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β-LACTAM PROSTAGLANDINS[1]

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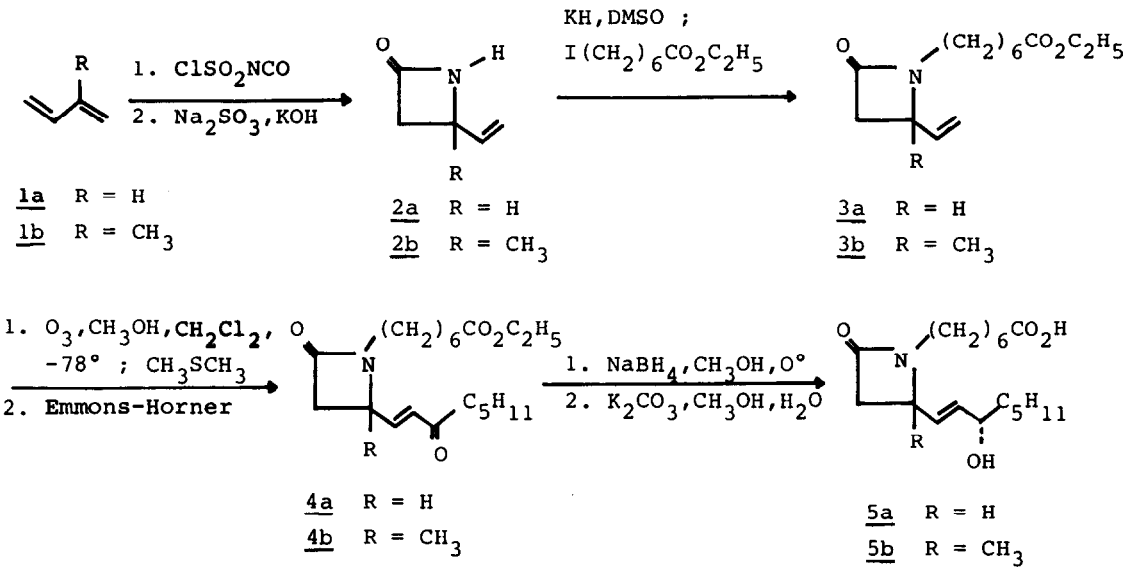
The interesting biological activity associated with β-lactams[2] coupled with the recent widespread interest in γ-lactam prostaglandins[3] prompted us to undertake the synthesis of β-lactam prostaglandins. We now wish to report a short, efficient approach to both 8-aza and 10-aza nor-prostaglandins of this type based on the 1,2-cycloaddition of chlorosulfonyl isocyanate to conjugated dienes[4].

The cycloaddition reactions using butadiene (1a) and isoprene (1b) were carried out as previously described[4] and readily afforded after reduction[5] the β-lactams (2a) and (2b), respectively (CHART I). These were each smoothly N-alkylated with ethyl 7-iodoheptanoate using potassium hydride in DMSO to provide the lactam esters (3a) (76% yield) and (3b) (90% yield)[6]. Ozonolysis of compounds (3a) and (3b) was immediately followed by the Emmons-Horner reaction with the sodio derivative of dimethyl 2-oxoheptylphosphonate in DME to give enones (4a) [60% yield ; IR : ν_{max} (film) 1755, 1735, 1700, 1675, 1635 cm^{-1} ; NMR : δ (CCl_4) 0.90 (t, J = 5 Hz, 3-H), 1.20 (t, J = 7 Hz, 3-H), 4.00 (m,q, J = 7 Hz, 3-H), 6.14 (d, J = 16 Hz, 1-H), 6.58 ppm (dd, J = 7.5 Hz, 16 Hz, 1-H) ; m/e 351 (M^+)] and (4b) [70% yield ; IR : ν_{max} (film) 1755, 1740, 1700, 1675, 1630 cm^{-1} ; NMR : δ (CCl_4) 0.90 (t, J = 5 Hz, 3-H), 1.20 (t, J = 7 Hz, 3-H), 1.53 (s, 3-H), 2.77 (s, 2-H), 4.00 (q, J = 7 Hz, 2-H), 6.02 (d, J = 16 Hz, 1-H), 6.64 ppm (d, J = 16 Hz, 1-H)].

Reduction of enones (4a) and (4b) with sodium borohydride in methanol at 0° in both cases produced ca. 3:2 ratio of C-15 α and β-alcohols in 85% yield, which could be easily separated by silica gel chromatography. The more abundant (more polar) isomers, assigned the α-configuration[7], were then hydrolyzed using aqueous methanolic potassium carbonate to afford the novel

CHART I



1a R = H
1b R = CH_3

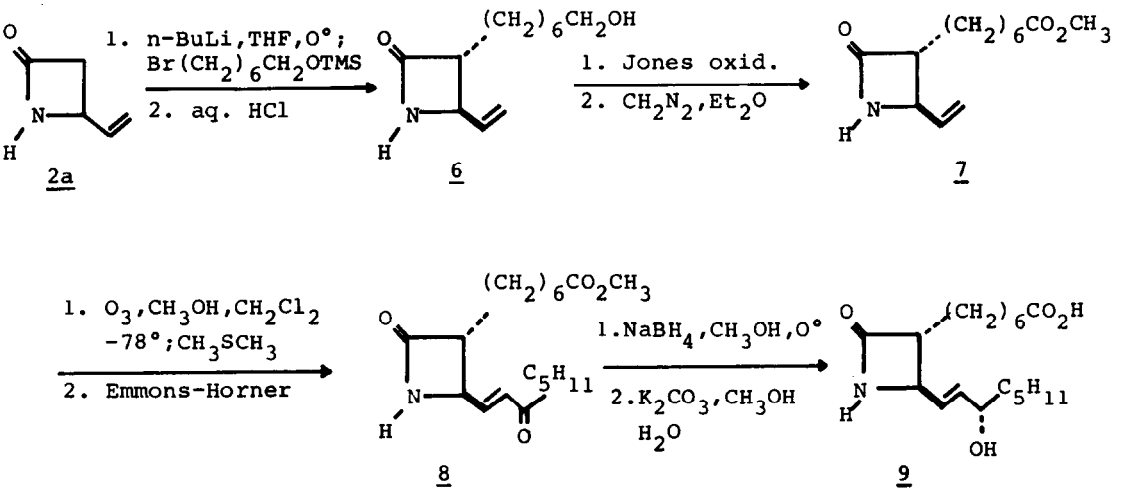
2a R = H
2b R = CH_3

3a R = H
3b R = CH_3

4a R = H
4b R = CH_3

5a R = H
5b R = CH_3

CHART II



2a

6

7

8

9

8-aza-11-nor PGE_1 (5a) [80% yield ; IR : ν_{max} (film) 3400, 1735 cm^{-1} ; NMR δ ($CDCl_3$) 0.88 (t, J = 4 Hz, 3-H), 2.27 (t, J = 7 Hz, 2-H), 3.05 (t, J = 6 Hz, 2-H), 4.02 (m, 2-H), 5.60 ppm (m, 2-H) ; m/e 353 (M^+)] and 8-aza-12-methyl-11-nor PGE_1 (5b) [100% yield ; IR : ν_{max} (film) 3400, 1730 cm^{-1} ; NMR δ ($CDCl_3$) 0.88 (t, J = 4 Hz, 3-H), 1.48 (s, 3-H), 2.27 (t, J = 7 Hz, 2-H), 2.77 (s, 2-H), 3.0 (t, J = 6 Hz, 2-H), 4.08 (m, 1-H), 5.62 ppm (m, 2-H) ; m/e 349 (M^+-H_2O)].

Lactam (2a) was also used for the synthesis of 10-aza-11-nor PGE_1 (9) (CHART II). The dianion of (2a), generated using 2 equivalents of n-butyllithium in THF at 0°, as expected[8] underwent C-alkylation using 1 equivalent of 7-trimethylsilyloxy-1-bromoheptane to afford, after brief exposure to aqueous acid, lactam alcohol (6) in 63% yield. Oxidation of (6) with Jones reagent followed by esterification with diazomethane then gave the lactam ester (7)[9] in 62% yield. Conversion of (7) to enone (8) was effected by ozonolysis followed by treatment with the sodio derivative of dimethyl 2-oxoheptylphosphonate [58% yield ; IR : ν_{max} (film) 3300, 1760, 1740, 1700, 1670, 1630 cm^{-1} ; NMR : δ (CCl_4) 0.88 (t, J = 5 Hz, 3-H), 3.55 (s, 3-H), 3.84 (dd, J = 2 Hz, 6 Hz, 1-H), 6.14 (d, J = 16 Hz, 1-H), 6.68 ppm (dd, J = 6 Hz, 16 Hz, 1-H)]. Treatment of enone (8) with sodium borohydride in methanol at 0° produced in 70% yield a mixture of C-15 allylic alcohols. The more polar α-isomer[7] was readily separated by silica gel chromatography and gave on hydrolysis the new β-lactam prostaglandin (9) [80% yield ; IR : ν_{max} (film) 3300, 1740 cm^{-1}; NMR : δ ($CDCl_3$) 0.88 (t, J = 5 Hz, 3-H), 2.30 (t, J = 7 Hz, 2-H), 2.83 (m, 1-H), 3.77 (m, 1-H), 4.08 (m, 1-H), 5.67 ppm (m, 2-H)].

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