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TOTAL SYNTHESIS OF 11-NOR PROSTAGLANDINS[1]

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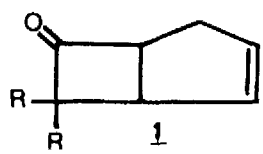
Although many modified prostaglandins have been described[2], so far there has been no mention of a total synthesis of a prostaglandin that contains a cyclobutane instead of the cyclopentane unit. This is particularly surprising in view of the interesting structures that such prostaglandins themselves subsequently might afford. Pursuing our effort aimed at the preparation of novel prostaglandins[3], we wish to report the synthesis of 11-nor $PGF_{2\alpha}$ (7b) and 11-nor PGE_2 (8).

Reduction of the readily available dichloro-cyclobutanone (1a)[4] with zinc in acetic acid afforded the bicyclic ketone (1b) [b.p. : 60° (15 mm) ; I.R. : ν_{max} (film) 3050, 1780, 1605 cm^{-1} ; NMR : (CCl_4) δ 2.4-2.9 (m, 3-H), 3.0-3.5 (m, 2-H), 3.6-4.0 (m, 1-H), 5.80 ppm (broad singlet, 2-H)] in 95% yield[5,6]. Treatment of ketone (1b) with lithium aluminium hydride in tetrahydrofuran solution at -78° gave selectively (90%) the endo-alcohol (2) [I.R. : ν_{max} (film) 3330, 3050 cm^{-1} ; NMR : δ ($CDCl_3$) 1.2-3.3 (m, 7-H), 4.4 (m, 1-H), 5.8 ppm broad singlet, 2-H)] by hydride attack from the exo-side of bicyclic ketone (1b).

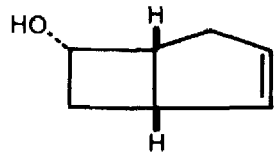
Ozonolysis of the olefinic bond of compound (2), followed by treatment of the ozonide with hydrogen peroxide and formic acid afforded the crystalline acid lactone (3a) [m.p. : 55-58° ; I.R. : ν_{max} (film) 3150, 1775, 1725 cm^{-1}] in over 88% yield. The acid (3a) was then converted to its methyl ester (3b) [I.R. : ν_{max} (film) 1775, 1730 cm^{-1} ; NMR : δ ($CDCl_3$) 2.3-2.8 (m, 4-H), 2.9-3.7 (m, 2-H), 3.7 (s, 3-H), 4.95 ppm (m, 1-H)] for further identification and characterization.

The acid (3a) could be reduced to the primary alcohol (3d) by conversion to the mixed methyl carbonic anhydride (3c) by reaction with methyl chloroformate in tetrahydrofuran solution in the presence of triethylamine[7], followed by treatment with either zinc borohydride in tetrahydrofuran or sodium borohydride in methanol. The γ-lactone group was not affected by these conditions but the

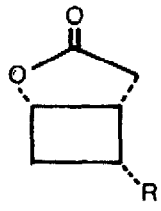


1

a, R=Cl
b, R=H

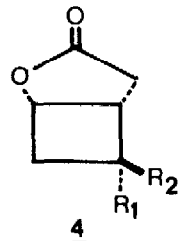


2



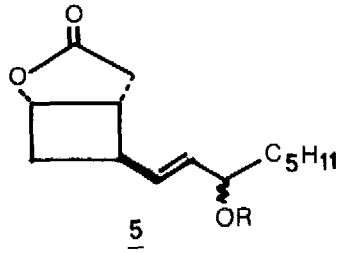
3

a, $R=CO_2H$ d, $R=CH_2OH$
b, $R=CO_2Me$ e, R=CHO
c, $R=CO_2CO_2Me$



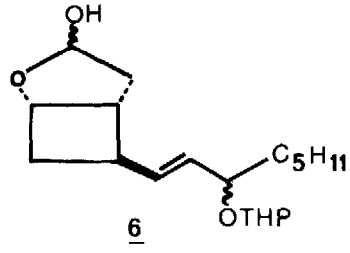
4

a, $R_1=CH=CH-\overset{O}{\overset{\|}{C}}-C_5H_{11}$
$R_2=H$
b, $R_1=H$
$R_2=CH=CH-\overset{O}{\overset{\|}{C}}-C_5H_{11}$



5

a, R=H
b, R=THP



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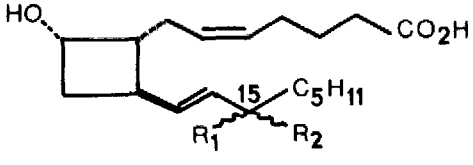
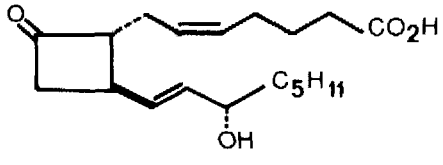


7

a, $R_1=H; R_2=OTHP$
b, $R_1=\alpha\text{-}OH; R_2=\beta\text{-}H$



8

alcohol (3d) [I.R. : ν_{max} (film) 3450, 1770 cm^{-1} ; NMR : δ ($CDCl_3$) 5.0 ppm (m, 1-H)] was obtained in only ca. 25% yield. The conversion of acid (3a) to the corresponding alcohol (3d) was substantially increased, however, when this reduction was performed with borane in tetrahydrofuran[8], thus providing the desired compound (3d) in ca. 75% yield.

Oxidation of the primary alcohol (3d) to the corresponding aldehyde (3e) [I.R. : ν_{max} (film) 2850, 2740, 1770, 1720 cm^{-1} ; NMR : δ ($CDCl_3$) 9.75 (broad singlet, 1-H), 5.0 ppm (m, 1-H)] was carried out in 70% yield by treatment with pyridinium chlorochromate[9] in methylene chloride-chloroform. The reactions used in the concluding steps of the synthesis, for the most part, have been worked out previously[10]. Treatment of the aldehyde (3e) with the sodium salt of dimethyl-2-oxoheptylphosphonate gave mainly[11] the 8,12-cis compound (4a), which after equilibration with DBU, readily furnished the expected enone isomer (4b) [I.R. : ν_{max} (film) 1775, 1690, 1670, 1625 cm^{-1} ; U.V. : λ_{max} (MeOH) 226 nm (ε 11300) ; NMR : δ ($CDCl_3$) 4.95 (m, 1-H), 6.0 (d, J = 16 Hz, 1-H), 6.9 ppm (dd, 6 Hz and 16 Hz, 1-H)]. Reduction of the keto-group with sodium borohydride in abs. methanol at 0° afforded nearly quantitatively the epimeric alcohols (5a) (ca. 1:1). This mixture was smoothly converted to the corresponding tetrahydropyranyl ethers (5b), followed by reduction of the lactone group with diisobutylaluminium hydride in toluene solution, thus providing the mixture of hemiacetals (6). Reaction of (6) in DMSO with excess Wittig reagent generated from (4-carboxybutyl)triphenylphosphonium bromide and dimsylpotassium[12], then gave the novel nor-prostanoic acids as the tetrahydropyranyl ether derivatives (7a).

The completion of the total synthesis of these 11-nor primary prostaglandins[13] was achieved as follows. Whereas treatment of the ether derivatives (7a) with aqueous acetic acid followed by separation[14] of C-15 epimers afforded dl-11-nor $PGF_{2\alpha}$ (7b) [I.R. : ν_{max} (film) 3400, 3020, 1720 cm^{-1} ; NMR : δ ($CDCl_3$-D_2O) 4.05 (m, 1-H), 4.40 (m, 1-H), 5.50 ppm (m, 4-H)], oxidation[9] of the methyl esters (CH_2N_2) of (7a), followed by brief exposure to acid, separation of C-15 epimers, and hydrolysis provided dl-11-nor PGE_2 (8) [I.R. : ν_{max} (film) 3400, 3020, 2600, 1780, 1715 cm^{-1} ; NMR : δ ($CDCl_3$-D_2O) 4.15 (m, 1-H), 5.45 (t, 2-H), 5.75 (t, 2-H)].

The noteworthy features of this synthesis are its simplicity and selectivity, as well as the high yields obtained at most steps. At present, we are actively engaged in modifying 11-nor PGE_2 (8) so as to provide other novel prostanoids.

Acknowledgements :

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12. We have found that dimsylpotassium (DMSO-KH, 25°, < 5 min) is easier to prepare than dimsylsodium (DMSO-NaH, 70°, ca. 1 hr) and gives better reproducibility in this and related reactions.
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14. Compound (7b) was purified and separated from its C-15 epimer by conversion to the corresponding methyl ester (CH_2N_2, Et_2O), preparative TLC, and hydrolysis (K_2CO_3, H_2O, CH_3OH).