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Omriolide A and B; two new rearranged spongian diterpenes from the marine sponge *Dictyodendrilla aff. retiara*

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Abstract—Two new rearranged spongian diterpenes designated omriolide A and B were isolated from the southern Kenyan sponge *Dictyodendrilla aff. retiara* collected at Wasini Is., Shimoni Channel. Omriolide A possesses an octalin linked to a unique trioxatricyclo[5.2.1.0^{4,10}]decane ring system, forming a tricyclic 'cap'. Omriolide B comprised a tricyclo[5.4.0.0^{2,4}]undecane linked to a dioxabicyclo[3.3.0]octane. The structures of both diterpenes were elucidated by interpretation of MS results and, mainly, 1D and 2D NMR spectra.

Rearranged spongian diterpenes are well-known secondary metabolites characterized by a carbobicyclic portion (the 'left' part) and a second, highly oxygenated half (the 'right' half of the molecule).[1–4] The carbobicyclic part derives from rings AB of the spongian skeleton and shows up in different bicyclo[5.3.0], [4.4.0] or [4.3.0] decane or nonane ring systems, or even tricyclic ring systems (as in cheloviolin).[3] The second, 'right', half of the molecules, obtained from rings CD of the spongian skeleton, appears as a five- or six-membered lactone, a variety of dioxabicyclo[3.3.0]- or [3.2.1]lactol-lactones or even dioxatricyclo[5.2.1.0^{4,10}]systems.[5] Examples are shown in Figure 1.[1–6]

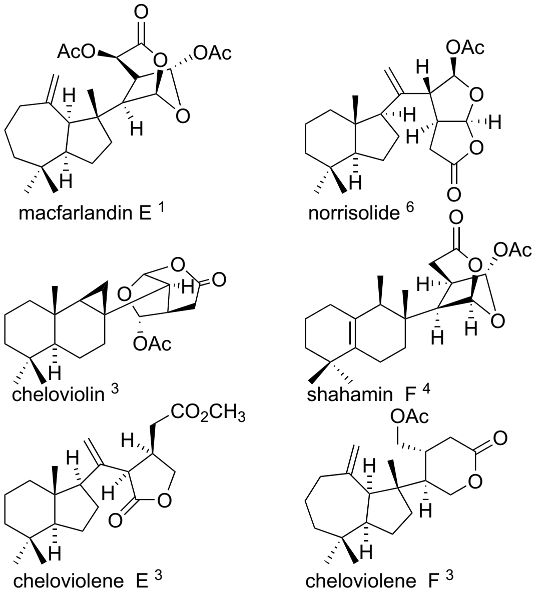

Figure 1. Examples of rearranged spongan diterpenes.

As part of our ongoing efforts to isolate biologically active compounds from marine invertebrates,[7,8] the constituent of the southern Kenyan sponge *Dictyodendrilla aff. retiara*, collected at Wasini Is. Shimoni Channel 04°39.23′S; 39°21.33′E (2–3 m, February 2004) was examined and two new diterpenes designated omriolide A (**1**) and B (**2**) were isolated.

Freeze-dried sponge (15 g) was homogenized and successively extracted with petroleum ether, ethyl acetate and ethyl acetate–MeOH (1:1). The petroleum ether fraction (290 mg) was repeatedly chromatographed on a Sephadex LH-20 column, eluting with a mixture of heptane–CH_2Cl_2–MeOH (2:1:1) to afford mixtures of omriolide A and B (**1** and **2**), which were further separated on a silica gel column eluted with mixtures of heptane–ethyl acetate to afford, with 5–10% ethyl acetate, omriolide A (7 mg)[9] and omriolide B (8 mg).[10]

Keywords: Rearranged spongian diterpenes; Trioxatricyclo-[5.2.1.0^{4,10}]octane heterocycle.

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Table 1. NMR data for omriolide A (**1**)

C No.	δ_c, ppm[a,b,h]	δ_H, ppm (mult)[c,d,e,i,j] (J in Hz)	HMBC (C to H)[f,g]
1	36.7 CH_2	1.55 1.06	2a, 3a, 20
2	18.6 CH_2	1.66 1.52	1a, 1b, 3a, 3b
3	41.0 CH_2	1.44 1.18	2a, 18, 19
4	32.7 C		5, 6, 18, 19
5	56.3 CH	1.83 bt ($\Delta\omega_{1/2} = 7$)	6, 7, 9, 18, 19, 20
6	130.8 CH	5.85 dd (10.0, 1.2)	5
7	127.9 CH	5.58 dd (10.0, 3.1)	5, 9w, 14
8	91.5 C		5, 6, 7, 9, 14, 15, 17
9	50.1 CH	2.23 q (7.4)	5, 7, 17, 20
10	38.4 C		1a, 5, 6, 7, 9, 17, 20
11	172.0 C		13, 16
12	73.8 CH	4.55 d (8.7)	14, 16
13	52.5 CH	4.11 td (8.7, 6.2)	14, 16
14	60.3 CH	2.73 dd (8.7, 6.3)	5, 7, 9, 12, 13, 15, 16
15	98.5 CH	5.95 bd (6.3)	13, 14, 16, 17
16	102.1 CH	6.03 d (6.2)	12, 13, 14, 15
17	8.9 CH_3	1.08 d (7.4)	7, 9
18	21.7 CH_3	0.82 s	3b, 5, 19
19	32.3 CH_3	0.92 s	18
20	13.8 CH_3	0.90 s	1a, 5, 9

[a] Bruker ARX-500 instrument, chemical shifts refer to $CDCl_3$ ($\delta_c = 77.0$).

[b] Multiplicities were determined by DEPT and HMQC experiments.

[c] Bruker ARX-500 instrument, chemical shifts refer to $CDCl_3$ ($\delta_H = 7.26$).

[d] The CH correlations were assigned by a HMQC experiment.

[e] Multiplicities and coupling constants in parentheses.

[f] a and b denote downfield and upfield resonances, respectively, of a geminal pair.

[g] HMBC data were obtained from an experiment with a delay of 55 ms optimized for an 8 Hz coupling.

[h] $^1J_{CH}$ values in Hertz measured from the HMBC experiment are: 121(#5), 155(#6), 155(#7), 123(#9), 159(#12), 149(#13), 139(#14), 174(#15), 188(#16), 126(#17), 124(#18) and 124(#19).

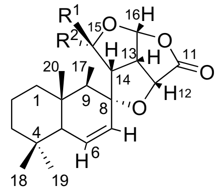
[i] A broad peak appears at 3.25 ppm attributed to the hydroxyl proton.

[j] Key J_{HH} values are: $J_{6,7} = 10.0$, $J_{9,17} = 7.4$, $J_{12,13} = 8.7$, $J_{13,14} = 8.7$, $J_{13,16} = 6.2$, $J_{14,15} = 6.3$.

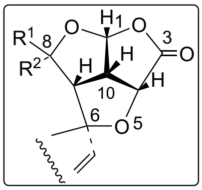
The EI mass spectrum of omriolide A (**1**) exhibited a molecular ion M^+ at m/z 348 that, together with the ^{13}C NMR data, suggested a formula of $C_{20}H_{28}O_5$ possessing seven degrees of unsaturation for **1**. The ^{13}C, ^1H NMR and HMBC spectra (Table 1) revealed the presence of (a) a lactone [δ 172.0 s (C-11), 102.1 d, 6.03 d (CH-16)], the low field resonating methine of which (CH-16) has to carry two oxygen atoms, a functionality that was confirmed by the large $^1J_{C(16)H}$ coupling constant (187 Hz);[11] (b) a lactol (δ 98.5 d, 5.95 bd, $^1J_{C(15)H} = 173$ Hz, CH-15);[11] (c) a methinoxy group (δ 73.8 d, 4.55 d, CH-12) located α to the lactone-carbonyl, possessing three-bond CH correlations to CH-14 and CH-16; (d) two additional vicinal methines, CH-13 and CH-14, which form one spin system with H-12, -15 and -16, as determined by the COSY spectrum and confirmed by HMBC correlations (Table 1)—the above functionalities (a)–(d) established, as a partial structure, a dioxabicyclo[3.3.0]octanolide system as in norrisolide;[6] (e) a quaternary oxygen-carrying low field resonating carbon atom (C-8, δ 91.5 s); and (f) a disubstituted Z double bond (δ 130.8 d and 127.9 d).

A key atom for completing the structure of the 'right' half as well as establishing the connection between the two halves was the quaternary C-8 atom that exhibited seven CH correlations (Table 1)—five to the 'left' half and two to the 'right' part.

Noticeable in the 'right' part of **1** were H-13 and H-14. The coupling constants of H-13 with H-12 (8.7 Hz), H-14 (8.7 Hz) and H-16 (6.2 Hz), as well as two CH correlations of C-13 with H-14 and H-16, positioned H-13 among H-12, -14 and -16. The low field resonance of H-13 (4.11 ppm) and its large $^1J_{CH}$ value (149 Hz)[11] could suggest a methinoxy group. However, the δ_C 52.5 ppm value of C-13 (rather than the expected ca. 80 ppm value) excluded this assumption. Therefore, the anomalous δ_H and $^1J_{CH}$ values pointed to high strain in the 'right' half system. The same conclusion was also reached from the chemical shifts of CH-14 (δ 60.3 d and 2.73 dd) as well as its large $^1J_{CH}$ value (140 Hz). Three CH correlations of C-14, with H-12, -13 and -16, together with all the other above-mentioned evidence, suggested a unique 6,6-disubstituted-2,5,9-trioxatricyclo[5.2.1.$0^{4,10}$]decan-3-one ring system.[13] The all cis stereochemistry of this tricyclic 'cap' became clear from three measured NOEs between H-13 and its surrounding three protons (H-12, -14 and -16) (Fig. 2). This suggested that the stereochemistry is in full agreement with the coupling constants of H-13 with its neighbors, which fit the 0°, 0° and ca. 10–20° dihedral angles with H-12, -14 and -16, respectively. To the best of our knowledge, this 'cap' presents a new heterocyclic ring system. Indeed, a tricyclic ring system of this kind is known as part of a more complex polycyclic system in the oxasteroid hirundigenin,[14] however, in the latter, the stereochemistry is different and hence no 'cap' is formed.



1 R1=OH , R2=H
15-epi R1=H , R2=OH



The 2,5,9-trioxatricyclo [5,2,1,$0^{4,10}$]-decane-3-one system - the "cap".

The 'left' half of omriolide A was determined according to 1D and 2D NMR data (Table 1) to be an 8,8-disubstituted-4,4,9,10-tetramethyl-6-octalin. $\Delta^{5(10)}$- and $\Delta^{1(10)}$ octalins are known within the rearranged spongians[4] and their suggested biogenesis is self-evident. The Δ^6 isomer reported here is new and its biogenesis seems to be

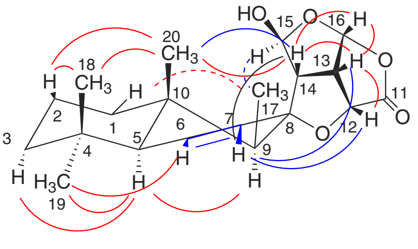


Figure 2. Key NOEs for omriolide A.

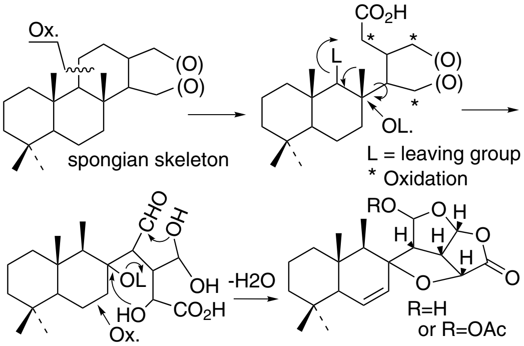


Figure 3. Suggested biogenesis for omriolide A.[15]

different, namely, the double bond is obtained by oxidation and not as a result of quenching of a carbocation (Fig. 3).[15] As mentioned above, C-8 is the linking atom of the two parts of the molecule. To fulfill the seven degrees of unsaturation and all the above-mentioned connectivities, C-8 has to be a spiro-carbon atom connecting ring B of the octalin and the oxygenated part. The connectivities of CH-14 to both halves are also satisfied by the suggested spiro structure.

The trans stereochemistry of the octalin as well as the configuration of the spiro-carbon (C-8) was determined by NOE correlations (Fig. 2). NOEs between Me-20 and Me-18, H-2 (axial) and H-14 on one side of the octalin and between H-5 (axial) and H-9 (axial) and Me-19 on the other side established the trans octalin configuration. An additional correlation between Me-20 and Me-17 determined the β-equatorial configuration of the latter methyl group. Three correlations between the olefinic H-7 proton and the 'right' half protons H-12, -13 and -14 and between Me-17 and H-15, on the other side of the 'cap' established the stereochemistry of C-8 as shown in Figure 2. Additionally, the correlation between Me-17 and H-15 established the α-stereochemistry of H-15.

The EI (and CI) mass spectrum of omriolide B (**2**) exhibited a molecular ion [M^+] at m/z 434 (and 435). The molecular formula $C_{24}H_{34}O_7$ with 8° of unsaturation was determined by HREIMS and ^{13}C NMR data. The ^{13}C, ^1H NMR and HMBC spectra (Table 2) revealed the presence of (a) three methyl singlets and two acetates; (b) seven methylenes including a cyclopropanic one (δ 0.42 t and 0.37 dd, $J_{gem} = 5.6$ Hz) and one α to a carbonyl (δ 2.94 d and 3.59 d, $J_{gem} = 18.6$ Hz, most likely vicinal to another deshielding group); (c) three non-oxygenated methines including a cyclopropanic one (δ 1.01 dd); (d) two methinedioxy groups (δ_C 97.3 d and 109.3 d); (e) three quaternary sp^3 carbon atoms; (f) one oxygen carrying quaternary carbon atom; (g) a lactone (δ 172.8 s).

On the basis of this analysis, omriolide B contains five rings. Interpretation of the COSY spectrum revealing four spin systems (H-1–H-3; H-5–H-7 and to H-17; H-9 to H-17 and H-12–H-15)[16] and especially the HMBC correlations (Table 2) established the planar structure of **2** (Fig. 4).

Table 2. NMR data for omriolide B (**2**)

C No.	δ_c, ppm[a,b]	δ_H, ppm (mult)[c,d,e,h] (J in Hz)	HMBC (C to H)[f,g,i]
1	43.5 CH_2	1.58 1.40	5, 20
2	20.0 CH_2	1.71 1.52	
3	41.8 CH_2	1.45 bd (13.1) 1.19 td (13.1, 5.0)	1a, 18, 19
4	32.4 C		18, 19
5	55.0 CH	0.67 d (11.9)	1a, 3b, 6a, 7a, 18, 19, 20
6	17.1 CH_2	1.43 0.86	5, 7b
7	32.3 CH_2	2.01 bd (12.5) 1.85 dt (12.5, 5.6)	17a, 17b
8	18.1 C		6a, 7a, 14, 17a, 17b
9	34.2 CH	1.01 dd (9.9, 5.6)	7a, 20
10	33.3 C		20
11	172.8 C		12a, 12b, 16
12	36.3 CH_2	3.59 d (18.6) 2.94 d (18.6)	7b, 14
13	88.2 C		12a, 12b, 14, 15, 22
14	55.6 CH	2.68 d (5.0)	7b, 12a, 12b, 15, 17a, 17b
15	97.3 CH	6.24 d (5.0)	14, 16, 24
16	109.3 CH	6.02 s	12a, 12b
17	11.5 CH_2	0.42 t (5.6) 0.37 dd (9.9, 5.6)	7a, 7b, 9, 14
18	21.4 CH_3	0.75 s	3b, 19
19	33.0 CH_3	0.83 s	18
20	21.0 CH_3	0.95 s	
21	170.2 C		22
22	21.3 CH_3	2.13 s	
23	168.5 C		15, 24
24	21.2 CH_3	2.04 s	

For footnotes b–g, see Table 1.

[a] Bruker Avance-400 instrument, chemical shifts refer to $CDCl_3$ ($\delta_c = 77.0$).

[h] $^1J_{CH}$ values in Hertz measured from the HMBC experiment are: 128(#14), 193(#16), 129(#22) and 130(#24).

[i] Key J_{HH} values are: $J_{3a,3b} = 13.1$, $J_{7a,7b} = 12.5$, $J_{7b,9} = 5.6$, $J_{9,17a} = 5.6$, $J_{9,17b} = 9.9$, $J_{12a,12b} = 18.6$, $J_{17a,17b} = 5.6$.

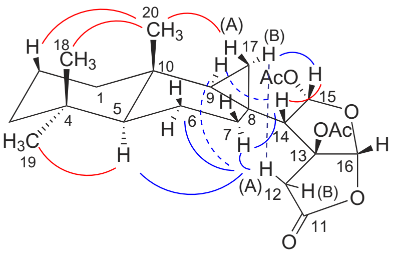
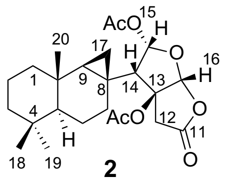


Figure 4. Key NOEs for omriolide B.

Namely, another rearranged spongian comprised a 'left' tricyclic carbocyclic ring system and a 'right' dioxabicyclo[3.3.0]octane heterocycle. The carbotricyclic part was found to be identical to the suggested corresponding part in cheloviolin (Fig. 1), isolated from the Australian *Chelonaplysilla violacea* the structure of which was suggested on the basis of ^1H NMR only.[3] We report here, for the first time, the complete ^1H, ^{13}C data and CH correlations for this tricyclic system (Table 2). The 'right' oxygenated part possesses the same lactol–lactone ring system as that of norrisolide,[6] but differs in the configuration of the 15-acetate group and carries an additional acetate on C-13. The stereochemistry of **2**, including the relative configuration of the two halves, was established on the basis of measured NOEs, the key ones are shown in Figure 4. Rotation around the C-8/C-14 bond of **2** is responsible for the NOEs of H-12 to H-5, -6, -7 and to H-17B on the other side of the molecule.



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Both omriolide A and B lacked cytotoxicity against several tumor cells as well as activity on the Golgi membrane on which norrisolide was found to be highly active.[17]

The suggested absolute stereochemistry of compounds **1** and **2**, although not proven, is as suggested for the known spongians.

Acknowledgements

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References and notes

1. Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1986**, *51*, 4564–4567.
2. Bobzin, S. C.; Faulkner, D. J. *J. Org. Chem.* **1989**, *54*, 5727–5731.
3. Berquist, P. R.; Bowden, B. F.; Cambie, R. C.; Craw, P. A.; Karuso, P.; Poiner, A.; Taylor, W. C. *Aust. J. Chem.* **1993**, *46*, 623–632.
4. Carmely, S.; Cojocaru, M.; Loya, Y.; Kashman, Y. *J. Org. Chem.* **1988**, *53*, 4801–4807.
5. Morris, S. A.; De Silva, E. D.; Andersen, R. J. *Can. J. Chem.* **1991**, *69*, 768–771.
6. Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, J.; Clardy, J. *J. Org. Chem.* **1983**, *48*, 1141–1142.
7. Berer, N.; Rudi, A.; Goldberg, I.; Benayahu, Y.; Kashman, Y. *Org. Lett.* **2004**, *6*, 2543–2545.
8. Chill, L.; Rudi, A.; Benayahu, Y.; Kashman, Y. *Tetrahedron Lett.* **2004**, *45*, 7925–7928.
9. Omriolide A (**1**); an oil; $[\alpha]_D$ −18 (c 0.005, CH_2Cl_2); IR ($CHCl_3$) ν_{max} 2325, 1726, 1223 cm^{-1}; EIMS m/z% 348 $[M]^+$ (5), 330 $[M-18]^+$ (6), 286 $[M-18-CO_2]^+$, 164 $[M-170-15]$ (70), 149 $[M-170-29]$ (40), [170 = the cap]; HREIMS 348.1931 (Calcd for $C_{20}H_{28}O_5$ 348.1937).
10. Omriolide B (**2**); an oil; $[\alpha]_D$ −10 (c 0.007, CH_2Cl_2); IR ($CHCl_3$) ν_{max} 2926, 1753, 1719, 1215 cm^{-1}; CIMS m/z% 435 $[MH]^+$ (10), 391 $[MH-CO_2]^+$ (15), 375 $[MH-HOAc]^+$(65), 315 $[MH-2HOAc]^+$ (100); HREIMS 434.2309 (Calcd for $C_{24}H_{34}O_7$ 434.2305).
11. ^{13}C–^{1}H spin-coupling constants ($^1J_{CH}$) have been found to be valuable, configurational and conformational probes as demonstrated for carbohydrates.[12] $^1J_{CH}$ values for sp^3 C-atoms of alkanes (125 Hz) go up due to strain or electron withdrawing groups to 140–150 Hz, and up to 160–170 Hz for methindioxy groups.
12. Serianni, A. S.; Wu, J.; Carmichael, I. *J. Am. Chem. Soc.* **1995**, *117*, 8645–8650, and references cited therein.
13. Supporting information for the H-15 lactol group came from the mono acetate (δ_H 6.92; 2.01, 3H) obtained with Ac_2O in pyridine and the easy epimerization of **1** to the 15-epimer (δ 5.54 d, $J = 6.1$ Hz) under acidic conditions.
14. Kenard, O.; Fawcett, J. K.; Watson, D. G.; Kerr, K. A.; Stoeckel, K.; Stoeklin, W.; Reichstein, T. *Tetrahedron Lett.* **1968**, 3799–3804.
15. Other biogeneses, changing the order of the transformations, are of course possible.
16. $^4J_{[12-14]}$—a weak 'w' coupling.
17. Brady, T. P.; Wallach, E. K.; Kim, S. H.; Guizzunti, G.; Malhotra, V.; Theodorakis, E. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5035–5039.