Tetrahedron Letters No. 45, pp 4099 - 4102, 1976. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 9,11-DESOXY-9,11-VINYLENO-$PGF_{2\alpha}$ AND ITS DIASTEREOISOMER, ANALOGS OF THE PG ENDOPEROXIDE(PGH_2)

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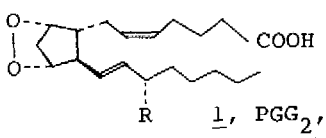
(Received in Japan 19 August 1976; received in UK for publication 23 September 1976)

The two prostaglandin(PG) endoperoxides(PGG_2 1 and PGH_2 2) which had been postulated to be intermediates in the biosynthesis of PG_2 from arachidonic acid, have recently been isolated and characterized by two research groups.[1,2,3]

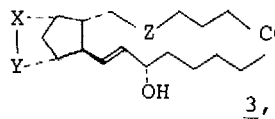
The fact that these endoperoxides possess an interesting spectrum of biological activity[1,2] has prompted us to synthesize some analogs of PGH_2 and examine their biological activities.

As an extention of our previous synthetic approach[4,5,6] for PGs and their analogs, which was, in principle, utilizing the norbornene adducts as key intermediates, we report herein a synthesis of 9,11-desoxy-9,11-vinyleno-$PGF_{2\alpha}$ 3 and its diastereoisomer 4, although the synthesis of the same analog 3[7] or similar analogs[8,9,10] have, quite recently, been reported from several laboratories.



1, PGG_2, R= -OOH

2, PGH_2, R= -OH



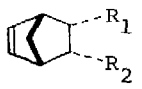
3, X-Y= -CH=CH-, Z= -CH=CH-

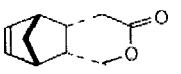
Half-acylation of the cis-diol 5[11] with pivaloyl chloride gave the monopivalate 6(70%), which was converted to the cyano ester 7 by tosylation and subsequent cyanation. Hydrolysis of 7 followed by treatment with hydrochloric acid gave the lactone 8, the key intermediate of this synthesis(85% from 6; ν_{max} 1740; m/e 164(M^+)). Reduction of 8 with diisobutylaluminium hydride gave the hemiacetal 9, which was reacted with 5-triphenylphosphoniopentanoic acid

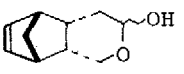
disodium salt, followed by esterification to afford the hydroxy ester 10(77% from 9; ν_{max} 2950, 2850, 1740; m/e 264(M^+), 246(M^+-18)). Oxidation of 10 with Collins reagent gave the endo-aldehyde 11(n.m.r. 9.35, d) which was epimerized to the exo-aldehyde 12(n.m.r. 9.65, d) by refluxing in benzene in the presence of piperidine and acetic acid. The exo-aldehyde 12 thus obtained was condensed, without purification, with the sodium salt of dimethyl-2-oxoheptylphosphonate to afford the enone 13(60% from 10; ν_{max} 1740, 1695, 1670, 1620; m/e 358(M^+), 293(M^+-65)). The enone 13 was reduced with zinc borohydride to give the alcohol 14(ν_{max} 3050, 2950, 2850, 1740; m/e 342(M^+-18)), which was saponified to afford the objective 3[12](ν_{max} 3050, 2850, 1710; m/e(bis-TMS) 475(M^+-15)).

On the other hand, the diastereoisomer 4 was obtained by the similar prosedures described above. Oxidation of 6 with Collins reagent followed by epimerization, reduction, tosylation and cyanation gave the cyano ester 15. Hydrolysis of 15 followed by oxidation afforded the endo-aldehyde 16(n.m.r. 9.50, d) which was condensed with sodium salt of dimethyl-2-oxoheptylphosphonate to give the enone 17(ν_{max} 2250, 1700, 1670, 1630; m/e 258(M^++1), 257(M^+)). Reduction of 17 with zinc borohydride gave the alcohol 18. Reduction of 18 with diisobutylaluminium hydride gave the aldehyde 19, which was reacted with 5-triphenylphosphoniopentanoic acid disodium salt afforded the objective 4[12](ν_{max} 3050, 2950, 2925, 1710).

Both the present analog 3 and 4 are very potent in inducing blood platelet aggregation.[13] Also the present analogs 3 and 4 have shown several significant PG-like pharmacological responses such as inhibition of gastric secretion and stimulation of smooth muscle. The analog 3 is, furthermore, found to exhibit the anti-reserpine and anti-tetrabenazine actions in mice and rats.[14]



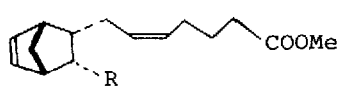




5, R_1=R_2= $-CH_2OH$ 8 9

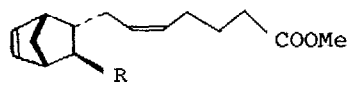
6, R_1= $-CH_2OH$, R_2= $-CH_2OCOC(CH_3)_3$

7, R_1= $-CH_2CN$, R_2= $-CH_2OCOC(CH_3)_3$



10, R= $-CH_2OH$

11, R= -CHO



12, R= -CHO

13, R= $-CH=CHCO(CH_2)_4CH_3$

14, R= $-CH=CHC(OH)-(CH_2)_4CH_3$

15, R_1= $-CH_2CN$, R_2= $-CH_2OCOC(CH_3)_3$

16, R_1= $-CH_2CN$, R_2= -CHO

17, R_1= $-CH_2CN$, R_2= $-CH=CHCO(CH_2)_4CH_3$

18, R_1= $-CH_2CN$, R_2= $-CH=CHC(OH)-(CH_2)_4CH_3$

19, R_1= $-CH_2CHO$, R_2= $-CH=CHC(OH)-(CH_2)_4CH_3$

4

References and Notes

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7. E.J. Corey, M. Shibasaki, K.C. Nicolaou, C.L. Malmsten and B. Samuelsson Tetrahedron Letters, 737(1976): Synthesis of the same analog 3 has been described, the synthetic route of which was different from that of this paper. Some of the present work, moreover, has already been described in Japan Patent Application(Application No. Sho-50-80292, Application Date, June 27, 1975).

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10. A.G. Abatjolou and P.S. Poitghese, ibid., 1457(1976): Synthesis of the analog (X-Y= $-CCO_2Et=CCO_2Et$, Z= $-CH_2CH_2-$ in the formula 3) has been described.

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12. This product was composed of a mixture of the desired 15-α-OH compound and its 15-epimer, which was subjected to the biological examination without separation. The ratio was found to be almost 1:1 by TLC(Benzene:AcOEt:AcOH= 20:2:1); 0.30:0.32 for 3 and its epimer; 0.31:0.33 for the mixture of 4 and its epimer.

13. Inspite of the difference of the stereochemistry between 3 and 4, their potency was found to be almost the same.

14. Further investigations are still underway and the results obtained there will be published in the future.