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THE SYNTHESIS OF 13,14-DIHYDRO-13,14-METHYLENE-PGF$_{2\alpha}$ AND PGE$_2$[1]

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The pronounced biological activity of 13,14-dihydro-PGF$_{2\alpha}$[2] arose our interest in the synthesis of the corresponding cyclopropyl compounds, the 13,14-dihydro-13,14-methylene-prostaglandins.

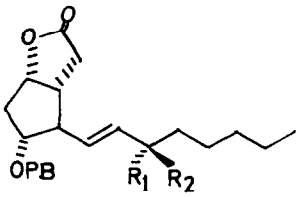
The reaction of the Corey-intermediate 1a[3] with dimethyloxosulfoniummethylid[4] resulted in the elimination of p-phenylbenzoic acid and formation of dienones, whereas 1b failed to react under a variety of conditions of the Simmons-Smith reaction[5].

Thus we used the new Pd(OAc)$_2$/CH$_2$N$_2$ reagent[6a] which adds cis to α,ß-unsaturated carbonyl systems[6b]. On treatment of 1a with excess CH$_2$N$_2$ in the presence of catalytic amounts of Pd(OAc)$_2$ we obtained a 92% yield of a 2:1-mixture of two cyclopropyl ketones (2a and 3a) which could be readily separated (SiO$_2$ column) to give pure 2a [mp 112-114°, $[\alpha]_D$ + 2.3° ($CHCl_3$)] and 3a [mp 105°, $[\alpha]_D$ -211° ($CHCl_3$)]. Transesterification (K_2CO_3-MeOH) of 2a and 3a yielded the alcohols (2d and 3d).

Reduction of 2a ($NaBH_4$ - 1-propanol - THF, 0°) provided two epimeric alcohols 2b (δ = 3.08 ppm, q, J = 6.5 Hz, 15-H) and 2c (δ = 2.96 ppm, q, J = 7 Hz, 15-H)[9] whereas 3a yielded 3b (δ = 2.96 ppm, q, J = 7 Hz, 15-H) and 3c (δ = 3.05 ppm, q, J = 6.5 Hz, 15-H).

The (15S)-configuration was established for the less polar reduction products (2b and 3b) by reaction of 1b[3] with a large excess of CH$_2$N$_2$ in the presence of Pd(OAc)$_2$ during 35 min to give a 20% yield of a mixture of epimeric 13,14-methylene alcohols which were identical with 2b and 3b. As a side product the ether 1c (δ = 3.15, s, OCH_3; 3.48, q, J = 6 Hz, 15-H; 5.47 ppm, m, 13- and 14-H) was isolated in ca. 20% yield. (Scheme I)

Scheme I

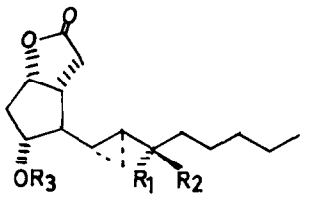


PB = p-phenylbenzoyl

1a R_1, R_2 = O

1b R_1 = OH; R_2 = H

1c R_1 = OCH_3, R_2 = H



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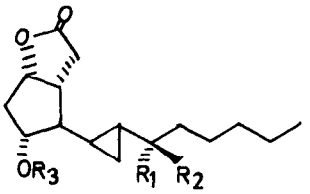

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a) R_1, R_2 = O; R_3 = PB

b) R_1 = OH; R_2 = H; R_3 = PB

c) R_1 = H; R_2 = OH; R_3 = PB

d) R_1, R_2 = O, R_3 = H

The CD spectra (dioxane) of 2d (λ_{max} = 282 nm, $\Delta\varepsilon$ = +1.16) and 3d (λ_{max} = 282 nm, $\Delta\varepsilon$ = -1.11, mirror image of the 2d-spectrum) combined with the nmr data (see below) permit the assignment of the (13R,14S)-configuration to 2d and the (13S,14R)-configuration to 3d. The assignment of 2d is based on the results of Pelissier et al.[7] and Tocanne[8] who calculated the preferred conformation of the carbonyl-group in 2-alkyl-cyclopropyl ketones and assigned their absolute configuration on the basis of their CD and nmr spectra.

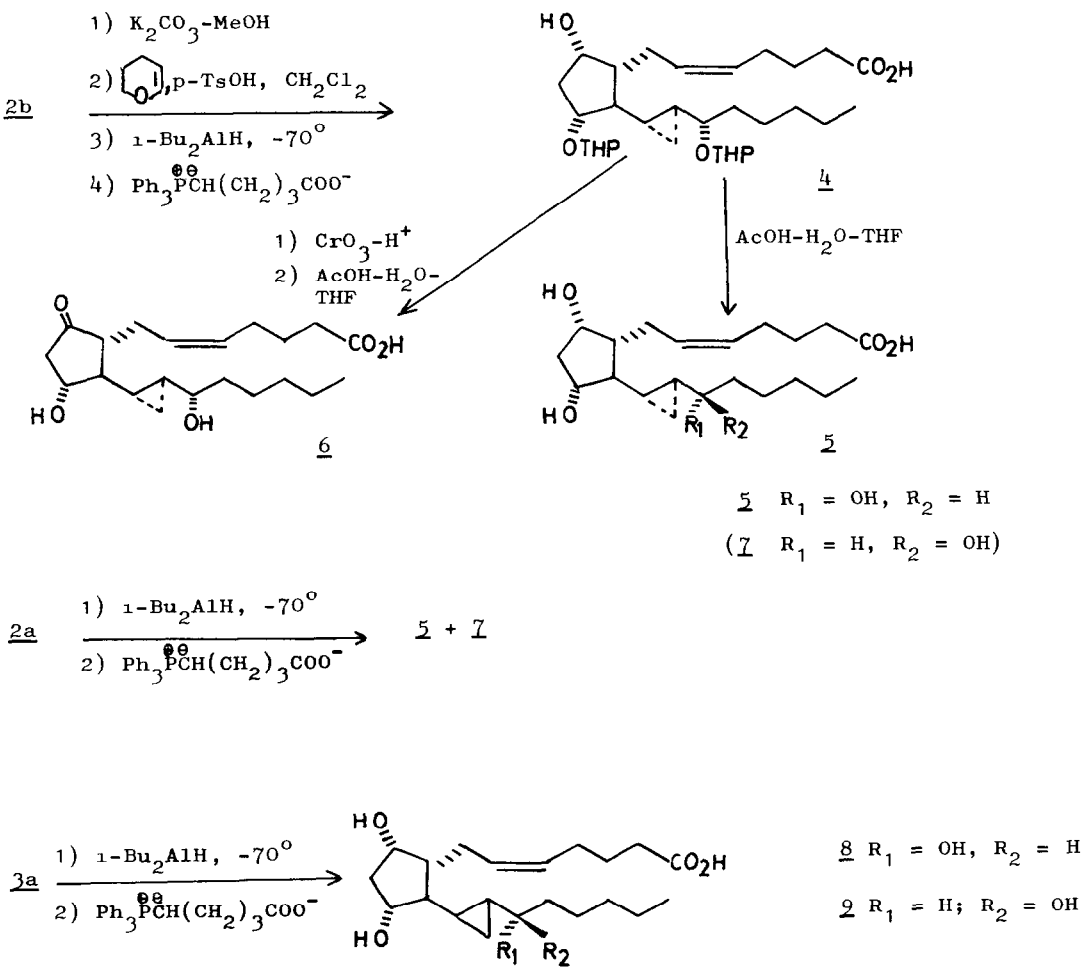
When 2b was submitted to the sequence of reactions as described in scheme II[3], the $PGF_{2\alpha}$-analogue 5 as well as the PGE_2-analogue 6 were obtained.

Reduction of 2a with diisobutylaluminium hydride and Wittig-reaction (see scheme II) afforded an easily separable mixture of 5 (δ = 3.09 ppm, m, W 1/2 = 14 Hz, 15-H) and 7 (δ = 2.96 ppm, q, J = 7 Hz, 15-H). Since 5 has the (15S)-configuration the (15R)-configuration was assigned to the less polar derivative 7 The tlc data thus agree with the reported slightly less polar nature of the (15R)-epimer[10].

3a gave analogously 8 (δ = 2.86 ppm, q, J = 7 Hz, 15-H) and 9 (δ = 3.06 ppm, q, J = 6.5 Hz, 15-H).

Since the 15-H in 2c, 3b, 7 and 8 in its weighted average is slightly more above the anisotropic cyclopropane ring[11] than the 15-H in 2b, 3c, 5 and 9 the observed chemical shifts support the configurational assignment by CD and tlc data. The analogous preparation of 10,11-methylene-PGA_2-methylester[12] will be described elsewhere[13].

Scheme II



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