

SYNTHESIS OF 9-OXAPROSTAGLANDINS

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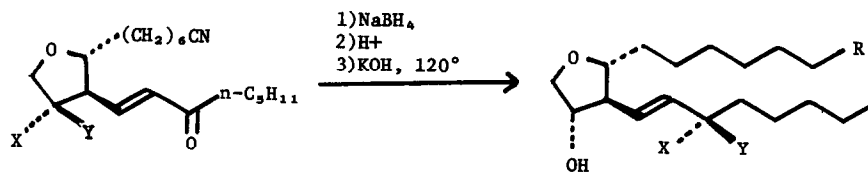
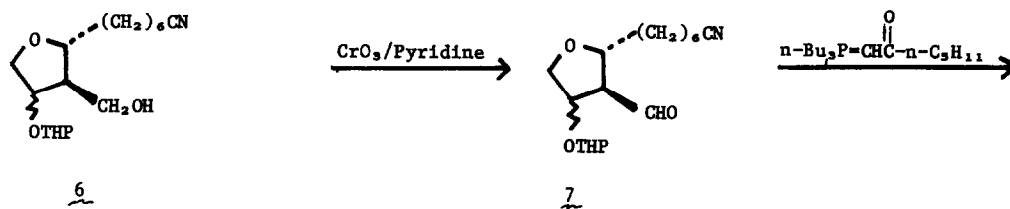
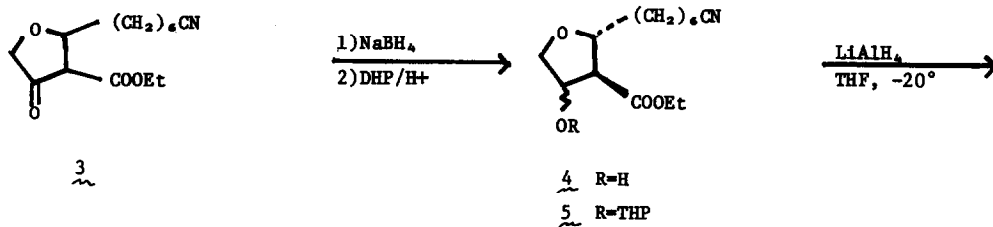
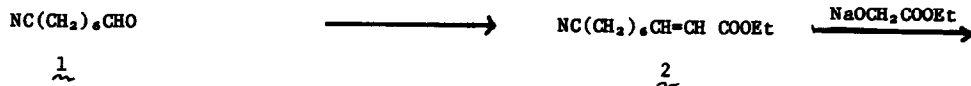
We have recently described the synthesis of 9-desoxy-9-thiaprostaglandin- $E_1^1$ . In this paper we wish to report an alternative synthetic method for the preparation of prostaglandin analogs in which the  $C_9$  is replaced by a heteroatom. The synthetic scheme<sup>2</sup> is illustrated in the following preparation of 9-desoxy-9-oxaprostaglandin- $E_1^3$  (14)

Reaction of 7-cyanoheptanal<sup>4</sup> (1) with sodium triethyl phosphonoacetate gave the ethyl 9-cyano-2-nonenolate (2) (85%; bp. 143-45°, 0.2 mm) which was converted to the tetrahydrofuranone 3<sup>5</sup> (55%;  $\nu_{\max}^{\text{CHCl}_3}$  2255, 1775, 1725  $\text{cm}^{-1}$ ) by reaction<sup>6,7a,b</sup> with ethyl sodium glycolate. Reduction of 3 (NaBH<sub>4</sub>/ethanol/0°) gave a mixture of two epimeric alcohols 4<sup>8</sup> (85%; evaporative dist. b.p. 170°;  $\nu_{\max}^{\text{film}}$  3540, 2245, 1725, 1706  $\text{cm}^{-1}$ ) which were subsequently converted (dihydropyranone/picric acid/CH<sub>2</sub>Cl<sub>2</sub>) to the tetrahydropyranyl ether 5 ( $\nu_{\max}^{\text{CHCl}_3}$  2245, 1725,  $\text{cm}^{-1}$ ). Reduction of the ester group in 5 (LAH/THF/-20°) and oxidation (CrO<sub>3</sub>/pyridine)<sup>9</sup> of the resulting alcohol 6 (80%;  $\nu_{\max}^{\text{film}}$  3400, 2245  $\text{cm}^{-1}$ ) gave the aldehyde 7 (75%;  $\nu_{\max}^{\text{CHCl}_3}$  2735, 2247, 1721  $\text{cm}^{-1}$ ). Wittig reaction of 7 with 1-tributylphosphoranylidene-2-heptanone<sup>10</sup> gave the  $C_9$ -epimeric enones 8 and 9 which were separated by prep. tlc (silica gel, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 1:4, 35%;  $R_{f_8}$  = 0.55;  $\nu_{\max}^{\text{film}}$  2245, 1692, 1670, 1625  $\text{cm}^{-1}$ : 20%,  $R_{f_9}$  = 0.38;  $\nu_{\max}^{\text{film}}$  2240, 1685, 1662, 1620  $\text{cm}^{-1}$ ). The stereochemical assignments are based on the nmr spectra<sup>1</sup> of the alcohols 10 [nmr (CDCl<sub>3</sub>)  $\delta$  6.7 (1H, 2d, CH=CHCO, J=16), 6.2 (1H, d, CH=CHCO, J=16)] and 11 [nmr (CDCl<sub>3</sub>)  $\delta$  6.87, (1H, 2d, CH=CHCO, J=16), 6.19 (1H, d, CH=CHCO, J=16)], obtained by hydrolysis (AcOH/H<sub>2</sub>O) of 8 and 9 respectively.

Reduction of the C<sub>15</sub>-carbonyl in 8 (NaBH<sub>4</sub>/ethanol) followed by hydrolysis (CH<sub>3</sub>OH/p-TsOH) of the tetrahydropyranyl group gave a mixture of the C<sub>15</sub>-epimeric alcohols which were separated by prep.tlc to give the polar isomer 12 (silica gel, EtOAc/CH<sub>2</sub>Cl<sub>2</sub>, 4:1, R<sub>f</sub>=0.4;  $\nu_{\max}^{\text{CHCl}_3}$  3610, 3440, 2245 cm<sup>-1</sup>) and the less polar 13 (R<sub>f</sub>=0.53). Hydrolysis of 12 (KOH/CH<sub>3</sub>OH/120°) gave the dl-9-desoxy-9-oxaprostaglandin-E<sub>1</sub> (14) (40% from 8; mp. 51-53°;  $\nu_{\max}^{\text{CHCl}_3}$  3600, 3400, 1700 cm<sup>-1</sup>).

#### Acknowledgment

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- 8 X=OTHP, Y=H
- 9 X=H Y=OTHP
- 10 X=OH Y=H
- 11 X=H Y=OH

- 12 X=OH, Y=H, R=CN
- 13 X=H, Y=OH, R=CN
- 14 X=OH, Y=H, R=COOH

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