

MARINE PROSTANOIDS - A REVIEW

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ABSTRACT

The occurrence and structure of prostaglandins including clavulones, punaglandins and claviridenones in marine organisms is reviewed. By comparison of the spectral data reported the identity of 20-acetoxy claviridenones b and c with 20 acetoxy clavulones has been established.

Prostaglandins represent a large and still expanding group of biologically potent lipid acids first discovered in seminal fluids and extracts of Icelandic sheep (Bergstrom, 1967). They have also been known to occur in various terrestrial animal organs and in recent years shown to be distributed in marine life such as fish (Nomura, 1978).

Several reviews which dealt with marine prostanoids include those of Nomura Tadashi (1979) which has stressed the distribution, structure, biosynthesis and their function in marine animals. Crabbè in 1979 discussed the synthesis of modified prostaglandins from the PGA_2 of corals. Prostaglandins of fish along with the hormones of hypothalamus, pituitary glands, thyroid glands and sex glands have been reviewed by Lin (1984) and finally in 1985 Nagasaka presented the chemistry and synthesis of recently discovered anti-tumor marine prostanoids clavulones, chlorovulones and punaglandins. From the biosynthetic point of view Corey has discussed this subject on several occasions.

In the present review an attempt has been made to review all known marine prostanoids that have appeared in the literature through December 1989. Emphasis will be placed on the compounds actually isolated, and their chemistry. No synthetic chemistry will be considered.

In 1969 Weinheimer and Spraggins made a remarkable discovery of the presence in relatively large amounts of two non-mammalian type of prostaglandin derivatives 15-*epi*- $PGA_2(1)$ and its diester (2) in air dried cortex of the Caribbean seaweed *Plexaura homomalla*. They differed from the mammalian prostaglandins (3) in having the unnatural R configuration at C_{15} and unlike the terrestrial ones they did not exhibit blood pressure lowering effect. They do not occur in easily detectable amount in any related corals or other marine animals investigated so far.

This interesting discovery brought considerable attention to *P. homomalla* particularly because of their high concentrations and as potential synthetic precursors to

biologically active prostaglandins A₂, E₂, or F₂ and stimulated worldwide survey of PG's in marine life. This resulted in isolation by Light and Samuelson (1972) of minute amounts of 15S isomers besides the predominant 15R compounds consisting of complex mixture including 11(15R) - dihydroxy-9-oxo-prost-5, 13-dienoic acid (5), its methyl ester (6), (15R) - PGA₂ ester (4) from *P. homomalla* of Florida. It is interesting that *P. homomalla* from the Caribbean exclusively produce 15S prostaglandins and some 15R isomers. Rarely did the samples contain both isomers (Schneider, Hamilton and Rhuland, 1972). The presence of natural mammalian type (15S) - PGA₂ (7) and (15S) PGE₂(8) was detected in some sample *P. homomalla* (Schneider, Hamilton and Rhuland, 1972). It was observed that the two epimers differ only slightly in the polarity and both the forms may be present in a single sample. The presence of (15S) - PGA₂(7) was confirmed by its conversion to (15S)-PGE₂ and (15S) - PGF₂ and base catalyzed rearrangement to (15S) - PGB₂.

A re-examination of the extracts of *P. homomalla* var. (S) by Bundy, Daniel, Lincoln and Pike (1972) allowed a more detailed analysis showing that more related products were present to which the structure (15S) - 15-hydroxy-9-oxo-(5 trans PGA₂) (9) was assigned.

Monoacetates of PGF_{2α} methyl ester (10), PGF_{2α} methyl ester (11), PGF₂ (12), and small amounts of PGE₂ (8) have been reported (Schneider, Bundy, Lincoln, Daniel and Pike, 1977) in addition to (15S) - PGA₂ (7) in *P. homomalla* from Cayman Island. This gorgonian was also found to contain yet another prostaglandin characterized as 5,6 trans PGA₂ (9) by its subsequent conversion to 5,6 trans PGE₂ (13). 13-14 Cis PGA₂ - 15 acetate (14), 13-14 dihydro PGA₂ acetate methyl ester (15) and 13,14 dihydro PGA₂ internal Michael adduct (16) have been reported from the sample from Cayman Island by Schneider, Morge and Henson in 1977. Compound (14) was identified by its conversion to methyl ester whose configuration at C₁₅ was established as 15S by its ozonization to α - acetoxyheptanoic acid with an ORD curve identical to that of (s) d-acetoxyheptanoic acid obtained by ozonization of (15S) - PGA₂ acetate methyl ester. UV absorption of its methyl ester at 217 nm was shifted to 325 nm due to elimination of CH₃COOH on addition of a base. The HNMR of this elimination product (17) was found to be identical to the one formed from PGA₂ acetate methyl ester (Grudzinskas and Weiss, 1973). IR of the methyl ester was indicative of absence of trans double bond. 13-14 Cis nature of the double bond was established by alkaline epoxidation of methyl ester to a mixture of 10, 11 epoxides which on reduction yielded PGE₂ (18) identical to the synthetic product reported by Kluge, Untch and Fried (1972). The extract of the same gorgonian also contained the adduct (16) and 15 α-acetate methyl ester (15) of (13) and (14).

Later on, by monitoring the activity towards isolated guinea pig ileum PGF_{2α} (19) was detected in the Japanese coastal gorgonian *Euplexaura erecta* (Komoda, Kanayasu and Ishikawa).

The occurrence of prostanoids in marine life other than gorgonians has also been reported. By monitoring the antihypertensive activity by bioassay towards the pentobarbitone anaesthetized hypertensive rats Gregson, Marwood and Quinn, 1979, isolated PGE₂(20)PGF₂α from the marine red alga *Gracilaria lichenoides*. This is the only report of the occurrence of prostaglandins in plants.

The Red Sea soft coral *Lobophyton depressum* was shown to contain four PGF derivatives(15S)-PGF₂α-11-acetate methyl ester (21), its 18-acetoxy derivative (22) as well as two corresponding free carboxylic acids (23) and (24).

More recently new prostanoids possessing antitumor activities and having oxygenated functions at C-4, C-12 positions and olefins at C-7, C-14 positions designated as clavulones have been identified in Japanese the soft coral *Clavularia viridis* Quo and Gaimard (Hiroyuki, Yasumasa, Iguchi and Yamada, 1982). The structure of these clavulones I, II and III, (25), (26) and (27) was assigned on the basis of spectral data and chemical evidence. The presence of a cross conjugated system was indicated by the UV data of allylic alcohol (28) obtained by NaBH₄ reduction of the clavulone (25) and the ketone (29), a pyridinium chlorochromate oxidation product of the alcohol (28).

The UV data on the ketone (30) and the mass spectrum of its dihydro derivative (31) obtained by hydrogenation of (25) with Pd/C established the nature and α-β positions of the side chain in a α-β unsaturated cyclopentenone system.

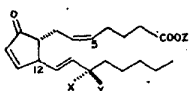
The stereochemistry of the chiral centres of these new prostanoids, clavulones, at the C-4 position was established by isomerisation of (25) with oxalic acid in CH₃OH to (26) and (27) and by converting the aldehyde (32) obtained by ozonolysis of (25) to the lactone (33) with known stereochemistry (unpublished data).

The examination of CD spectra of the *p*-bromobenzoate derivatives (34) and (35), prepared from the clavulone established the stereochemistry at C-12.

The antileukemic effect of these compounds on human promyelocytic leukemia (HL-60) cells has also been studied (Fukushima, Kato, Otao, Yamada, Kikuchi and Kitagawa, 1983).

Further investigation (Iguchi and Yamada, 1983) on the same soft coral *Clavularia viridis* led to the isolation of oxygenated prostanoids (36), (37) and (38) having an acetoxy group at C-20 position. These were the first examples of C-20 oxygenated prostanoids from a marine source, 20-hydroxy prostaglandins are recognized metabolites of mammalian prostanoids (Green and Samuelsson, 1976).

The structure and stereochemistry were obtained by CD spectra and comparison of their ¹H and ¹³CNMR with those of clavulones (25), (26) and (27).



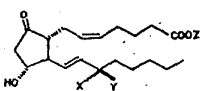
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2 : X = H, Y = OAc, Z = Me

3 : X = OH, Y = H, Z = H

4 : X = H, Y = OH, Z = Me

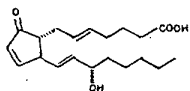
7 : X = OAc, Y = H, Z = Me



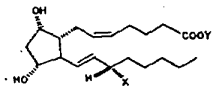
5 : X = H, Y = OH, Z = H

6 : X = H, Y = OH, Z = CH₃

8 : X = OH, Y = H, Z = H



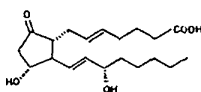
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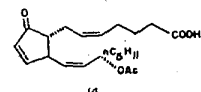
10 : X = OAc, Y = Me

11 : X = OH, Y = Me

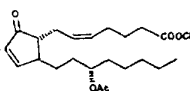
12 : X = OH, Y = H



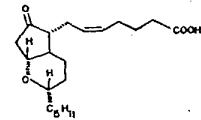
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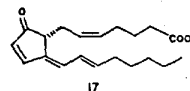
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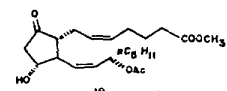
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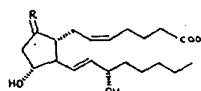
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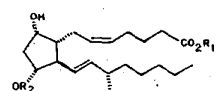


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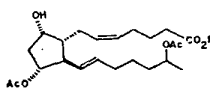
19 : R = α-OH; β-H, R' = H

20 : R = O; R' = H



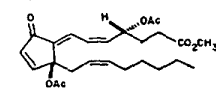
21 : R₁ = Me, R₂ = Ac

23 : R₁ = H, R₂ = Ac

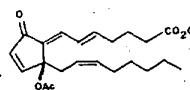


22 : R = H

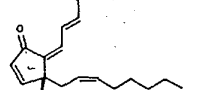
24 : R = Me



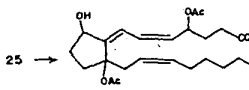
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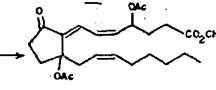
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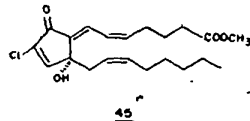
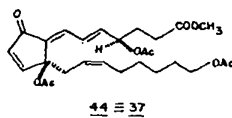
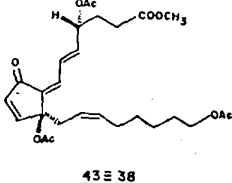
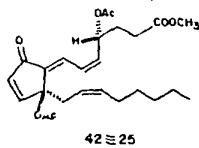
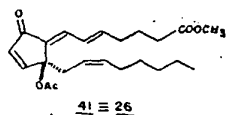
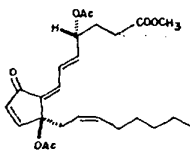
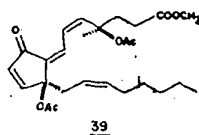
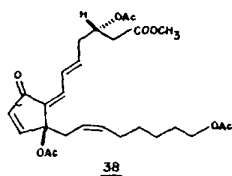
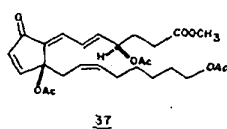
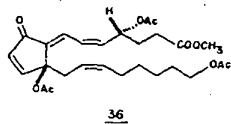
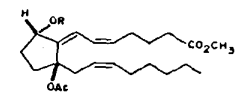
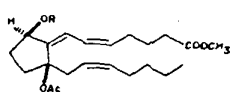
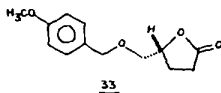
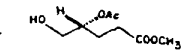
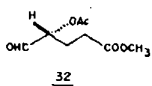
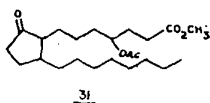
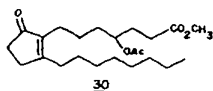
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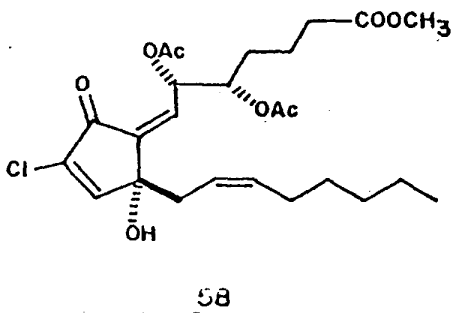
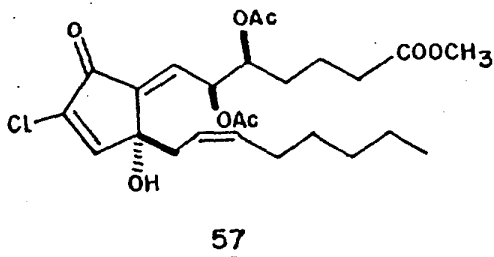
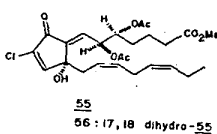
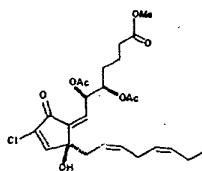
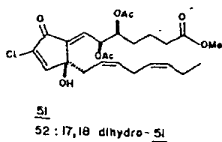
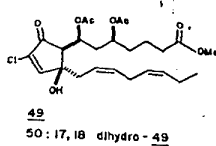
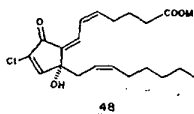
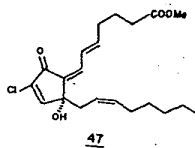
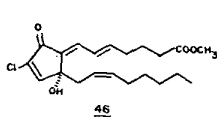


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From the same source, *C. viridis*, Kitagawa and co-workers (1985) published the isolation of claviridenone *a, b, c* and *d* (39), (40), (41), (42) and 20-acetoxy claviridenone-*b* (43) and 20-acetoxy claviridenone *c* (44), the stereostructure being determined on the basis of physical and physico-chemical evidence including the application of the CD excitation chirality method (Harada and Nakanishi, 1972; Harada, Iwabuchi, Yokota, Uda and Nakanishi, 1981; Harada and Nakanishi, 1982). While preparing this review we compared physico-chemical data of claviridenones *c, b* and *d* with that of clavulone I, II and III (25-27) and established that they are identical. The comparison of ¹HNMR and ¹³CNMR spectral data of (37) and (38) with the spectral data of (43) and (4) isolated independently by two different groups of Japanese workers indicated that they are also identical.

Further, investigation of clavulone congeners from *C. viridis* resulted in the isolation of series of new halogenated prostanoids, chlorovulones, with strong anti-tumor activity. Their stereostructures were established as I, II, III and IV, *i.e.* (45), (46), (47), (48) on the basis of spectral data and CD measurement of chlorovulone derivatives (Nagaoka, Iguchi, Miyakoshi, Yamada and Yamada, 1986) and enantio-selective synthesis of chlorovulone II (46).

Chlorovulone I(45), showed 13 times stronger antiproliferative and cytotoxic activities in human promyelocytic leukemia (HL-60) cells *in vitro* than clavulone I.

Recently, punaglandins (Baker, Okuda, Yu and Schueer, 1985) characterized by C-12 oxygen and unprecedented C₁₀ chlorine functions, with the structure related to those of clavulones isolated from *Clavularia viridis* were detected in *Telestoa riisii*, and octocoral that lacks symbiotic algae. The following structures were proposed originally for PuG 1-6, *i.e.* (49) - (54) based on the spectroscopic data and biosynthetic pathway of related marine prostanoids clavulones or claviridenones but later, the structures of PuG 3 and 4 *i.e.* (51) and (52) were first revised (Nagaoka, Miyaoka, Miyakoshi and Yamada, 1986), followed by second revision (Suzuki, Mosita, Yanagisawa and Noyori, 1986) of (52) to (57) and (58).

The revision of structure was based on the synthesis of possible diastereoisomers with respect to C-5, C-6 and C-12.

In the family of punaglandins, PuG-3, (51) and PuG-4, (52), have received particular attention because of the potent inhibitory effect on L1210 leukemia cell proliferation (Fukushima and Kato, 1984).

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