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THE STRUCTURE OF PROSTAGLANDIN B_1 DIMER

Masaaki Toda*, Shigeru Takaoka, Mitoshi Konno, Shigehiro Okuyama,
Masaki Hayashi and Nobuyuki Hamanaka
Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618, Japan
Takashi Iwashita
Suntory Institute for Bioorganic Research, Shimamoto, Mishima, Osaka 618, Japan

ABSTRACT: Dimeric derivatives of prostaglandin B_1 were prepared under alkaline conditions and the structures were determined by NMR spectroscopies.

Prostaglandin Bx (PGBx), a new oligomeric derivative of prostaglandin B_1 (PGB_1) was first synthesized by B. D. Polis[1], which was shown to restore oxidative phosphorylation to degraded isolated rat liver mitochondria *in vitro*.[2] The molecular weights of the most active fraction of PGBx fall between 2000 and 2600.[2] During the course of mechanistic studies for oligomerization of PGB_1 under various alkaline conditions, we have succeeded in isolating PGB_1 dimers, intermediate of PGBx. In this paper, we disclose the structure of PGB_1 dimer.

PGB_1 methyl ester was treated with NaOMe (1 equiv) in dry MeOH at 25° for 48 hr. The crude reaction products were separated by gel filtration chromatography on Sephadex LH-20 (MeOH) to afford the mixture of dimers, which were further separated by thin layer chromatography ($CHCl_3$-MeOH/ 30:1) to afford dimer I (Calcd for $C_{42}H_{68}O_8$: m/e 700.491386, Found: m/e 700.493276) in 4% yield.[3]

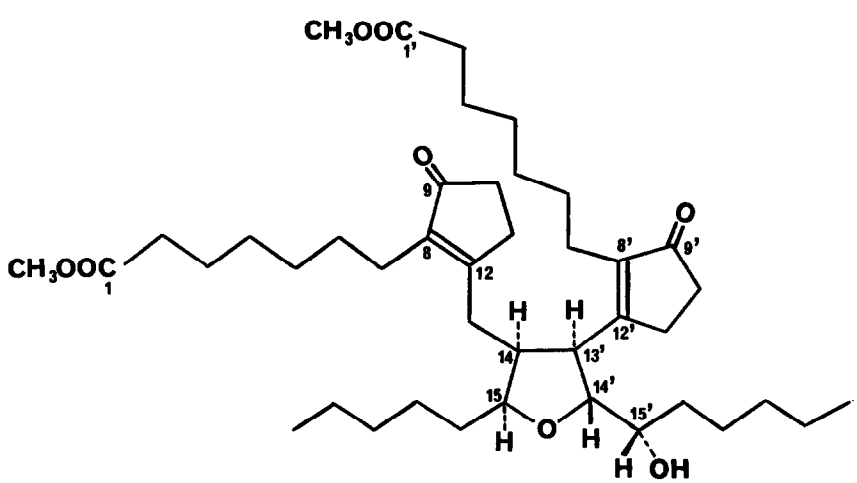

Fig 1 PGB_1 Dimer I

Dimer I has a hydroxyl group, a newly formed ether bond and two cyclopentenone rings [λ(EtOH) 238.5 nm (ε, 27200)[4]]. Acetylation of dimer I with acetic anhydride and pyridine at r.t. overnight afforded dimer I acetate [m/e 742, δ($CDCl_3$) 4.92 (1H,dt, $H_{15'}$) and 2.08 ppm (3H,s, $-COOCH_3$)] quantitatively. The planar structure of dimer I is revealed from the detailed ^{1}H-NMR (Table I) and ^{13}C-NMR (Table II)[5,6] examinations as shown in Fig 1. Double-resonance studies of ^{1}H-NMR of dimer I acetate confirmed a chain connectivities (H-15, H-14, H-13', H-14' and H-15') around the tetrahydrofuran ring. Furthermore nuclear Overhauser effect (NOE)[7] were measured between the protons around the tetrahydrofuran ring. There were clean NOEs between H-14 and H-15, and H-13' and H-14. However NOEs between H-13' and H-14', and H-14' and H-15 were not observed. These spectroscopic findings coupled with the stereochemistries at C-15 and C-15' having been s-configurations confirmed the complete structure of dimer I as shown in Fig 1.

On the other hand, PGB_1 methyl ester was treated with 1N NaOH (5 equiv) in 50% MeOH at 25° for 60 hr followed by treatment with diazomethane. The crude reaction products were separated as described in isolation of dimer I to afford dimer II (Calcd for $C_{42}H_{68}O_8$: m/e 700.491386, Found: m/e 700.487878) in 8% yield.[8]

Dimer II (^{1}H-NMR and ^{13}C-NMR spectra are summarized in Table I and II) has two hydroxyl groups (secondary and tertiary), a cyclopentenone ring[9] [λ(EtOH) 248 nm (ε, 14400)]. Acetylation of dimer II with acetic anhydride and pyridine at r.t. for 2 days gave dimer II monoacetate [m/e 742, δ($CDCl_3$) 4.87 (1H,m, $H_{15'}$) and 2.06 ppm (3H,s, $-OCOCH_3$)] and dimer II diacetate [m/e 784, NMR spectra are summarized in Table I]. Comparison of ^{1}H-NMR of dimer I and dimer II shows that the latter has the tetrahydrofuran ring moiety possessing the same stereochemistry[10] as dimer I. These findings and inspection of the data in Table I and II reveals the structure of dimer II as shown in Fig 2. Furthermore NOEs between H-10' and H-11' (15%), H-13' and H-15' (8.5%) and H-11' and H-14' (5.5%) were observed. These spectroscopic studies showed the stereostructure of dimer II except C-8, C-9 and C-12[11] as shown in Fig 2.

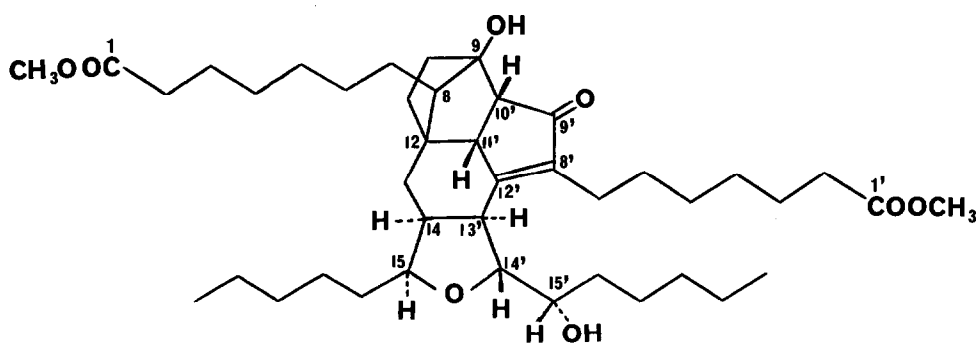

Fig 2 PGB_1 Dimer II

Table I ^{1}H-NMR Spectra of Dimer I, Dimer I Acetate, Dimer II and Dimer II Diacetate (δ in $CDCl_3$)

	Dimer I	Dimer I Acetate	Dimer II	Dimer II Diacetate
H-13'	3.37(dd)	3.05(dd)	3.44(dd)	3.27(dd)
H-14'	3.80(dd)	3.97(dd)	4.07(dd)	4.25(dd)
H-15'	3.36(dt)	4.92(dt)	3.37(dt)	4.85(dt)
H-14	2.29(m)		2.14(m)	2.15(m)
H-15	3.76(dt)	3.77(dt)	3.82(br. t)	3.80(br. t)
$COOCH_3$	3.66, 3.67	3.65, 3.66	3.67, 3.68	3.68
H-10'			2.33(d)	3.14(d)
H-11'			2.61(d)	2.61(d)
15-OAc		2.08(s)		2.05(s)
9-OAc				2.09(s)
$J_{13',14'}$	9.0	7.0	10.0	10.0
$J_{13',14}$	9.5	9.5	7.0	6.0
$J_{14',15'}$	3.0	5.0	4.0	4.5
$J_{14,15}$	8.0	9.0	~0	~0
$J_{10',11'}$			5.5	5.5

Table II ^{13}C-NMR Spectra of Dimer I and Dimer II (δ in $CDCl_3$)

Dimer I

C-9	208.99^{s}	C-14'	85.05^{d}
C-9'	208.99^{s}	C-15	82.97^{d}
C-1	174.25^{s}	C-15'	71.37^{d}
C-1'	174.25^{s}	COOMe	51.48^{q}
C-12'	169.52^{s}	C-13'	49.36^{d}
C-12	168.22^{s}	C-14	47.83^{d}
C-8'	144.20^{s}	C-13	35.08^{t}
C-8	141.99^{s}		

Dimer II

C-9'	209.26^{s}	C-10'	53.30^{d}
C-1	{174.16^{s}	COOMe	51.44^{q}
C-1'	{174.10^{s}	C-8	{48.75^{d}
C-12'	172.00^{s}	C-11'	{48.32^{d}
C-8'	146.07^{s}	C-12	48.42^{s}
C-14'	85.95^{d}	C-13'	43.87^{d}
C-15	82.65^{d}	C-14	41.76^{d}
C-9	82.27^{s}	C-13	36.35^{t}
C-15'	72.24^{d}		

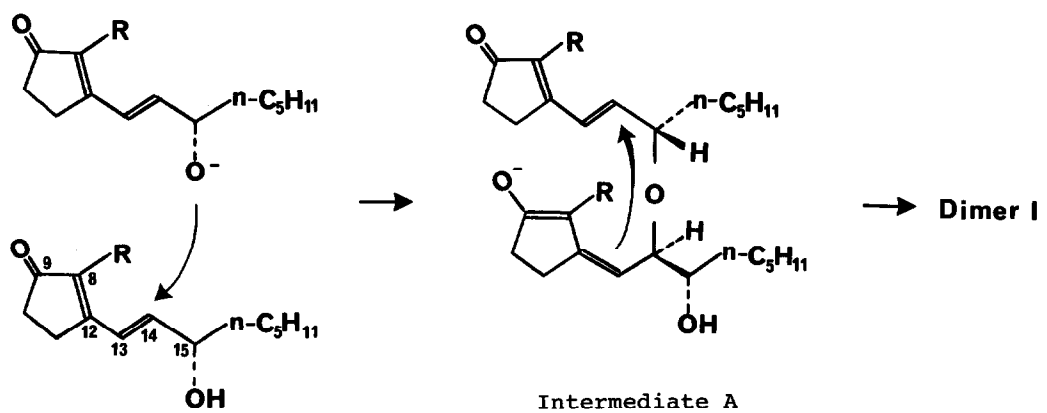

Chart 1 Plausible Formation Pathway of PGB_1 Dimer 1

Dimerization of PGB_1 most likely proceeds by way of intermediate A as shown in Chart 1. It is apparent that dimer II is formed from dimer I by the Michael addition between C-11' and C-12 followed by the aldol condensation between C-10' and C-9. Dimer I was smoothly converted to PGBx with 1N NaOH (15 equiv) in 50% EtOH at 80°, however oligomerization of dimer II under the same condition was very slow. The biological studies of PGB_1 dimers will be reported elsewhere and further studies for the formation of 15-keto PGB_1 under various alkaline conditions are in progress.

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REFERENCES AND NOTES

1) B.D. Polis, S. Kwang, E. Polis, G.L. Nelson and H.M. Shmukler: Physiol. Chem. & Physics, 11, 109 (1979). B.D. Polis, S. Kwang, E. Polis and G.L. Nelson: Ibid., 12, 167 (1980).

2) B.D. Polis, E. Polis and S. Kwang: Proc. Natl. Acad. Sci. USA, 76, 1598, (1979).

3) Starting material was recovered in 60% yield and two other PGB_1 methyl ester dimers (m/e 700) and 14-methoxy PGB_1 methyl ester (m/e 382) were isolated respectively in 2%, 3% and 5% yields.

4) For UV spectrum of 15(ξ)-13,14-dihydro-PGB_1 methyl ester; 237.5 nm (ε, 15600), see M. Miyano: Tetrahedron Lett., 1969, 2771.

5) ^{13}C-NMR spectrum of PGB_1 and 13,14-dihydro-PGB_1, see B.D. Polis, E. Polis and S. Kwang: Physiol. Chem. & Physics, 13, 111 (1981). The ^{13}C-NMR chemical shift assignments were confirmed by selective proton irradiation experiments.

6) ^{1}H-NMR and ^{13}C-NMR spectra were measured on Nicolet NT-360 and Varian XL-200 spectrometers.

7) L.D. Hall and J.K.M. Sanders: J. Amer. Chem. Soc., 102, 5703 (1980) and references cited therein.

8) Other PGB_1 methyl ester dimer and 14-methoxy PGB_1 methyl ester were isolated respectively in 5% and 1% yields. Furthermore trimers and tetramers were formed in about 30 % yield.

9) Another cyclopentenone moiety included in dimer I disappeared in dimer II.

10) The stereochemistry was confirmed by NOE[7] as discussed in dimer I.

11) Further spectroscopic evidence for stereochemical assignments at C-8, C-9 and C-12 could not be obtained.

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