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SYNTHESIS OF 8-AZAPROSTAGLANDIN E_1 AND E_2

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In searching for prostaglandins with more specific biological activities and free of undesirable side-effects, we chose to synthesize prostaglandin analogs containing a nitrogen atom in the five membered ring A recent publication[1] concerning the synthesis of 11-deoxy-8-azaprostaglandin E_1 (6b) prompts us to report an alternative synthetic route[2] leading to 6b and 11-deoxy-8-aza-prostaglandin E_2 (9b).

The ester function of methyl D,L-pyroglutamate 1 was selectively reduced with lithium borohydride in THF affording carbinol 2a [95%; m.p. 65-67°; ir 3640, 3300, 1670 cm^{-1}]. Acetylation of the hydroxyl function - to prevent O-alkylation in the next step of the synthesis - provided 2b [95%; ir 3420, 3200, 1730, 1680 cm^{-1}; nmr 2.10 (s, CH_3CO)]. Reaction of the sodium salt of 2b with methyl 7-bromoheptanoate to give 3a, followed by subsequent methanolysis of the protecting acetate function, furnished the primary alcohol 3b [40-45%; ir 3650, 3400, 1720, 1660 cm^{-1}; nmr 3.68 (s, OCH_3)]. Oxidation of the alcohol with DMSO-DCC[3] gave the unstable aldehyde 4, which was not purified but directly treated with the sodio derivative of dimethyl 2-oxo-heptylphosphonate[4] in THF.

The enone 5 [60%; nmr 6.60 (q, $J_{12,13}$= 8, $J_{13,14}$= 16, 13-CH), 6.22 (d, $J_{13,14}$= 16, 14-CH), 3.69 (s, OCH_3), 0.94 (t, $J_{19,20}$= 6; 20-CH_3)] thus obtained was reduced with zinc borohydride[4] in dimethoxyethane and the resulting mixture of C_{15}-epimeric alcohols was separated by column chromatography over silica gel into a more polar [6a; ir 3650, 3450, 1720, 1660 cm^{-1}; nmr 5.72 (q, $J_{13,14}$ = 15.5, $J_{14,15}$= 5.3, 14-CH), 5.52 (q, $J_{12,13}$= 7.5, $J_{13,14}$= 15.5, 13-CH),

3.66 (s, OCH_3), 0.91 (t, $J_{19,20}$= 6, 20-CH_3); m/e 353 (M), 335 (M-H_2O), 322 (M-OCH_3), 252 (M-$C_5H_{11}CHOH$), 226 (M-$C_5H_{11}CH(OH)CH=CH$)] and a less polar isomer (7a; spectra very similar to 6a).

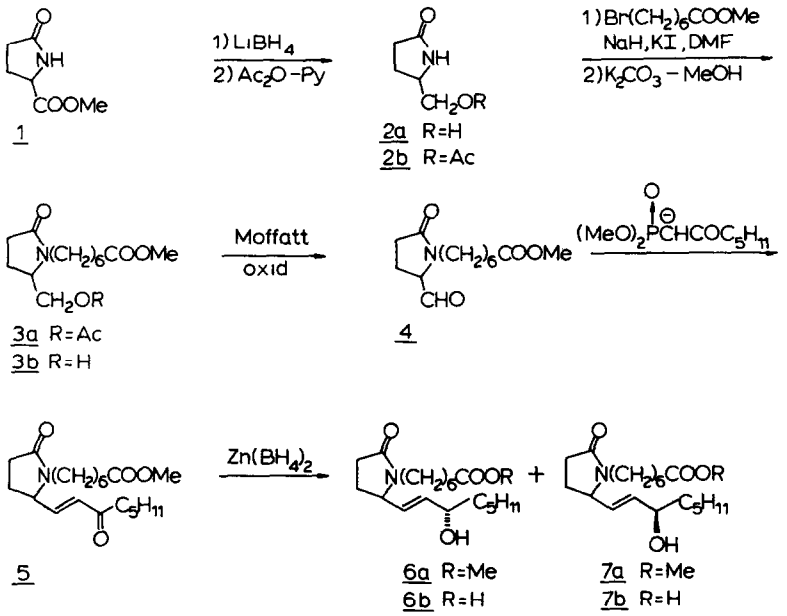
The "natural" relative configuration at C_{15} was tentatively assigned to the more polar isomer by analogy with the chromatographic behaviour of similar derivatives of the natural prostaglandins.

Saponification of themethyl ester with one equivalent of potassium hydroxide in aqueous ethanol afforded PGE_1 analog 6b.

The corresponding prostaglandin E_2 analog was prepared in an analogous way. Alkylation of 2b with methyl 7-bromo-5-heptynoate, followed by methanolysis of the acetate and partial catalytic hydrogenation of the triple bond led to the formation of the alcohol 8 [55-60% from 2b; ir 3450, 1725, 1670 cm^{-1}; nmr 5,2 - 5,8 (m, 5-CH, 6-CH)[5], 3.68 (s, OCH_3); m/e 255 (M), 224 (M-CH_2OH), 192 (M-CH_2OH-CH_3OH)]. Moffatt oxidation of 8, followed by Horner reaction of the obtained crude aldehyde with dimethyl 2-oxoheptylphosphonate and subsequent reduction of the resulting enone [50-60%; nmr 6.58 (q, $J_{12,13}$= 8, $J_{13,14}$= 16, 13-CH), 6.14 (d, $J_{13,14}$= 16, 14-CH), 5,2 - 5,8 (m, 5-CH, 6-CH), 3.67 (s, OCH_3), 0.93 (t, $J_{19,20}$= 6; 20-CH_3)] with zinc borohydride produced a mixture of the C_{15}-epimeric alcohols.

Chromatographic separation afforded the more polar isomer with "natural" stereochemistry at C_{15}, 9a [ir 3640, 3480, 1720, 1665 cm^{-1}; nmr 5.2 - 5.9 (m, 4 vinyl H's), 3.66 (s, OCH_3), 0.90 (t, $J_{19,20}$= 6, 20-CH_3); m/e 351 (M), 333 (M-H_2O), 320 (M-OCH_3), 250 (M-$C_5H_{11}CHOH$), 224 (M-$C_5H_{11}CH(OH)CH=CH$)] and the less polar 15-epicompound 10a (spectra very similar to 9a). Saponification of methyl ester 9a gave the desired PGE_2 analog 9b.

Prostaglandin analogs 6b and 9b showed to be substrates for 15-hydroxy--prostaglandin dehydrogenase, wheras the corresponding C_{15}-epimers 7b and 10b were not consumed. Methyl ester 6a was more active in several biological assays[6] (like inhibition of gastric ulcers and decrease of blood pressure) than its C_{15}-epimer 7a. Details will be published in the full paper.



1

2a R=H
2b R=Ac

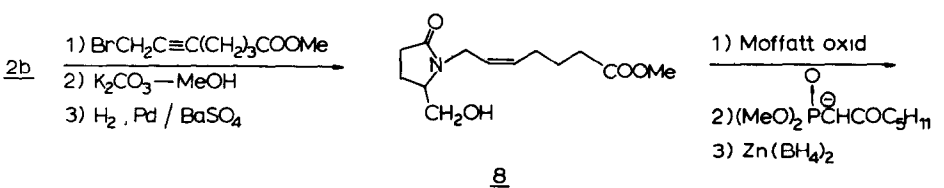
3a R=Ac
3b R=H

4

5

6a R=Me
6b R=H

7a R=Me
7b R=H



8

9a R=Me
9b R=H

10a R=Me
10b R=H

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5. Prostaglandin numbering.
6. Kindly performed by Hoffmann-La Roche Inc., Nutley, U.S.A. We thank dr. W. Leimgruber for making these results available to us.