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NATURALLY OCCURRING PROSTAGLANDIN-1,15-LACTONES

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Abstract. Three prostaglandin-1,15-lactones, PGE_3-1,15-lactone-11-acetate (**1**), PGE_2-1,15-lactone (**2**) and PGE_3-1,15-lactone (**3**), have been isolated for the first time from a natural source, the nudibranch mollusc *Tethys fimbria*, and their structures elucidated by spectral means and comparison with synthetic compounds.

Following the first synthesis of $PGF_2\alpha$-1,15-lactone[1] by the "double activation" method[2], several prostaglandin lactones have been synthesized and reported to represent a therapeutically useful class of antifertility agents[3]. We report now that prostaglandin-1,15-lactones are naturally occurring molecules.

During a study on the chemical aspects of the ecology of nudibranchs[4] and other opisthobranch molluscs, we observed that the lipophylic extracts from the mantles of the nudibranch *Tethys fimbria* Linnaeus contained small amounts of metabolites which were absent from the hepatopancreas extracts of the same animal. Since it is expected[5] that potential allomones of naked molluscs should be present on their skin area, we decided to investigate the chemical nature of these metabolites.

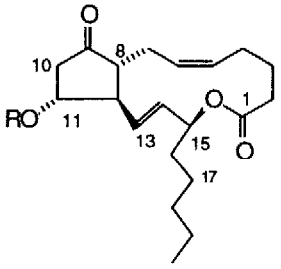
The diethyl ether solubles of an acetone extract of the mantles of 26 *T. fimbria* specimens were chromatographed on a Si-gel column using $CHCl_3$ and increasing amounts of CH_3OH as eluents. Fractions containing the acetate **1** (SiO_2-tlc, Rf 0.7; C_6H_6-$(C_2H_5)_2O$, 8:2) were further purified by preparative HPLC (μ-Porasil; *n*-hexane-EtOAc, 9:1) to afford 8 mg of **1** (together with 12 mg of its transformation product **4**; see below), while fractions containing **2** and **3** (Rf 0.15) were subjected to Si-gel column chromatography (C_6H_6-$(C_2H_5)_2O$, 8:2) and then to preparative HPLC (μ-Porasil; *n*-hexane-EtOAc, 8:2) to afford, in order of increasing polarity, 3 mg of **2** and 2 mg of **3**.

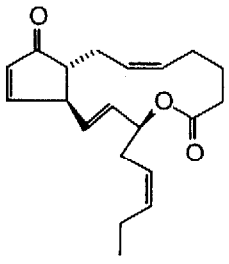
Inspection of ^1H- and ^{13}C-NMR spectra of **1-3** (Table) established the close similarity of the three compounds and, in particular, that presumably **1** was the acetyl derivative of **3** and that the difference between **2** and **3** resided in the presence of an additional double bond in **3**.

2 has a molecular formula $C_{20}H_{30}O_4$ by HREIMS (found 334.2152; calculated 334.2136). All the 20 carbons were visible in the ^{13}C-NMR spectrum (Table) and DEPT experiments established the presence of 18 proton bound carbons (1 methyl, 9 methylenes and 8 methines), the remaining

two carbons showing carbonyl resonances at δ 213.4 (ketone) and 173.3 (lactone or ester). Since four sp^2 carbons were found, besides the carbonyl carbons, two rings should be present in the molecule to account for the remaining two unsaturations arising from the molecular formula, presumably a carbocyclic ring and a lactone ring.

The proton connectivities in the C-2/C-8 and C-10/C-16 fragments were established by ^1H-^1H COSY and decoupling experiments, the two chains being linked to each other by means of the C-8 and C-12 methines. The chemical shift value of the C-15 proton (δ 5.19) established that this carbon is involved in the lactone linkage.





1 ; R = Ac , Δ^{17} *Z*
2 ; R = H
3 ; R = H , Δ^{17} *Z*
5 ; R = Ac

4

A distinguishing feature of the ^1H-NMR spectrum is the resonance of the C-10 methylene as the AB part of an ABX system, the X part being the carbinol proton at δ 4.14; in addition, one of the two C-10 protons (δ 2.80) shows a long range coupling through the ketone carbonyl with the C-8 proton (J *ca.* 1 Hz) which is typical of the 10β proton of prostaglandins of the E series[6].

All these data suggested the PGE_2-1,15-lactone structure for **2**. A literature search revealed that this compound was synthesized in 1983 by Bundy *et al.*[3]; chromatographic and spectral comparison of **2** with a synthetic specimen[7] showed that they were identical, including the relative stereochemistry. Furthermore, the CD spectra[8] of **2** and of the synthetic specimen were identical, with maxima at 298 (Δε = -4.7) and 197 nm (Δε = -23.4), thus establishing the absolute configuration.

The structure of **3**, $C_{20}H_{28}O_4$ by HREIMS (found 332.1953; calculated 332.1980) was inferred by comparison of the ^1H- and ^{13}C-NMR data with those of **2**, where relevant, and by acetylation (Ac_2O, py) affording **1**.

Compound **1** was collected *ca.* 90% pure after the first chromatographic purification. When subjected again to Si-gel column chromatography it afforded relevant amounts of the AcOH elimination product **4**, paralleling the behaviour on Si-gel of PGE_2-1,15-lactone-11-acetate[3]. However a pure sample of **1** was obtained by preparative HPLC on μ-Porasil (*n*-hexane-EtOAc, 9:1).

TABLE - Selected NMR Data for Lactones **1-5**[a]

	δ^1H, multiplicity, J Hz					δ^{13}C[d]				
C	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
1						172.9	173.3	173.0	172.9	173.2
5	5.36 m	5.35 m	5.35 m	5.40 m	5.35 m	129.6	129.3[e]	129.4[f]	129.5	129.3[h]
6	5.60 m	5.60 m	5.60 m	5.90 m	5.58 m	129.0	129.0[e]	129.0[f]	129.5	129.3[h]
8	1.88[b]	1.85[b]	1.85[b]	1.93[b]	1.86[b]	57.2	58.1	58.1	57.9	57.3
9						211.5	213.4	213.7	209.1	211.7
10α	2.15[b]	2.22[b]	2.23[b]		2.16[b]					
10β	2.95 ddd 19.0 8.1 1.1	2.80 ddd 18.7 7.7 1.1	2.80 ddd 18.4 8.4 1.4	6.15 dd 5.7 2.2	2.92 ddd 19.0 8.1 1.1	43.2	45.6	45.6	133.5	43.2
11	5.06 aq[c]	4.14 aq[c]	4.13 m	7.40 dd 5.7 1.8	5.08 aq[c]	72.5	71.9	71.9	161.9	72.5
12	2.47[b]	2.28[b]	2.30[b]	3.13 m	2.46[b]	51.5	55.1	55.1	51.1	51.7
13	5.83 dd 15.8 8.4	5.81 dd 15.7 8.7	5.84 dd 15.8 8.6	5.95 dd 15.7 8.7	5.78 dd 15.8 8.4	132.1	132.5	132.5	134.1	131.8
14	6.03 dd 15.8 6.2	6.12 dd 15.7 6.2	6.12 dd 15.8 6.2	6.05 dd 15.7 6.6	6.02 dd 15.8 6.2	133.5	134.1	134.1[g]	131.9	134.1
15	5.19 m	5.19 dt 8.5 5.8	5.22 dt 6.5 7.3	5.20 dt 6.7 7.7	5.15 m	71.4	71.9	71.3	71.4	71.9
17	5.27 m		5.35 m	5.30 m		123.2		123.4	123.2	
18	5.50 m		5.52 m	5.50 m		134.7		134.7[g]	134.7	
19						20.8		20.8	20.8	
20	0.97 t 7.5	0.90 t 6.7	0.98 t 7.5	0.97 t 7.4	0.88 t 6.7	14.0	14.0	14.1	14.2	13.9
$CH_3\underline{C}O$						170.4				170.4
$\underline{CH_3}CO$	2.06 s				2.04 s	20.8				20.8

[a]Spectra were recorded on Bruker WM-500 and WM-300 spectrometers in $CDCl_3$ solutions. Assignments were made by ^{1}H-^{1}H-, ^{1}H-^{13}C-COSY and decoupling experiments (compounds **1** and **4**) and by ^{1}H-^{1}H-COSY and decoupling experiments (compounds **2**, **3** and **5**). The multiplicity of proton bound carbons was determined by DEPT sequence.

[b]Overlapped to other signals.

[c]Apparent quartet.

[d]Other methylene carbons: **1**; 23.9, 25.4, 25.7, 31.8, 34.1. **2**; 22.5, 24.0, 25.3, 25.5, 25.7, 31.5, 34.1, 34.2. **3**; 24.1, 25.4, 25.7, 32.0, 34.0. **4**; 24.1, 25.8, 25.9, 30.8, 34.8. **5**; 22.6, 23.9, 25.3, 25.5, 25.7, 31.6, 33.9, 34.1.

[e,f,g,h]Chemical shift values with identical superscripts may be interchanged.

The structure of **1** as PGE_3-1,15-lactone-11-acetate was evident from its NMR data and by comparison with those of the acetyl derivative **5** prepared from synthetic **2** (Table). Furthermore, the stereochemistry at C-11 was corroborated by observing that when the C-11 proton was irradiated in NOE difference spectra only the C-10β proton showed an enhancement, the C-10α proton remaining practically unaffected. The *Z* stereochemistry of the C-17/C-18 double bond was inferred by the ^{13}C chemical shift value of C-19[9], while the stereochemistry at C-15, which cannot be simply inferred from the NMR data[10], was assumed to be *S* since **1** cooccurs with **3** in the same animal. The CD spectrum[8] of **1** was superimposable to that of **5**, with maxima at 298 ($\Delta\varepsilon$ = -4.3), 227 ($\Delta\varepsilon$ = +2.4) and 197 nm ($\Delta\varepsilon$ = -15.4), establishing also in this case the absolute configuration.

The artifact **4**, less polar than **1** on SiO_2-tlc, was an UV absorbing compound (λ_{max} 215 nm, ε 8.500) having a molecular formula of $C_{20}H_{26}O_3$ by HREIMS (found 314.0846; calculated 314.0875) and thus has the PGA_3-1,15-lactone structure. The NMR data (Table) are in agreement with the proposed structure.

The prostaglandin lactones isolated from *T. fimbria* add to the list of modified marine prostanoids[11-13] whose function in the producing organisms is to be discovered. However it has been reported[14] that PGA_2, which is contained at levels as high as 8% of the dry weight in the gorgonian *Plexaura homomalla*[10,15], induces an emetic response in test fish at 0.1 - 0.2 mg oral doses.

It could be hypothesized that compounds **1-3** may either exert a biological activity as lactones or represent a storage form of prostaglandins. Research is in progress on the biosynthesis of these compounds and on their biological role in *T. fimbria*[16].

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