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A SYNTHESIS OF PROSTAGLANDIN $F_2\alpha$ ($PGF_2\alpha$)

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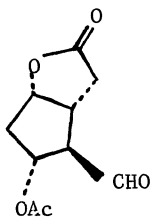
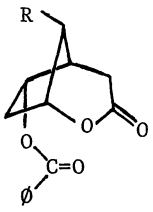
$PGF_2\alpha$ 15 was synthesized via the δ-lactone aldehyde 2, which is much more stable than the Corey's aldehyde 1.[1)]

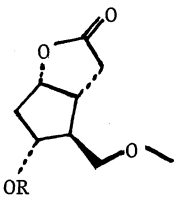
Although the γ-lactone aldehyde 1 has now been demonstrated to be one of the most versatile key intermediate for prostaglandin synthesis,[1)] the extreme thermolabilities for 1 made this route very difficult for the actual execution. We wish to report herein a new route to prostaglandins through the δ-lactone aldehyde 2, which is much more stable and easy to handle.[2)]



(1)



(2) R= CHO
(10) R= CH_2OCH_3
(11) R= CH_2OH



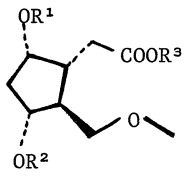
(3) R= $COCH_3$
(4) R= H
(5) R= THP

(THP= 2-tetrahydropyranyl)

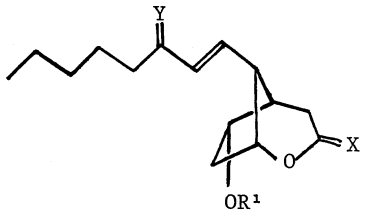
Successive treatment of the acetate 3 with (1) potassium carbonate in methanol, (2) dihydropyran and p-toluenesulfonic acid in methylene chloride, (3) 4N-sodium hydroxide in methanol and careful neutralization, (4) diazomethane in ethyl acetate (-78°C), (5) benzoyl chloride and pyridine in methylene chloride, afforded the acyl ester 7[3)] in 86% over-all yield.

Saponification of 7 with 1N-sodium hydroxide in methanol at room temperature gave the acid 8[3)] and the recovered acid 6[3)] in 44% and 36% yield, respectively.

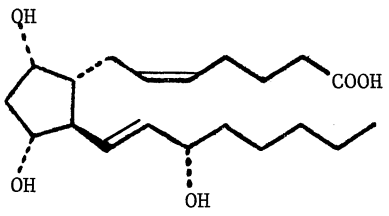
Hydrolysis of 8 with 1N-hydrochloric acid in tetrahydrofuran followed by lactonization of 9 with p-toluenesulfonic acid in benzene gave the δ-lactone 10[3),4)] in 83% yield. The hydroxy compound 13 was obtained by successive treatment of 10 with (1) boron tribromide in methylene



(6) R^1= H, R^2= THP, R^3= H
(7) R^1= COϕ, R^2= THP, R^3= CH_3
(8) R^1= COϕ, R^2= THP, R^3= H
(9) R^1= COϕ, R^2= H, R^3= H



(12) X= O, Y= O, R^1= COϕ
(13) X= O, Y= , R^1= COϕ
(14) X= , Y= , R^1= H



(15)

chloride, (2) Collins reagent in methylene chloride, (3) sodium hydride and dimethyl 2-oxoheptylphosphonate in tetrahydrofuran,[5] (4) sodium borohydride in methanol, in 61% over-all yield from 10.

Diisobutylaluminum hydride reduction of 13 in toluene gave the hemiacetal 14[3] (86% yield after column chromatography on silica gel), which was converted into $PGF_2\alpha$ 15[6),7] by Wittig reaction with 4-carboxy-n-butylidene triphenylphosphorane (5 equiv.) in dimethyl sulfoxide in 26% yield after column chromatography on silica gel. 15-Epi-$PGF_2\alpha$ was obtained in 24% yield together with $PGF_2\alpha$.

Reference and Footmotes

1) E. J. Corey, T. K. Schaaf, W. Huber, U. Kolliker, and N. M. Weinshenker, J.Amer.Chem.Soc., 92 397 (1970).

2) The aldehyde 2 was stable after concentration by rotary evaporator (bath temp. 30°C) and standing overnight at +20°C. This stability will make industrial production of PGs very easy.

3) Ir and nmr spectra were in agreement with the assigned structure.

4) Ir absorption of 1740 cm^{-1} shows δ-lactone.

5) Only the trans isomer was obtained.

6) The 5,6-cis isomer was formed stereoselectively.

7) Ir and nmr spectra, R_f values on tlc and the biological activity were completely identical with those of the authentic sample.

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