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New Polypropionate Pyrones from the Philippine Sacoglossan Mollusc *Placobranchus ocellatus*

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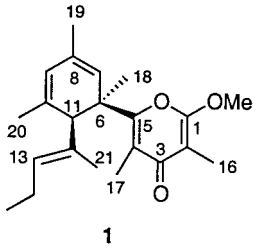
Abstract—Six new propionate-derived metabolites, **4**–**9**, have been isolated along with the known 9,10-deoxytridachione (**1**) from the sacoglossan mollusc *Placobranchus ocellatus* collected in the Philippines. The structures of the new compounds were determined by spectrometric methods.

Chemical and ecological studies of opisthobranch molluscs have been ongoing for a number of years,[1,2] stimulated at least in part by the fact that these animals lack an external protective shell and thus appear particularly vulnerable to predation. A chemical defensive strategy has long been hypothesized[3,4] for these molluscs and ichthyotoxicity and feeding deterrence has been confirmed for some of their metabolites.[2] The source of these defensive chemicals has been traced in many cases to diet and in some instances to de novo biosynthesis. Where defensive chemicals are sequestered from dietary sources, e.g. algae or sponges, metabolite variation is found to occur with changes in geographical location. Conversely, invariance in metabolite content with geographical change in collection site has come to be taken as suggestive of de novo biosynthesis.[5]

Some molluscs within the order Sacoglossa are unique in that they assimilate from dietary algae active chloroplasts that carry out photosynthesis in the animal.[6] In early studies in this area Ireland and Scheuer confirmed that the sacoglossan *Placobranchus ocellatus*, which harbors algal chloroplasts, biosynthesized the polypropionate metabolite 9,10-deoxytridachione and further showed that it underwent photochemical isomerization in vivo to photodeoxytridachione (**2**).[7] The polypropionate skeleton has since emerged as a common feature of many molluscan metabolites.[1]

9,10-Deoxytridachione (**1**) [(−)-enantiomer] was first isolated from the sacoglossan mollusc *Tridachiella diomeda*.[8] Compound **1** with unspecified optical rotation has also been reported from *Placobranchus ocellatus*[7] and *Elysia timida*.[9] The (+)-enantiomer of 9,10-deoxytridachione (**2**) and *iso*-9,10-deoxytridachione have been isolated from the sacoglossan molluscs *Elysia chlorotica*[10] and *Elysia timida*,[9] respectively. In 1996, tridachiahydropyrone (**3**), having a modified propionate-based skeleton was reported by Cimino and coworkers from *Tridachia crispata* collected on the Venezuelan coast.[11] Earlier studies from our laboratory on *T. crispata* collected off Jamaica resulted in the isolation of eight propionate-derived metabolites patterned after **1** and **2**.[12] As part of our ongoing study of the chemistry of marine organisms,[13] we have analyzed the extracts of *P. ocellatus* (order Sacoglossa, family Elysioidea) collected from the Philippines, and isolated the (+)-enantiomer of 9,10-deoxytridachione (**1**) and six new compounds. The new compounds **4**–**7**, designated tridachiapyrones G–J, are structurally related to **1**, while compounds **8**–**9** are structurally related to **3** and are designated as tridachiahydropyrones B–C. In this paper we report the isolation and structure elucidation of these new compounds.



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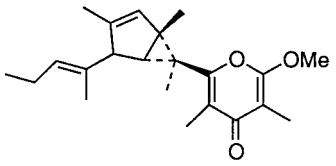

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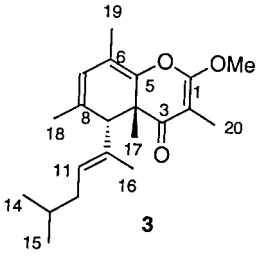

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Keywords: mollusc; polypropionate metabolites; peroxides; sacoglossan; *Placobranchus ocellatus*.

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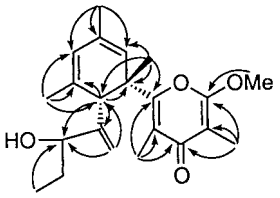
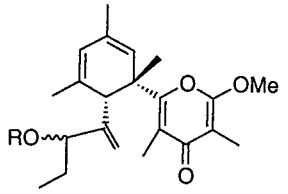
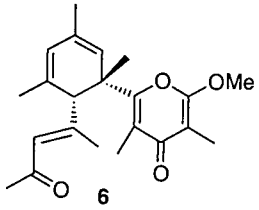


Figure 1. Substructures developed for compound **2**.



4 R = H, 13 *R* or *S*
5 R = H, 13 *S* or *R*
7 R = OH, 13 *R* or *S*



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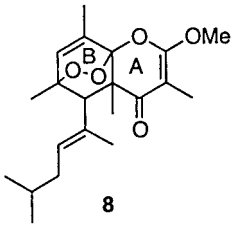

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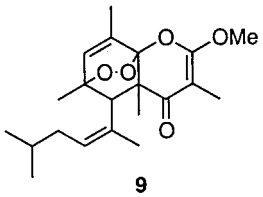

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Results and Discussion

Samples of *P. ocellatus* were collected from the Philippines and extracted with MeOH and then MeOH–CH_2Cl_2 (1:1). The combined, concentrated extracts were subjected to solvent partitioning[14] to yield hexane- and CH_2Cl_2-soluble materials. Both fractions contained propionate-derived compounds, and therefore were fractionated over Si gel open column and reversed-phase HPLC to give compound **1** ((+)-enantiomer) and **4**–**6** from the CH_2Cl_2 fraction, and **1** ((+)-enantiomer) and **7**–**9** from the hexane fraction.

The major compound obtained possessed ^1H and ^{13}C NMR data identical with those of (+)- and (−)-9,10-deoxytridachione (**1**),[8,10] but its specific rotation ($[\alpha]_D$=+366.6°, CH_2Cl_2) was close to that reported for (+)-9,10-deoxytridachione ($[\alpha]_D$=+400, $CHCl_3$) by Dawe and Wright[10] but of opposite sign to that reported by Ireland and Faulkner ($[\alpha]_D$=−194, $CHCl_3$).[8] Therefore, this compound was identified as 9,10-deoxytridachione (**1**, (+)-enantiomer).[15]

Tridachiapyrone G (**4**), $[\alpha]_D$=+229°, was obtained as a glass. The molecular formula of **4**, $C_{22}H_{30}O_4$, was determined by HRFABMS. The IR spectrum of **4** contained bands at 3400, 1655, 1565 cm^{-1} consistent with the presence of a hydroxyl group and a γ-pyrone moiety. The latter was supported by UV absorption at 260 (ε 12300) nm. The NMR data, which were unambiguously assigned by COSY, NOESY, HMQC, and HMBC experiments, were similar to those of **1**, the major differences being the ^1H and ^{13}C NMR shifts surrounding C-12 (i.e. C-11, C-12, C-13, C-18, C-21). The presence of a terminal double-bond and an oxymethine in **4** was indicated by NMR data

Table 1. NMR data for tridachiapyrones G–J (**4**–**7**) (spectra were recorded in $CDCl_3$)

Position	^{13}C[a]		^1H[b]			
	4	**7**	**4**	**5**	**6**	**7**
1	161.8	161.8				
2	99.0	99.1				
3	181.6	181.7				
4	120.2	120.3				
5	160.7	160.4				
6	47.8	47.4				
7	124.2	123.7	5.48 (s)	5.42 (s)	5.60 (s)	5.57 (s)
8	127.9	128.0[c]				
9	122.3	122.4	5.70 (s)	5.72 (s)	5.78 (s)	5.71 (s)
10	136.2	135.7[c]				
11	52.4	52.9[c]	3.02 (s)	2.56 (s)	2.78 (s)	3.07 (s)
12	148.6	143.0[c]				
13	75.1	87.5	3.29 (br)	3.26 (m)	5.93 (s)	5.54 (br)
14	28.9	[d]	1.41 (m), 1.32 (m)	1.63 (m), 1.24 (m)		1.69 (m), 1.33 (m)
15	10.7	10.6	0.77 (t, 7.0)	0.89 (t, 7.0)	2.020 (s)	0.71 (t, 7.0)
16	6.8	6.8	1.84 (s)	1.86 (s)	1.825 (s)	1.82 (s)
17	12.4	12.4	1.97 (s)	1.99 (s)	2.024 (s)	1.97 (s)
18	26.3	26.1	1.49 (s)	1.48 (s)	1.50 (s)	1.48 (s)
19	21.3	21.4	1.81 (d, 2.0)	1.81 (d, 1.0)	1.835 (d, 1.0)	1.81 (s)
20	22.2	22.2	1.74 (s)	1.73 (s)	1.73 (br s)	1.76 (s)
21	114.0	116.5	5.02 (s)	5.05 (s), 5.23 (s)	1.825 (s)	5.12 (s), 5.19 (s)
Ome	55.6	55.6	3.99 (s)	3.98 (s)	3.99 (s)	4.00 (s)
OH			1.64 (br)	[d]		7.91 (br)[e]

[a] ^{13}C NMR at 125 MHz, referenced to $CDCl_3$ (δ 77), assignment aided by HMQC and HMBC experiments.
[b] ^1H NMR at 500 MHz, referenced to residual solvent $CDCl_3$ (δ 7.24), assignment aided by COSY and NOESY experiments.
[c] Broad signals, but clearly observed in the HMBC spectrum of **7**.
[d] Not observed.
[e] Peroxide OH.

Table 2. NMR data for tridachiahydropyrones B–C (**8**–**9**) (spectra were recorded in $CDCl_3$)

Position	^{13}C[a]		^{1}H[b]	
	8	**9**	**8**	**9**
1	163.0	163.0		
2	89.9	89.9		
3	196.1	196.1		
4	50.5	50.3		
5	106.8	106.8		
6	137.3	137.3		
7	131.2	130.3	6.18 (s)	6.18 (s)
8	80.9	80.9		
9	56.1	53.7	3.55 (s)	3.25 (s)
10	129.2	132.7		
11	134.9	127.5	5.87 (t, 7)	5.03 (t, 7)
12	37.3	37.4	1.90 (t, 7)	1.93 (t, 7)
13	28.6	28.9	1.68 (m)	1.60 (m)
14	22.6	22.6	0.88 (d, 7.0)	0.88 (d, 7.0)
15	22.4	22.4	0.88 (d, 7.0)	0.88 (d, 7.0)
16	15.0	19.4	1.46 (s)	1.83 (s)
17	18.9	20.2	1.05 (s)	0.90 (s)
18	19.4	19.6	1.23 (s)	1.34 (s)
19	15.0	15.4	2.05 (s)	2.03 (s)
20	6.8	6.8	1.67 (s)	1.69 (s)
Ome	55.4	55.4	3.90 (s)	3.91 (s)

[a] ^{13}C NMR at 125 MHz, referenced to $CDCl_3$ (δ 77), assignment aided by HMQC and HMBC experiments.
[b] ^{1}H NMR at 500 MHz, referenced to residual solvent $CDCl_3$ (δ 7.24), assignment aided by COSY and NOESY experiments.

[δ_H 5.02 (s, 2H, H-21), 3.29 (br, H-13); δ_C 114.0 (t, C-21), 148.6 (s, C-12), 75.1 (d, C-13)]. Corresponding changes were also observed for H/C-11 and H/C-14 [e.g. H-11: δ 3.02 in **4** vs δ 2.77 in **1**; C-11: δ 52.4 in **4** vs δ 59.6 in **1**]. HMBC data (Fig. 1) provided confirmation for the structure of tridachiapyrone G as **4**. The relative stereochemistry of C-6 and C-11 was assigned from a NOESY correlation observed between H-11 and H-18. A trace compound, tridachiapyrone H (**5**) had the same UV absorption and molecular formula ($C_{22}H_{30}O_4$) as those of **4** suggesting that these compounds are isomers. Comparison of the ^{1}H NMR data for **5** with those for **4** demonstrated that most of these data were virtually identical except for some changes surrounding the oxymethine carbon. From these data it was inferred that tridachiapyrone H was either the 11-epimer of **4** or the 13-epimer of **4**. The possibility that **5** was an 11-epimer of **4** was eliminated because a NOESY correlation between H-11 and H-18 was observed in the NOESY spectrum of tridachiapyrone H (**5**). Therefore **5** must be the 13-epimer of **4**, but unfortunately, the configuration of 13-OH in **4** and **5** could not be assigned due to the scarcity of samples isolated.

Tridachiapyrone I (**6**) was obtained as a glass. Its molecular formula, established by HRFABMS to be $C_{22}H_{28}O_4$, differed from that of **1** by replacement of two hydrogens with an oxygen. Comparison of the ^{1}H NMR spectrum of **6** with that of **1** indicated that the signals for the C-14 methylene protons in **1** were absent in the ^{1}H NMR spectrum of **6** (Table 1), and the triplet for Me-15 in **1** was replaced by a methyl singlet at δ 2.02 in the spectrum of **6**. This suggested that **6** had a ketone at C-14 in place of a methylene as in **1**. The downfield shifts of H-13 [δ 5.93 (s) in **6** vs. δ 5.09 (t) in **1**] and H-21 [δ 1.83 (s) in **6** vs δ 1.32 (s) in **1**] due to deshielding by the carbonyl were consistent with a ketone at C-14. NOEs were observed between H-11 and Hs-13, -18 and -20, thus establishing a 12*E*-configuration and a *cis* arrangement of H-11/H-18. Therefore, structure **6** was assigned to tridachiapyrone I.

Tridachiapyrone J (**7**), $[\alpha]_D=+59.2°$ (*c* 0.56, CH_2Cl_2), was obtained as a glass. Both FABMS and MALDI-TOF MS of **7** gave a pseudo-molecular ion at *m/z* 375 $[M+H]^+$ and a significant ion peak at *m/z* $[M-OH]^+$. The molecular formula of **7**, $C_{22}H_{30}O_5$, was deduced from HRFABMS. This formula contains one oxygen more than that of **4** and **5**. The hydroperoxy group was postulated because of the significant peak at *m/z* $[M-OH]^+$ in FAB, MALDI-TOF and EIMS.[16] Also in the EIMS an intense peak was observed at *m/z* 341 (53%) which could be attributed to the loss of a −OOH fragment from the molecule. The ^{1}H NMR spectrum of **7** was essentially identical to that of tridachiapyrone G (**4**) except that the H-13 signal appeared at δ 5.54 (br) in the spectrum of **7** vs 3.29 (br) in the spectrum of **4** and one of the 14-methylene protons was also shifted downfield (Table 1). The ^{13}C data of **7** also matched closely those of **4** except for the downfield shift of C-13 and upfield shift of C-12. These shifts were ascribed to the presence of a hydroperoxy group at C-13. HMQC and HMBC data proved the assignment of NMR data, and confirmed structure **7** for tridachiapyrone J. The relative stereochemistry of C-6 and C-11 in **7** was assumed to be the same as in **4** by comparing their NMR data and based on biogenetic grounds, but again, the relative configuration of C-13 was not assigned.

Tridachiahydropyrones B (**8**) and C (**9**) were isolated as a mixture, the ratio being 4:5 as judged by the integration of the ^{1}H NMR spectrum of the mixture. FAB and MALDI-TOF mass spectra showed an ion peak at *m/z* 363 $[M+H]^+$. HRFABMS revealed an exact mass of 363.2155 suggesting a molecular formula $C_{21}H_{30}O_5$ for both **8** and **9**. Tridachiahydropyrones B (**8**) and C (**9**), containing two more oxygens than **3**, possessed the diagnostic NMR data reported for the α-methoxy-β-methyl-γ-pyrone system and the side chain of **3**,[11] signaling that **8** and **9** were analogs of **3**. The presence of the α-methoxy-β-methyl-γ-pyrone residue was also supported by a UV absorption at 278 (ϵ 11300) nm and an IR band at 1620 cm^{-1}. A detailed analysis of COSY, HMQC, and HMBC data of both isomers **8** and **9** provided the basis for assigning the NMR data for **8** and **9** (Table 1), although two sets of signals with some overlapping were present in the ^{1}H and ^{13}C NMR spectra of the mixture of **8** and **9**. The NMR data of **8** were very similar to those of **3** except for principal differences associated with the protons and carbons in ring B. The ^{13}C NMR signals for C-5 and C-8 of the diene system in **3** were missing; instead ^{13}C resonances were observed at δ 106.8 (C-5), attributed to a ketal carbon, and at δ 80.9 (C-8), assigned to a quaternary carbon connected to an oxygen. Because no hydroxyl absorption was noted in the IR spectrum, the ketal oxygen at C-5 and the oxygen at C-8 must link together to form a peroxide bridge to account for the seventh unit of unsaturation deduced from the molecular formula. The existence of the peroxide was substantiated by EIMS fragmentation ion peaks at *m/z* 346 $[M-O]^+$, 330 $[M-O_2]^+$, and 315 $[M-O_2-Me]^+$ corresponding to successive losses of one oxygen, two oxygens, and two oxygens plus a methyl,

respectively. The differences in the chemical shifts of the protons and carbons of ring B of **8** and **9** compared to **3** were attributed to this peroxide bridge.

Comparison of the NMR data for **8** and **9** revealed that the difference in the structures of **8** and **9** could be attributed to a difference in double-bond geometry in the alkenyl chain. The *E* geometry was assigned to the double bond (C-10–C-11) in **8** because the chemical shifts of Me-16 (δ_H 1.46, δ_C 15.0) resembled those of the same methyl of tridachiahydropyrone (**3**) (δ_H 1.53, δ_C 13.7). Accordingly, the *Z* configuration was assigned to the double bond in **9**. The downfield shift of C-16 (δ_C 19.4) and upfield shift of C-9 in **9** when compared to **8** also supported structure **9** (Table 2). Therefore, the isomeric structures **8** and **9** were proposed for tridachiahydropyrones B and C, respectively, but the configurations of the chiral carbons were not assigned.[17]

The hydroperoxide **7** could result from enzymatic or photochemical oxidation of **1** ((+)-isomer), and compounds **4** and **5** could arise by reduction of **7**. Peroxides **8** and **9** are envisioned as arising by 1,4-addition of molecular oxygen to a precursor such as **3**. Peroxides **8** and **9** represent additions to a substantial list of fatty acid, polyketide, norterpene, and sterol peroxides isolated from marine organisms.[1,18] They could thus be natural products, but since they were isolated in small quantities it is possible they are artifacts from oxidation during storage or workup. Peroxide formation of 1,4-cyclohexadiene-type compounds during isolation procedures and subsequent rearrangement to epoxides, has been noted before.[19]

Experimental

General experimental procedures

Merck Si gel 60 (230–240 mesh) was used for vacuum flash chromatography. HPLC was conducted using a UV detector and a Spherex 5 C-18 column. IR spectra were taken on a Bio-Rad 3240-SPC FT instrument, UV spectra on a Hewlett–Packard spectrophotometer. NMR experiments were conducted with a Varian VXR-500 instrument equipped with a 3 mm $^1H/^{13}C$ switchable gradient microprobe (MDG-500-3) and a pulsed field gradient driver; signals are reported in parts per million (δ), referenced to the solvent used. FABMS were measured on a VG ZAB-E mass spectrometer, and optical rotations on a Rudolph Autopol III Automatic Polarimeter. MALDI-TOF mass spectra were taken on a PerSeptive Biosystems Voyages Elite instrument, and EIMS on a Hewlett–Packard 5985B mass spectrometer.

Animal material

The sacoglossan molluscs, *P. ocellatus*, were collected in February 1994 near Buyong in the Philippines, and frozen shortly after collection. A voucher specimen has been deposited at the University of Oklahoma (4PH94).

Extraction and isolation

Frozen specimens of the mollusc (283 g wet wt; 14 g dry wt after extraction) were thawed and extracted with MeOH (450 mL×2) followed by MeOH–CH_2Cl_2 (1:1) (450 mL×2). All extracts were combined and after removal of solvents in vacuo the combined extract was dissolved in H_2O–MeOH (1:9; 250 mL), and the solution extracted twice with hexane (250 mL each) to give, after evaporation of solvent, 0.63 g hexane-soluble fraction. The aqueous MeOH phase therefrom was diluted with H_2O (71 mL) to 30% H_2O in MeOH and extracted with CH_2Cl_2 (250 mL×2) to yield 0.82 g of CH_2Cl_2-soluble material. The CH_2Cl_2 fraction was fractionated by vacuum liquid chromatography over Si gel using increasing amounts of EtOAc in hexane as eluent (10% EtOAc–hexane to EtOAc) to give eight fractions (A–H). The major and known compound, (+)-9,10-deoxytridachione (**1**), was obtained from fractions C and D, after evaporation of solvents. Reversed-phase HPLC of Fraction G using 35% H_2O–CH_3CN yielded three new analogues of **1**, tridachiapyrones G–I (**4**–**6**). The hexane-soluble material was also subjected to Si gel chromatography in a similar manner to that employed for the CH_2Cl_2-soluble fraction. The second fraction therefrom was rechromatographed by reversed-phase HPLC using 20% H_2O–CH_3CN as eluent to afford tridachiahydropyrone D (**10**) and an inseparable mixture of tridachiahydropyrones B (**8**) and C (**9**). Rechromatography of the fourth fraction from the hexane-soluble material on a C_{18} open column using 20–10% H_2O–CH_3CN as eluent gave **1** and semipure tridachiapyrone J (**7**), which was further purified by reversed-phase HPLC using 35% H_2O–CH_3CN as eluent. The amounts and yields of compounds obtained from hexane and CH_2Cl_2-soluble fractions are as follows: **1** (~200 mg, 7.1×10^{-2}% of wet specimen wt), **4** (2.2 mg, 7.7×10^{-4}%), **5** (0.6 mg, 2.1×10^{-4}%), **6** (0.8 mg, 2.8×10^{-4}%), **7** (7.8 mg, 2.8×10^{-3}%), and a mixture of **8** and **9** (1.7 mg, 6.0×10^{-4}%).

(+)-9,10-Deoxytridachione (1). Glass; $[\alpha]_D=+366.6°$ (*c* 0.35, CH_2Cl_2); NMR data identical to lit;[8,10] FABMS *m/z* 343 $[M+H]^+$.

Tridachiapyrone G (4). Glass; $[\alpha]_D=+229°$ (*c* 0.16, CH_2Cl_2); IR (neat) ν_{max} 3400, 1655, 1565 cm^{-1}; UV (MeOH) λ_{max} 260 (ϵ 12300) nm; ^1H and ^{13}C NMR data, see Table 1; HRFABMS *m/z* 359.2243 $[M+H]^+$ (calcd for $C_{22}H_{31}O_4$, 359.2222).

Tridachiapyrone H (5). Glass; UV (MeOH) λ_{max} 260 (ϵ 11800) nm; ^1H NMR data, see Table 1; HRFABMS *m/z* 359.2221 $[M+H]^+$ (calcd for $C_{22}H_{31}O_4$, 359.2222).

Tridachiapyrone I (6). Glass; UV (MeOH) λ_{max} 252 (ϵ 13100) nm; ^1H NMR data, see Table 1; HRFABMS *m/z* 357.2090 $[M+H]^+$ (calcd for $C_{22}H_{29}O_4$, 357.2066).

Tridachiapyrone J (7). Glass; $[\alpha]_D=+59.2°$ (*c* 0.56, CH_2Cl_2); UV (MeOH) λ_{max} 252 (ϵ 13700) nm; IR (neat) ν_{max} 3350, 1650, 1580 cm^{-1}; ^1H and ^{13}C NMR data, see Table 1; FABMS *m/z* 375 (98%) $[M+H]^+$, 359 (57%) $[M-Me]^+$, 357 (100%) $[M-OH]^+$; HRFABMS *m/z* 375.2197 $[M+H]^+$ (calcd for $C_{22}H_{31}O_5$, 375.2171), 357.2111 $[M-OH]^+$ (calcd for $C_{22}H_{29}O_4$ 357.2066); MALDI-TOF MS (Matrix ATT) *m/z* 375 $[M+H]^+$, 357 $[M-OH]^+$; EIMS (12 eV) 374

(6%) $[M]^+$, 357 (77%) $[M-OH]^+$, 345 (100%), 341 (53%).

Tridachiahydropyrones B (8) and C (9). Glass; UV (MeOH) λ_{max} 278 (ϵ 11300) nm; IR (neat) ν_{max} 1620 (br), 1460, 1378, 1350 cm^{-1}; ^1H and ^{13}C NMR data, see Table 2; FABMS *m/z* 363 $[M+H]^+$; HRFABMS *m/z* 363.2155 $[M+H]^+$ (calcd for $C_{21}H_{31}O_5$, 363.2171); MALDI-TOF MS (Matrix ATT or THAP) *m/z* 363; EIMS (12 eV) *m/z* 362 (1.2%) $[M]^+$, 346 (3.3%) $[M-O]^+$, 330 (29.7%) $[M-O_2]^+$, 315 (100%) $[M-O_2-Me]^+$.

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15. The absolute stereochemistry of neither (+) nor (−)-9,10-deoxytridachione has been determined. Hence, the absolute configuration depictions for (+) and (−)-9,10-deoxytridachione in this paper and in the literature are arbitrary.
16. In contrast an $[M-OH]^+$ ion peak was not observed in the FABMS spectra of **4** and **5** which have only a hydroxyl group at C-13.
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