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NEW PROSTAGLANDIN (PGF) DERIVATIVES FROM THE SOFT CORAL LOBOPHYTON DEPRESSUM

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Abstract

Four PGF derivatives (15S)-$PGF_{2\alpha}$-11-acetate methyl ester (1a), the 18-acetoxy derivative of compound 1a (2a) as well as their two corresponding free carboxylic acids (1b & 2b) were isolated from a soft-coral and their structure elucidated, mainly on basis of their spectral data.

A decade has passed since the first discovery of prostaglandins (PGs), obtained in high percentage, from a marine origin.[1,2] Although tremendous work in the field of PGs has been going on during this period, the disclosure of the PGs from the horny-coral Plexaura homomalla[1,2] was the only case to be reported. Indeed, there were indications of the existence of PGs in other marine organisms, based on the presence of prostaglandin-endoperoxide synthetase in these animals[3], however, no particular compound was isolated. This report describes the first isolation of PGs from a soft-coral. The difficulties in the determination of PGs other than PGAs (which possess characteristic IR and ^{1}H-NMR absorptions of the unsaturated five membered ketone)[1], stems from the relative high percentage of different glycerides in many of the marine organisms and, especially, in the soft-corals.[4] Various prostanoic acids may also be part of the animal-glycerides. The low resolution ^{1}H-NMR spectra of the PGFs are very similar on first sight, to those of oxygenated, hydroxy and/or oxo carboxylic acid containing glycerides. Thus the search for the PGs can be best monitored by the biological activities of the various organism extracted fractions, or by the existence of a crystallising PG derivative (the existence of a PG will then of course result in a thorough search for other PGs in the extracts).

In the case of Lobophyton depressum, a soft-coral (Alcyonacea, Alcyoniidae) collected in the Gulf of Eilat (The Red Sea), a crystalline compound $C_{23}H_{38}O_6$ (1a) was obtained from the CH_2Cl_2 extract; mp 55° (hexane), mass spectrum (CI, m/e,%): 411([M+1]$^+$, 1), 392(7), 350(6), 332(98), 314(100), 288(29) and 282(15)[5]. ν_{max}^{KBr} 3700, 3610, 3510(OH), 1740, 1730(OCO), 970(C=C) cm^{-1}; δ($CDCl_3$, 270MHz): 0.88t(3H, J=6.0Hz), 1.26brs (6H,H-17, 18,19), 2.04s(OAc), 2.32t(2H, J=7.2Hz, H-2,2'), 2.39ddd(1H, J=15.2, 9.0 and 5.4Hz, H-10α),

2.55ddd(1H, J=11.8, 8.4 and 7.0Hz, H-12α), 3.67s(OMe), 4.08q(1H, J=6.1Hz, H-15β), 4.17dd(1H, J=5.4 and 3.5Hz, H-9β), 4.90ddd(1H, J=9.0, 7.0 and 3.8Hz, H-11β), 5.41m(2H, H-5 and 6), 5.53m(1H, H-13) and 5.55m(1H, H-14). All the above data suggested an acetyl $PGF_{2\alpha}$ methyl ester structure for 1a. Being aware of the 15R/15S configurational possibilities in the Plexaura homomalla PGs[6], the C-15 configuration in 1a was carefully examined biologically, by comparing the activity of the hydrolysed compound (1c) with that of an authentic $PGF_{2\alpha}$ sample[7], and spectroscopically, by comparing the NMR spectra of 1c with that of $PGF_{2\alpha}$ (in a phosphate buffer)[8]. Both tests proved compound 1a to possess the 15S configuration and to be the $PGF_{2\alpha}$ derivative. Furthermore, selective oxidation of the 15-hydroxy group with DDQ[6,9] and reduction back to the 15-epimeric pair of alcohols[6,9], revealed that 1a was the more polar compound of the two, thus believed to be the 15S epimer[6,10].

According to a double irradiation experiment the location of the acetate group in 1a was determined at C-11, whereby, the H-11 proton-signal (the one shifted upon hydrolysis) was connected through H-12 to theC-13,14-double bond protons in 1a and in its 15-keto derivative. Compound 1a is therefore methyl 11α-acetoxy-9α,15(S)-dihydroxy-5-cis-13-transprostadienoate.

A second closely related compound was found to accompany 1a in the CH_2Cl_2 extract. This compound 2a, an oil, was separated from the mother liquor of 1a after repeated chromatographies; $C_{25}H_{40}O_8$, ν_{max}^{neat} 3470(OH), 1740, 1730, 1715(OCO), 1465, 1435, 1375, 1260, 1030, 970 cm^{-1}, mass spectrum (CI, m/e,%): 450([M-H_2O]$^+$,5), 408(5), 390(12), 372(16), 348(20), 330(100), 312(66), 298(18) and 280(20)[5]; δ($CDCl_3$, 270MHz): 0.90t(3H, J=7.2, Me_{20}), 2.04s(6H, 2OAc), 2.31t(2H, J=7.0, H-2,H-2'), 2.38ddd(1H, J=15.3, 9.0 and 5.5, H-10α), 2.55ddd(1H, J=10.8, 8.4 and 6.8, H-12α) 3.67s (OMe), 4.08 dt(1H, J=5.6 and 4.0, H-15β), 4.17dd(1H, J=5.5 and 3.5, H-9β), 4.82q(1H, J=5.3, H-18), 4.90ddd(1H, J=9.0, 6.8 and 4.0, H-11β), 5.40m (2H, H-5 and 6), and 5.54m(2H, H-13 and 14). The ^{1}H- and ^{13}C-NMR spectra (vide infra) suggested 2a to be similar in structure to 1a. The following changes in the ^{1}H-NMR spectrum of 2a were observable: a. The H-17 to H-19 brs of 1a disappeared, b. A 6H-singlet due to two acetates appeared (at 2.04), c. The ^{1}H-multiplet at δ4.82 in 2a proved the additional acetate to be a secondary one; Compound 2a contained altogether two hydroxyls and two acetates.

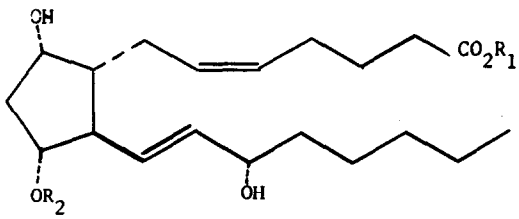
The disappearance of the δ1.26 six-proton signal of 1a in the ^{1}H-NMR spectrum of 2a together with the more explicit triplet shape of the C-20 terminal methyl signal suggested the second acetate to be located at C-17 or C-18[11]. Finally, according to the ^{13}C-NMR spectrum, this second acetate was found to be located at C-18. Comparison of the ^{13}C-NMR spectra of 1a and 2a revealed an almost absolute overlap of carbons 1 to 15[12]. On the other hand, carbons 16 to 20 differed clearly in the two compounds:

	C - 16,	17,	18,	19,	20
1a	37.2t	24.9t	31.8t	22.6t	14.0q
2a	32.7t	29.5t	75.2d	26.9t	8.5q

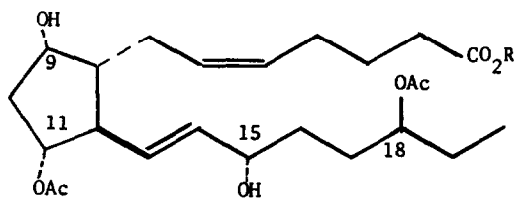
Carbons 16 and 20 in compound 2a are diamagnetically shifted while C-17 and C-19 are paramagnetically shifted, both shifts originating from the introduction of an acetate at C-18 thereby causing a γ-effect on the two former carbons and a β-effect on the latter two[14]. Compound 2a was determined therefore to be methyl 11α,18-diacetoxy-9α,15(S)-dihydroxy-5-cis-13-transprostadienoate (the 11,18-diacetate 18-hydroxy $PGF_{2\alpha}$ methyl ester).

The almost identical ^{1}H-NMR spectrum of protons 8 to 15 in 1a and 2a *vide supra* suggested 2a to have the same stereochemistry as 1a.

Two additional more polar compounds which were isolated from the crude ethyl-acetate extract of the *Lobophyton depressum* turned out to be the corresponding acetate and diacetate free acids 1b and 2b[15]. Esterification of the latter with CH_2N_2 gave compounds 1a and 2a respectively. The structure elucidation of other polar compounds of this soft-coral is under progress.



1a R_1=Me R_2=Ac
1b R_1=H R_2=Ac
1c($PGF_{2\alpha}$) R_1=H R_2=H



2a R=Me
2b R=H

References and Notes.

1. A.J. Weinheimer and R.L. Spragging, Tetrahedron Letters, 5185 (1969).
2. W.P. Schneider, R.D. Hamilton and L.E. Rhuland, J. Am. Chem. Soc., 94, 2122 (1972).
3. D.E. Morse, M. Kayne, M. Tidyman and S. Anderson, Biol. Bull., 154, 440 (1978).
4. In many cases as for example in the case of *Cladiella pachyclados* we have found glycerides up to ca. 25% of the dry weight of the animal.
5. E.O. Oswald, D. Parks, T. Eling and B.J. Corbett, J. Chromatography, 93, 47 (1974).
6. W.P. Schneider et al, J. Am. Chem. Soc., 99, 1222 and 6062 (1977) and ref. therein.
7. Tested by cyclic AMP production by rat Grapian follicle protein binding assay.
8. W.W. Conover and J. Fried, Proc. Nat. Acad. Sci. USA, 71, 2157 (1974).
9. The 15-keto derivative exhibited the following absorptions in the ^{1}H-NMR spectrum: δ2.55t(J=7.6, H-16,16'), 2.75ddd(H-12α), 4.99ddd(H-11β), 6.14d(J=15.9, H-14) and 6.69ddd(J=15.9 and 9.2, H-13). The 15R-epimer possesses an Rf=0.37 compared to Rf=0.28 of the natural and more polar 15S-epimer (toluene; ethylacetate 1;1). The 15R-epimer shows the following spectrum: δ1.29 brs(6H, H-17 to 19), 2.42ddd(H-10α), 2.55dt(H-12α), 4.08m(H-15α), 4.18brt(H-9β), 4.88ddd(H-11β), 5.52m(H-13) and 5.55m(H-14) (coupling constants being almost the same as in compound 1a).

10. N.M. Weinshenker and A. Longwell, Prostaglandins, 2, 207 (1972).

11. Carbons 16 and 19 were immediately excluded because of the multiplicities of H-15 and the terminal Me-group.

12.

C-1	-2	-3	-4	-5	-6	-7	-8	-9	-10	-11	-12	-13	-14	-15
1a 174.3	33.4	24.9	26.6	131.0	128.9	24.9	49.6	71.6	40.9	79.1	51.4	129.9	135.9	72.6
2a 174.3	33.4	24.9	26.6	131.4	128.8	24.7	49.7	71.8	41.0	79.1	51.4	130.1	135.5	72.4

all lines had the correct multiplicity. Compare with S.A. Mizsak and G. Slomp, Prostaglandins, 10, 807 (1975).

13. 15(S),18-dihydroxy-9-oxo-5-cis-transprostadienoic acid is the only 18-oxygenated PG which we could find; Hsu, Charles G., Jiu, James, Mizuba, Seth S. Searle, G.D. and Co. US 3,856,852, C.A. 82 P 139489C.

14. F.W. Wehrli and T. Wirthlin, Interpretation of Carbon-13 NMR Spectra, Heyden, London (1978).

15 As the acetate groups are much more labile to hydrolysis than the methyl-esters these compounds do not seem to be artifacts.

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