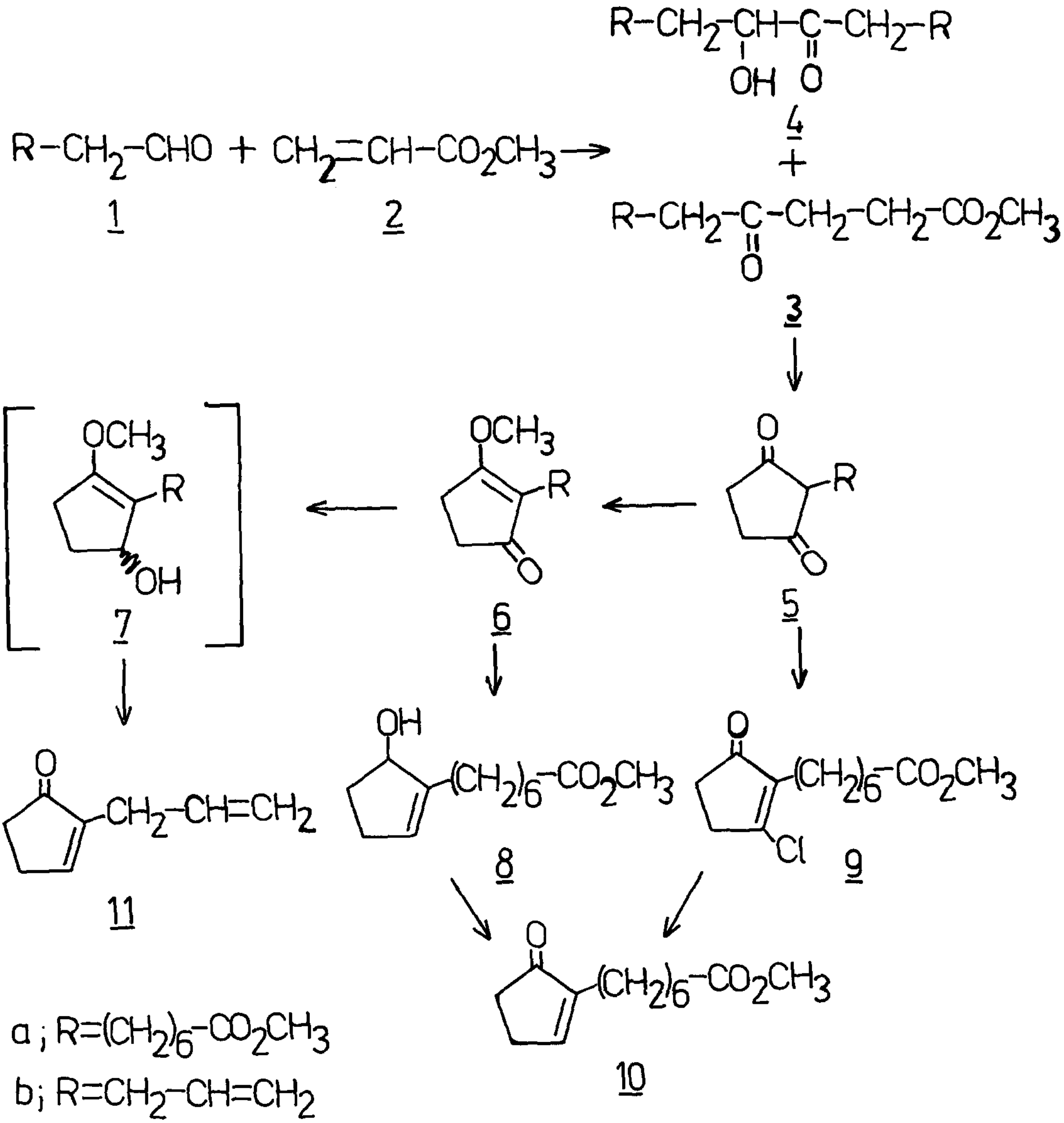
A great deal of interest has been generated in the conjugate addition of acyl carbanion equivalent in recent years$^{1-5)}$. The reaction is of particular interest in connection with the synthesis of jasmonoids, rethrolonoids, and prostanoids, because it allows one to prepare 1,4-dicarbonyl compounds, much sought as precursors of these natural products, from the easily accessible aldehydes and α,β-unsaturated carbonyl systems.

This preliminary report describes the synthesis of 11-deoxy prostaglandin synthons involving the addition of acyl carbanion equivalent to α,β-unsaturated ester which may provide a convenient method to prepare key intermediates for the synthesis of prostanoids.

Nucleophilic addition reaction of methyl 7-formyl-octanoate (<u>**1a**</u>), easily obtained from oleic acid$^{6)}$, to methyl acrylate (<u>**2**</u>) (2 equiv) catalysed by 3-benzyl-5-(2-hydroxyethyl)-4-methyl-thiazolium chloride (0,1 equiv) in boiling dioxane (24 hr) yielded a mixture of ketoester (<u>**3a**</u>)$^{7)}$ [b.p. 143-146°/0,15 mm; δ 2,31 (2H, t, J=7 Hz), 2,41 (2H, t, J=7 Hz), 2,63 (2H, t, J=5 Hz), 2,67 (2H, t, J=5 Hz), 3,66 (3H, s)] and α-ketol (<u>**4a**</u>) [b.p. 190-195°/0,15 mm; δ 3,66 (6H, s), 4,15 (1H, m)] (ratio 1:2; 95 %). This mixture was separated by fractional distillation and the hydroxyketone cleaved by lead tetraacetate to revert to aldehyde (1a), in 85 % yield. The ketoester (3a) was cyclized in boiling toluene (0,5 hr) using sodium ethoxide (2 equiv) to form 1,3-cyclopentanedion (5a) [80 %; m.p. 93-95°; ν_{max} 1740; δ 2-2,4 (4H, m), 2,51 (4H, s), 3,65 (3H, s)], which was directly converted into the corresponding enol ether (6a) (H_2SO_4, CH_3OH) [86 %; ν_{max} 1625, 1685, 1740; δ 2,12 (2H, t, J=7 Hz), 2,29 (2H, t, J=7 Hz) 2,32-2,53 (2H, m), 2,53-2,75 (2H, m), 3,65 (3H, s), 3,92 (3H, s)]. Reduction with sodium borohydride in methanol at 40° (2 hr) afforded the alcohol (8) [67 %, ν_{max} 3380, 1740, δ 2-2,4 (6H, m), 3,64 (3H, s), 4,64 (1H, m), 5,53 (1H, m), which upon oxidation with activated manganese dioxide in petroleum ether gave the cylopentenone (10)$^{8)}$, in 80 % yield.

In an alternate approach for the conversion of dion, 5a was treated with PCl_3 in boiling chloroform, and the chloroenone (9) [70 %; δ 2,28 (2H, t, J=7 Hz), 2,3 (2H, t, J=7 Hz), 2,44-2,6 (2H, m), 2,72-2,88 (2H, m), 3,66 (3H, s)] was dehalogenated by silver-zinc couple in methanol to give 10$^{8)}$, in 70 % yield.

In an analogous series of reactions 11 was also prepared. Thiazolium ion-catalysed reaction of aldehyde (1b)$^{9)}$ with methyl acrylate (2 equiv) at 80° (8 hr) gave a mixture of ketoester (3b) [b.p. 56-58°/0,05 mm; ν_{max} 1640, 1720, 1745; δ 2,25-2,85 (8H, m), 3,7 (3H, s), 4,9-5,15 (2H, m), 5,55-6,05 (1H, m)] and hydroxyketone (4b) [b.p. 63°/0,1 mm; δ 4,1 (1H, m), 4,8-6,15 (6H, m)], (ratio 3:2; 50 %). This mixture was separated by base-catalysed hydrolisis of the ketoester with aqueous NaOH to the corresponding ketoacid. Reesterification of the latter afforded pure 3b, which was cyclized in boiling toluene (0,5 hr) using sodium t-butoxide (2 equiv) to form crystalline dion (5b) (recrystallized from ethyl acetate) [m.p. 155°; δ 2,2 (4H, s), 2,45-2,7 (2H, m), 4,5-5,9 (3H, m)].



The corresponding enol ether (6b) [140°/16 mm; δ 2,15-2,55 (4H, m), 2,6-2,9 (2H, m), 3,95 (3H, s), 4,64-6,1 (3H, m)] was formed with an excess of diazomethane in ether and reduced with diisobutylaluminium hydride in dry THF at -20°. The resulting alcohol (7b) was without purification hydrolyzed an rearranged *in situ* with dilute acid to enone (11)[10] [b.p. 78-80°/13 mm; ν_{max} 1705, 1700, 1640; δ 2,2-2,6 (4H, m), 2,7-3 (2H, m), 4,9-6,9 (3H, m), 7,25 (1H, m)].

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