

Atomarianones A and B: two cytotoxic meroditerpenes from the brown alga *Taonia atomaria*

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Abstract—Two novel cyclized meroditerpenoids atomarianones A, and B (**1** and **2**), were isolated from the organic extract of the brown alga *Taonia atomaria* collected at Serifos island in the Central Aegean Sea. This is only the second report on metabolites having a functionalized indane moiety instead of a benzofurano- or a benzopyrano-ring connecting their aromatic and diterpenoid parts. Atomarianone A contains an unprecedented *cis* B–C ring fusion while atomarianone B is the epimer of A at C-7. Both metabolites were found to exhibit significant cytotoxic activity against two lung cancer cell lines.

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Taondiol and atomaric acid, the first metabolites in the family of cyclized meroditerpenoids were isolated in the early 70s by Gonzalez and co-workers from *Taonia atomaria* collected in the Canary Islands.¹ These tocopherol-like metabolites originating partly from mevalonate and partly from shikimate precursors (mixed biogenesis) were isolated along with isotaondiol and two minor unstable meroditerpenes that were considered to be precursors of atomaric acid.²

In the following years a number of cyclized meroditerpenes and acyclic precursors have been isolated from the Caribbean *Stypopodium zonale* and the Pacific *Stypopodium flabeliformae* alga, which are also members of the Dictyotaceae family and morphologically very similar to *T. atomaria*.³

After Gonzalez's pioneering work on the Atlantic *T. atomaria*, subsequent chemical studies on a *Taonia* species were reported almost 20 years later on *T. atomaria*

from the North Adriatic Sea and *T. lacheana* and *T. atomaria* f. *ciliata* from Sicily.⁴ Strikingly, the secondary metabolites found in these investigations were various types of sesquiterpenes without traces of meroditerpenes, thus introducing a serious chemotaxonomic uncertainty in these two genera.⁵ A recent investigation by our laboratory on *T. atomaria* from the Aegean Sea resulted in the isolation of a series of linear and chromenol type meroditerpenoids thus widening the dispute on the chemotaxonomic value of this class of metabolites or questioning the correct identification of the investigated organisms.⁶

Stypopodium meroditerpenes include sargaquinone,⁷ 2-(geranylgeranyl)-6-Me-hydroquinone,⁷ taondiol,⁷ atomaric acid,⁷ epitaondiol,⁷ stypodiol,⁷ epistypodiol,⁷ stypotriol,⁷ stypoldione,⁷ isoeptaondiol,⁸ styptoquinonic acid,⁹ stypolactone,¹⁰ and recently four more derivatives of atomaric acid.¹¹ This family of compounds proved to be quite bioactive^{7–9} as exemplified by stypoldione, which is a potent antimitotic agent.¹²

As part of our ongoing program aimed at the isolation of biologically active compounds from marine organisms of the Greek seas,¹³ we investigated further the

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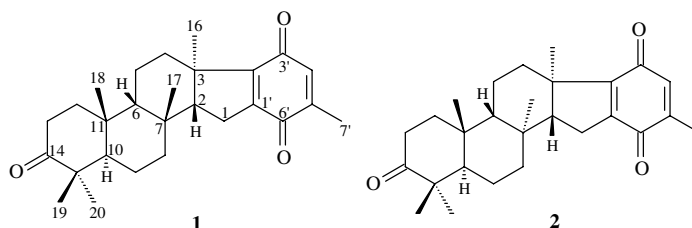


Figure 1. Structures of metabolites **1** and **2**.

minor secondary metabolite content of *T. atomaria* from the Central Aegean Sea and, herein, we report on two new cyclized meroditerpenoids, atomarianones A, and B (Fig. 1).

The crude (MeOH/DCM, 1:3) extract (37 g) of the freeze-dried alga was subjected to silica gel gravity chromatography using a step gradient elution sequence (*c*-hexane to EtOAc to MeOH). Final purification was achieved by repeated normal phase HPLC separations to yield 9.8 mg of **1** (0.026% of the extract) and 8.7 mg of **2** (0.024% of the extract).

Atomarianone A, was isolated as an optically active brown oil ($[\alpha]_D^{20} +3.3$, c 1.21, CHCl_3) and analyzed for $\text{C}_{27}\text{H}_{36}\text{O}_3$ by HREIMS ($[\text{M}]^+$ m/z 408.2675; calcd 408.2665), a formula indicating 10 degrees of unsaturation. The ^{13}C NMR spectrum (in C_6D_6) showed signals for 27 carbons and DEPT experiments distinguished them as 6 methyls, 7 methylenes (all sp^3), 4 methines (3 sp^3 and 1 sp^2), 4 sp^3 quaternary, 3 sp^2 quaternary, and 3 carbonyls (1 isolated ketone at δ 213.5 and 2 conjugated carbonyls, at δ 185.7 and 186.5). The above data required a pentacyclic structure with a benzoquinone ring. The ^1H NMR spectrum (in C_6D_6) showed five angular methyls (δ 0.88, 0.94, 0.95, 1.06, and 1.19 ppm), 1 olefinic methyl at δ 1.67, 1 sp^2 methinic proton at δ 6.06, two benzylic methylene protons at δ 2.13 (H-1_α) and 2.58 (H-1_β) forming an isolated spin system with a methinic proton at δ 1.40 (H-2) and signals for 14 protons divided into three isolated spin systems as established from TOCSY and HMBC experiments (C-12, C-13; C-8, C-9, C-10; C-4, C-5, C-6).

The long range ^1H – ^1H COSY correlation between the olefinic methyl and the olefinic methine and their intercorrelation in the HMBC spectrum proved their *ortho*-relationship. The two- and three-bond HMBC correlations of the olefinic methyl and the olefinic methine with carbons C-5', C-6', and C-2', C-6', respectively, along with biogenetic considerations indicated the presence of a trisubstituted methyl *para*-benzoquinone ring.

The lack of any oxygenated sp^3 quaternary carbon ruled out the presence of a benzopyran (taondiol-like) or a benzofuran (stypodioid-like) moiety in **1** and the heteronuclear correlations from the H-1_β signal at δ 2.58 to C-2, C-3, C-1', C-2', and from the H-2 at δ 1.40 to C-3, C-7 together with the correlations H_3 -16/C-2, C-3, C-4, C-2' confirmed the five-membered ring attached to the benzoquinone ring and completed the ^{13}C assignments of the indanedione moiety.

The diterpenoid part of **1** was elucidated from a series of HMBC correlations mainly from the angular methyl proton signals to the methine ring junction carbon signals. Easily distinguished were the *gem*-dimethyl groups H_3 -19 and H_3 -20, which were correlated with a common quaternary carbon at δ 48.0 (C-15) and with the ketone carbonyl group at δ 213.5 (C-14). In the same spectrum the correlations of H_3 -19, H_3 -20, H_3 -18 with C-10; H_3 -17, H_3 -18 with C-6 and H_3 -16, H_3 -17 with C-2 completed the assignment of the methyls and methines securing their positions at the A–B, B–C, and C–D ring junctions. Other correlations in the HMBC spectrum, in conjunction with HSQC and TOCSY data, resulted in the full assembling of the planar structure of **1**.

In the NOESY experiment, H_3 -18 showed correlation with H_3 -19 and H_3 -17 but not with H-10 , therefore requiring a *trans* A–B ring fusion. In addition both H_3 -17 and H_3 -18 showed strong correlations with methine H-6 , which subsequently exhibited an intense cross peak with methine H-2 . The latter was also enhanced by irradiation on H_3 -17. The aforementioned NOE data are supportive of the co-facial β orientation of H_3 -17, H_3 -18, H-2 , and H-6 as well as the *cis* B–C ring fusion. Crucial additional correlations were evident from the NOESY experiment performed in CDCl_3 (Supplementary data). Methine H-10 showed correlation with H-8_α , H-12_α , and H_3 -20; H-1_α correlated with H_3 -16 but not with H_3 -17 and H-1_β with H_3 -17 but not with H_3 -16. In both solvents (C_6D_6 and CDCl_3) strong correlations were observed between H-8_α and H_3 -16 and between H-8_β and H-1_α . No correlation, in either solvent, was observed between the H_3 -16 and H_3 -17 methyls, and between H-2 and H_3 -16. The latter NOE data suggested an α orientation for H_3 -16 and *trans* C–D ring fusion. The above correlations support the proposed unprecedented *trans*–*cisoid*–*cis*–*cisoid*–*trans* arrangement for the A/B/C/D ring system of atomarianone A. In addition to the spatial proximities indicated by the NOE enhancements, the coupling constants of some crucial, well-resolved methylenic proton signals (that we were able to observe either in C_6D_6 or in CDCl_3) allowed us to propose an all chair conformation for rings A–C. Complete ^1H and ^{13}C NMR assignments as well as heteronuclear connectivities and a full list of NOE correlations are given in Table 1.

Atomarianone B, was also isolated as an optically active brown oil ($[\alpha]_D^{20} +32.6$, c 1.09, CHCl_3), possessing the same molecular formula as **1** (HREIMS; $[\text{M}]^+$ m/z 408.2684), an identical IR spectrum and similar ^1H NMR and ^{13}C data in C_6D_6 (Table 1) and in CDCl_3 .

Table 1. NMR data of atomarianone A and atomarianone B (400 and 50.3 MHz in C₆D₆)

H/C	Atomarianone A (1)				Atomarianone B (2)			
	$\delta_{\text{H}}^{\text{a}}$	$\delta_{\text{C}}^{\text{b}}$	HMBC	NOESY	$\delta_{\text{H}}^{\text{a}}$	$\delta_{\text{C}}^{\text{b}}$	HMBC	NOESY
1 α	2.13, dd (12.7, 16.6)	26.9	C-2, C-1', C-2'	H ₃ -16, H-8 β	2.12, dd (12.4, 17.0)	25.9	C-2, C-1', C-2'	H ₃ -16, H ₃ -17
1 β	2.58, dd (5.9, 16.6)		C-2, C-3, C-1', C-2'	H ₃ -17	2.42, dd (6.2, 17.0)		C-2, C-3, C-1', C-2'	H β -8
2	1.40, dd (5.9, 12.7)	59.2	C-3, C-7	H-6, H ₃ -17	1.16, m ^c	62.7	C-7	H-4 β , H-6
3	—	47.3			—	48.3		
4 α	2.49, ddd (3.4, 3.4, 12.2)	35.1	C-6	H ₃ -16	2.47, dt (3.0, 13.5)	36.0	C-2, C-3, C-5, C-6	H ₃ -16
4 β	1.38, m ^c		C-3		1.38, m ^c		C-3, C-5	H-2, H-6
5 α	1.14, m ^c	22.3	C-7	H ₃ -16	1.18–1.30, 2H, m ^c	19.4	C-3, C-4, C-6	H ₃ -16, H-12 α
5 β	1.33, m ^c		C-11	H-12 α				H ₃ -18
6	0.77, dd (4.9, 12.7)	56.6		H-2, H ₃ -17, H ₃ -18	0.74, t (7.8)	52.7		H-2, H-4 β , H ₃ -18
7	—	38.0			—	35.9		
8 α	1.54, m ^c	29.8	C-17	H ₃ -16	1.18, m ^c	37.5	C-17	H-10, H ₃ -17
8 β	1.10, m ^c		C-6, C-17	H-1 α	1.11, m ^c		C-9	H-1 β
9 α	1.19, m ^c	20.1	C-15	H ₃ -19	1.20, m ^c	18.4	C-11	H ₃ -20
9 β	1.26, m ^c		C-7, C-11, C-15	H ₃ -17, H ₃ -18, H ₃ -19	1.09, m ^c		C-2, C-8	
10	1.25, m ^c	48.8	C-11, C-15		2.04, dd (2.6, 11.2)	45.2	C-8, C-9, C-11, C-12, C-15, C-18, C-20	H-8 α , H-12 α , H ₃ -17, H ₃ -20
11	—	37.8			—	35.9	C-11, C-13, C-14, C-18	
12 α	1.56, m ^c	36.4		H-5 β	1.56, ddd (3.7, 12.0, 12.0)	31.3		H-5 α , H-10, H ₃ -17
12 β	0.94, m ^c				1.13, m ^c			H ₃ -18
13 α	2.22, ddd (2.4, 4.9, 15.6)	35.4	C-12, C-14	H ₃ -18	2.34, ddd (5.7, 11.6, 16.0)	33.5	C-14	H ₃ -20
13 β	2.48, ddd (5.8, 14.2, 15.6)		C-12, C-14, C-15		2.23, ddd (3.7, 10.0, 16.0)		C-12, C-14	H ₃ -18
14	—	213.5			—	216.7		
15	—	48.0			—	46.8		
16	0.94, s	18.6	C-2, C-3, C-4, C-2'	H-1 α , H-4 α , H-5 α , H-8 α	0.94, s	18.8	C-2, C-3, C-4, C-2'	H-1 α , H-4 α , H-5 α
17	0.95, s	30.2	C-2, C-6, C-7, C-8	H-1 β , H-2, H-6, H-9 β , H ₃ -18	0.89, s	21.4	C-2, C-6, C-7, C-8	H-1 α , H-8 α , H-10, H-12 α
18	1.06, s	25.8	C-6, C-10, C-11, C-12	H-6, H-9 β , H ₃ -17, H ₃ -19, H-13 β	0.62, s	22.2	C-6, C-10, C-11, C-12	H-5 β , H-6, H-12 β , H-13 β , H ₃ -19
19	0.88, s	22.0	C-20	H-9 α , H-9 β , H ₃ -18, H-13 β , H ₃ -20	1.12, s	19.8	C-10, C-15, C-20	H ₃ -18
20	1.19, s	24.7	C-19, C-15	H ₃ -19	0.94, s	29.1	C-10, C-15, C-19	H-9 α , H-10, H-13 α
1'	—	147.5			—	147.6		
2'	—	155.5			—	155.3		
3'	—	185.7			—	185.7		
4'	6.06, br q (1.44)	133.5	C-2', C-6', C-7'		6.08, br q (0.84)	133.5	C-2', C-6', C-7'	
5'	—	144.9			—	144.9		
6'	—	186.5			—	186.6		
7'	1.67, d (1.44)	15.2	C-4', C-5', C-6'		1.68, d (0.84)	15.2	C-4', C-5', C-6'	

^a ¹H chemical shifts referenced to residual C₆HD₅ (7.16 ppm) followed by multiplicity and coupling constants (J/Hz). The stereochemical assignment of geminal protons CH_aH_b as α or β was based on the values of coupling constants and on NOE correlations.

^b ¹³C chemical shifts referenced to C₆D₆ (¹³C 128.0 ppm).

^c Overlapped by other signals (assignment based on HSQC and TOCSY experiments).

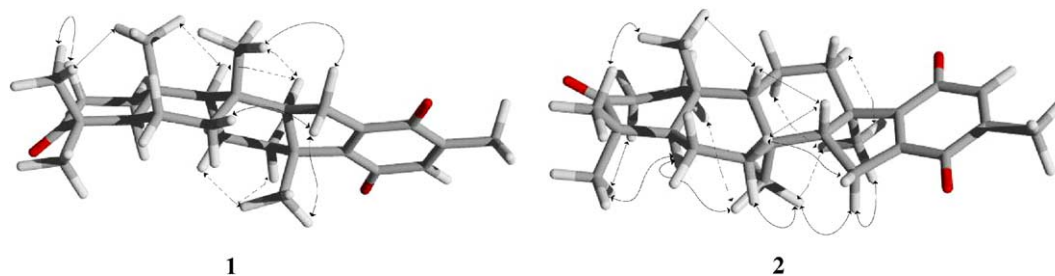


Figure 2. Minimum energy conformers of atomarianone A (**1**) and B (**2**), with selected NOE correlations.

(Supplementary data), suggesting only stereochemical differences between the two compounds. The major ^{13}C NMR differences were detected for: methylenes C-8 and C-12, methyl C-17, and methines C-2, C-6, C-10. The ^1H NMR spectrum of **2** showed upfield shifts for H-1 $_{\beta}$, H-2, H-8 $_{\alpha}$, H₃-18, H₃-20 and downfield shifts for H-10, H₃-19 with respect to **1**. The chemical shifts of the *p*-benzoquinone ring remained the same as in **1**. Consequently, these differences suggested that the stereochemical differences between the two metabolites should be both configurational and conformational. Nevertheless, since the most significant changes were observed around the B–C ring fusion we suspected an inversion of configuration at C-7. The observed NOE between H₃-18 and H₃-19 but not with H₃-17 along with the correlation between H-10 and H₃-17 and especially between H-12 $_{\alpha}$ and H₃-17 confirmed the inversion of configuration at C-7 suggesting that the H₃-17 is now on the α face of the molecule. The correlation between H-6 and H₃-18 supports the retention of their homofacial orientation and the *trans* B–C ring fusion. The retention of the relative stereochemistry at the C–D ring fusion (*trans*) is supported by an intense NOE cross peak between H₃-17 and H₃-16 (observed in CDCl_3) along with the correlation of H-1 $_{\alpha}$ with both H₃-17 and H₃-16 and the lack of correlation of H-1 $_{\beta}$ with either of the latter methyl groups. Based on the above mentioned results the *trans*–*cisoid*–*trans*–*transoid*–*trans* arrangement of rings A/B/C/D is proposed for atomarianone B.

From the comparison of the coupling constants of the isolated spin system C-12, C-13 in the two molecules, the aforementioned differences in the ^{13}C and ^1H NMR shifts with atomarianone A and the study of the Dreiding models of the two compounds we concluded that the conformational arrangement for atomarianone B was twist boat–twist boat–chair for the rings A–C. The large downfield shift of C-17 in **1** can be explained on the basis of the smaller γ -gauche shielding effect that this methyl experiences from C-5, C-9, and C-11. Methyl C-17 is axial with respect to the B ring but equatorial with respect to the C ring, while in **2**, C-17 is axial with respect to the C ring and pseudo-axial with respect to the B ring. The large difference in the ^{13}C chemical shift of C-8 can be explained on the same basis.¹⁴

The exceptional downfield shift of the H-10 in **2** (2.04 ppm in C_6D_6 , 2.31 ppm in CDCl_3) is probably

due to its relative position with respect to the carbonyl oxygen (*anti*, inside the deshielding cone of the carbonyl group¹⁵). Another trend in the chemical shifts of **1** and **2** that was supportive to the proposed conformation assignments was the opposite magnitude of $\Delta\delta_{(\text{CDCl}_3-\text{C}_6\text{D}_6)}$ for H₃-19 and H₃-20. In atomarianone A H₃-20 lies ‘in front’ of the carbonyl group and H₃-19 ‘behind’ it. As the solvent is changed from CDCl_3 to C_6D_6 , H₃-20 becomes deshielded whereas H₃-19 is shielded. Exactly the opposite occurs in **2**, which has the A ring in twist–boat conformation.¹⁶ It is worth noting that the two molecules retain the same conformation in the two NMR solvents as can be seen from the coupling constants of the A ring protons, which remain almost the same in both solvents (ring A is the most flexible and thus the most undisputed criterion). All the above mentioned data support the proposed conformational motives for the A–C rings in **1** and **2** (Fig. 2).

Compounds **1** and **2** were subjected to a conformational search using the XED¹⁷ molecular modeling software running on a Silicon Graphics Octane R12000/400 MHz workstation. All unique conformers were fully minimized using the AM1¹⁸ Hamiltonian as implemented in the PC GAMESS version¹⁹ of the GAMESS (US) quantum mechanics package²⁰ followed by 6–31G* single point calculations using PC GAMESS to evaluate the energy of the conformers at the ab initio level. The global minimum energy conformer of atomarianone A, bears an all chair conformation for rings A–C, whereas that of atomarianone B, bears rings A–C in a twist boat–twist boat–chair arrangement. The calculated proton distances for each molecule were in full agreement with the experimentally observed NOESY correlations (see Fig. 2).

To the best of our knowledge the closest, mixed biogenesis, analogues to **1** and **2** have been isolated from sponges and are the merosesterterpene disidein²¹ from *Dysidea pallescens* and the merotriterpenes toxicols²² from *Toxiclona toxius*, and haliclotriols²³ and adociasulfates²⁴ from *Haliclona* sp. and *Adosia* sp., respectively.

The cytotoxicity of atomarianones A and B was assayed against NSCLC-N6 and A549 lung cancer cell lines. Both metabolites showed significant cytotoxicity in the two cell lines with IC_{50} levels <7.35 μM .

During the preparation of this letter another article appeared reporting five new cyclized meroditerpenoids

from the brown alga *S. flabeliformae* from Papua New Guinea.²⁵ Flabellinol and flabellinone are the closest analogues to the atomarianones.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2005.10.007](https://doi.org/10.1016/j.tetlet.2005.10.007).

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