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TOTAL SYNTHESIS OF PROSTAGLANDIN D_2

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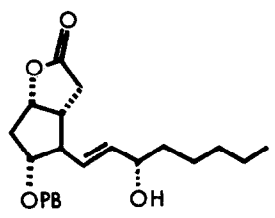
In 1972 Sih et al.[1] reported on the biosynthesis and chemistry of 9α,15(S)-dihydroxy-11-oxo-13-trans-prostenoic acid (PGD_1), and last year, Hayashi et al.[2] published a relatively simple procedure for the total synthesis of PGD_2. In the context of our work on prostaglandins, we too have synthesized PGD_2 and studied its NMR and UV spectroscopic properties. In the course of these investigations it became clear that Hayashi's[2] interpretation of the NMR spectrum of PGD_2 is incorrect. Sih's proton assignment[3] for PGD_1 is ambiguous and incomplete. Both authors fail to mention H(12), which is situated between a carbonyl group and a double bond. This special feature distinguishes prostaglandins of the D-series from all the other prostaglandins investigated so far. Furthermore, our PGD_2 displays UV-absorption in the presence of sodium hydroxide which differs markedly from that of PGD_1 described by Sih et al.[1].

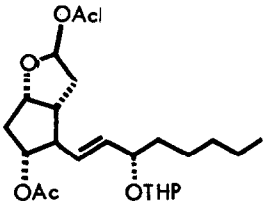
PGD_2 was synthesized from the known lactone I[4]. Etherification of the 15-hydroxyl group with dihydropyrane, hydrolysis of the 11-p-phenyl-benzoate ester grouping with MeOH/K_2CO_3, reduction of the lactone with diisobutyl-aluminum hydride, and acetylation of the two hydroxyl groups with acetic anhydride in the presence of pyridine led to compound II. Treatment of II with a mixture of HOAc, H_2O, THF (5:5:1) for 15 minutes at 25° afforded the lactol III, which was reacted under standard conditions with the Wittig reagent derived from 5-triphenyl-phosphonio-pentanoic acid and sodio methyl-sulfinylcarbanide in DMSO yielding a mixture of the two isomeric compounds IV and V in the approximate ratio of 3:1. Under basic conditions an acyl migration reaction involving IV and V seems to take place. A small amount of 15-tetrahydropyranyl-$PGF_{2\alpha}$ was also isolated. The mixture of IV and V was treated with dihydropyrane to give VI and VII. The free acids were liberated from VI and VII when the mixture was hydrolyzed with HOAc, H_2O, THF (5:5:1) for 15 minutes at 25°. The acetoxy groups were hydrolyzed in MeOH/K_2CO_3 and the resultant 11- and 9-hydroxyl groups in VIII and IX, respectively, were oxidized with Jones' reagent to the corresponding ketones. These, in turn, were transformed to a 3:1 mixture of racemic PGD_2 (X) and PGE_2 (XI) by treatment with a mixture of HOAc, H_2O, THF (6:3:1) at 40° for 6 hrs.

PGD_2 and PGE_2 were easily separated chromatographically on silica gel. On TLC plates with AcOEt, AcOH, isooctane, H_2O (11:2:5:10) as the liquid phase, PGE_2 and PGD_2 had R_f values of 0.18 and 0.28, respectively. PGD_2 was esterified with diazomethane to the corresponding methylester XII.



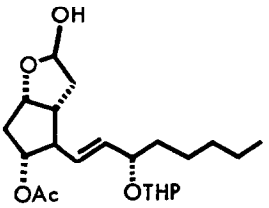
I

1. DHP (100%)
2. MeOH/K_2CO_3 (83%)
3. DIBAH (99%)
4. Ac_2O/Py (93%)



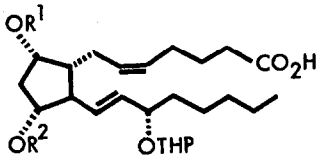
II

$HOAc/H_2O/THF$ (100%)



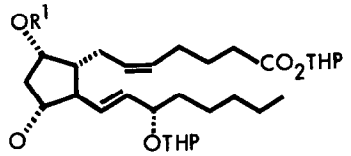
III

$Ph_3P{=}CH(CH_2)_3CO_2^{\ominus}$
$NaCH_2SOCH_3$/DMSO (86 - 93%)



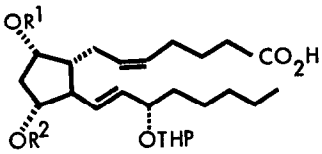
DHP (100%)

IV R^1=H, R^2=Ac
V R^1=Ac, R^2= H



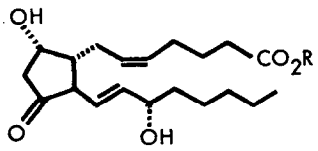
VI R^1=THP, R^2=Ac
VII R^1=Ac, R^2=THP

1. $HOAc/H_2O$ THF (100%)
2. MeOH K_2CO_3 (70%)



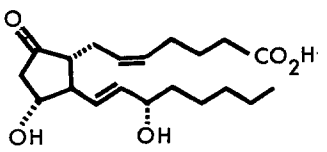
VIII R^1=THP, R^2=H
IX R^1=H, R^2=THP

1. CrO_3 (91%)
2. HOAc H_2O THF (63%)



X R=H(dl-PGD_2) (46%)
XII R = CH_3

+



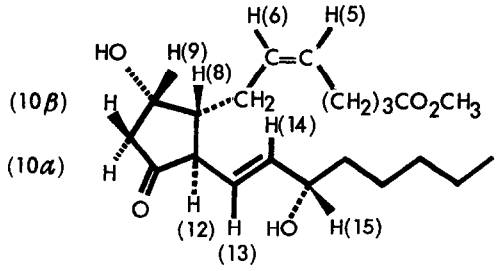
XI (dl-PGE_2) (17%)

A 10^{-4} molar solution of PGD_2 (X) in ethanol-water (1:9) did not show any appreciable UV absorption between 220 and 350 mμ. When the compound was dissolved in a mixture of ethanol and a 0.05-molar aqueous NaOH-solution (1:9; 10^{-4}-molar), the following absorption values were recorded:

minutes after mixing	λ_{max} mμ	ε_{max}
3.5	244	5200
145	247	5100
	277	4200 (shoulder)
24 x 60	242	4800
	285	5200

These absorption maxima are in accordance with the proposed structure for PGD_2 and its possible reaction products. We did not observe the absorption at 232 mμ after 145 minutes, reported by Sih et al.[1] (Fig. 11, p. 2276).

The structure X of racemic PGD_2 is confirmed by 100- and 270-MHz ^{1}H-NMR investigations on the ester XII.



XII

The sequence of protons on carbons 15, 14, 13, 12, 8, 9, and 10 especially can be unequivocally deduced from single and double resonance experiments; parameters for these protons are given in the following table:

H(C-15): 4.09 ppm (broad quartet J = 7 Hz)

H(C-14): 5.63 ppm (doublet of doublets, J = 7 and 16 Hz, becomes a doublet upon irradiation at 4.09 ppm, J = 16 Hz)

H(C-13): 5.43 ppm (doublet of doublets, J = 16 and 8.5 Hz, collapses to a doublet upon irradiation at 2.87 ppm, J = 16 Hz)

H(C-12): 2.87 ppm (doublet of doublets, J = 12 and 8.5 Hz, collapses to a doublet upon irradiation at 5.43 ppm, J = 12 Hz, and to a doublet upon irradiation at 1.95 ppm, J = 8.5 Hz)

H(C-8): 1.95 ppm (broad multiplet, simplifies to an eightline multiplet upon irradiation at 4.47 ppm, J = 12, 10.5, 4.5 Hz)

H(C-9): 4.47 ppm (broadened multiplet, $\nu_{1/2}$ = 10 Hz, becomes a doublet upon irradiation at 2.45 ppm, J = 4 Hz)

H_α(C-10), H_β(C-10): 2.45 ppm ('doublet', sharpens upon irradiation at 4.47 ppm)

The other proton signals observed (5.45–5.58 ppm multiplet for olefinic H, 3.68 ppm singlet for OCH_3 and 2.8–0.9 ppm multiplet for aliphatic H) are also in accord with the structure of PGD_2.

The *trans* coupling constant of 12 Hz between protons on C-12 and C-8 is remarkably large, while the other couplings between the protons in the five-membered ring are rather small, the *cis* coupling between H-8 and H-9 being about 4 Hz, and both couplings between H-9 and the protons on H-10 not exceeding about 3 Hz. These findings are compatible with an envelope conformation of the substituted cyclopentanone ring with C-8 out of the plane of the four other carbon atoms. In such a conformation H-12 and H-8 adopt quasi-axial positions and the dihedral angles between H-8 and H-9 and between H-9 and the two protons on C-10 are about 60°.

NOTES AND LITERATURE REFERENCES:

1) P.S. Foss, C.J. Sih, C. Takeguchi, and H. Schnoes, Biochemistry **11**, 2271 (1972).
2) M. Hayashi and T. Tanouchi, JOC **38**, 2115 (1973).
3) Sih et al.[1] erroneously refer to H(9) as the 'proton geminal to hydroxyl at C-11'.
4) E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf, R.K. Varma, JACS **93**, 1491 (1971).