3-Bromobarekoxide, an unusual diterpene from *Laurencia luzonensis*

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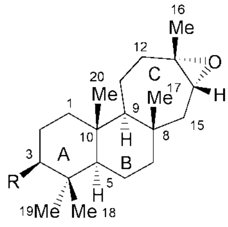
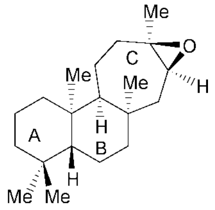
A new, rare diterpene characterized by a cycloheptane ring *trans*-fused to a *trans*-decalin moiety was isolated from *Laurencia luzonensis* and its absolute structure determined by X-ray crystallography.

The red alga of the genus *Laurencia* and the sea hares that feed upon it have been a bountiful source of metabolites. So far more than 300 have been characterized, most of which are sesquiterpenes and C_{15} acetogenins. However a few di- and triterpenes have also been described.[1] We now report on a rare diterpene consisting of a seven-membered ring fused to decalin (**1**) which was obtained from the hitherto unexamined species *Laurencia luzonensis*.



1 R = Br
3 R = H



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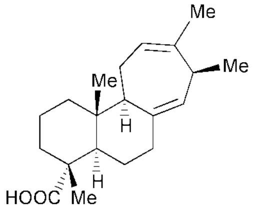

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A sample (3.5 kg), collected off the coast of Kudaka Island, Okinawa, in May 1998, was extracted by steeping with 95% ethanol. Concentration of the extracts and partitioning between water and ethyl acetate gave an oil (12.5 g). Successive chromatography over silica gel with solvent mixtures ranging from hexane, dichloromethane, and ethyl acetate afforded a fraction which was purified by HPLC (LiChrosorb Si60, hexane/AcOEt, 10:1). Subsequent recrystallization from CCl_4 furnished **1** (58.5 mg) as colorless crystals, mp 165 °C, $[\alpha]_D^{24} = 6.18$ (c 0.3, $CHCl_3$).

The molecular formula $C_{20}H_{33}OBr$ was deduced from the ^{13}C NMR spectrum and LR EIMS. The monobrominated nature of the compound was immediately evident from the molecular ion peak which appeared as a doublet of equal intensity (m/z 368, 370). The absence of olefinic and carbonyl signals in the NMR spectrum suggested a tetracyclic entity. The carbon signals at δ 60.52 (s) and 60.45 (d) together with the proton signal at δ 2.70 (dd, J = 7.5, 7.5 Hz) indicated an epoxide (Table 1). Therefore the remaining three rings are carbocyclic. Analysis of the 1D and 2D NMR spectra (COSY, HMQC, HMBC, NOESY) led to a diterpene structure composed of *trans*-decalin and an epoxide fused to a common seven-membered ring. Comparison of the NMR data of **1** (Table 1) with those reported for barekoxide (**2**), a related terpene isolated from the sponge *Chelonaplysilla erecta*,[2] revealed good agreement apart from the obvious differences between the A rings. Therefore, we initially assumed that **1** was simply the 3β-bromo derivative of **2** in which the A/B and B/C junctions are *trans* and *cis*-fused respectively. However, as the absolute configuration of **2** was unknown, determining that of **1** would provide an convenient proof of structure for both molecules. Accordingly, a single crystal of **1** was submitted to X-ray analysis.† It is immediately seen that the decalin moiety is certainly *trans*, but that the B/C ring junction is *trans* as well (Fig. 1). Despite the *syn*-axially disposed methyl groups, the cyclohexane and cycloheptane rings adopt chair conformations. Evidently, the structure previously assigned to **2** is doubtful. Clarification was secured by treating **1** with tributyltin hydride and AIBN in DMSO.‡ Reductive debromination gave the parent hydrocarbon **3** as colorless crystals, mp 140 °C, $[\alpha]_D^{24} = 5.2$ (c 0.256, $CHCl_3$). The ^1H and ^{13}C NMR spectra of **3** were essentially the same as those recorded for barekoxide (**2**).§ We therefore conclude that structure **2** is incorrect and should be revised to that of **3**. Furthermore, the sign of the specific rotation indicates that barekoxide of sponge origin¶ must have the same absolute configuration as the alga-derived product **3**.

Table 1 ^1H and ^{13}C NMR chemical shifts (ppm) of 3-bromobarekoxide (**1**) and long range CH correlations as obtained in the HMBC experiment

Carbon number	δ_C	δ_H (multiplicity, J in Hz)	CH correlation
1	41.68 t	1.80 (dt, 13.0, 3.5) 1.00 (br dd, 13.0, 3.5)	H2, H20
2	31.00 t	2.18 (dq, 12.5, 3.5) 2.07 (m)	H1, H3
3	69.52 d	3.98 (dd, 13.0, 4.5)	H1, H2, H18, H19
4	39.80 s		H2, H3, H18, H19
5	56.77 d	0.90 (dd, 11.5, 3.0)	H1, H6, H18, H19, H20
6	20.10 t	1.50 (m), 1.25 (m)	H5, H7
7	44.04 t	1.60 (m), 1.50 (m)	H5, H6, H15, H17
8	37.32 s		H7, H9, H15, H17
9	64.28 d	0.82 (br d, 10.0)	H11, H12, H15, H17, H20
10	38.82 s		H1, H2, H5, H9, H20
11	19.97 t	1.70 (m), 1.50 (m)	H9, H12
12	35.92 t	2.00 (m), 1.35 (m)	H9, H11, H16
13	60.52 s		H12, H15, H16
14	60.45 d	2.70 (dd, 7.5, 7.5)	H15, H16
15	47.07 t	1.85 (dd, 14.0, 7.5) 1.20 (dd, 14.0, 7.5)	H7, H9, H17
16	22.42 q	1.32 (s)	H12, H14
17	19.55 q	1.02 (s)	H9, H15
18	18.13 q	0.93 (s)	H3, H5, H19
19	30.50 q	1.05 (s)	H3, H5, H18
20	15.93 q	0.87 (s)	H1, H5, H19

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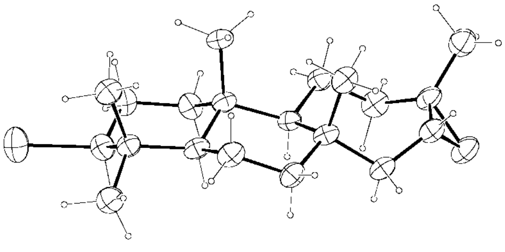
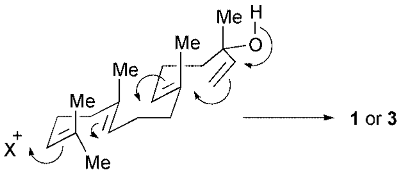


Fig. 1 Perspective view of the crystal structure of **1**. Ellipsoids are represented with 40% probability.



5 X = Br or H

Scheme 1

The present findings correctly establish the absolute structure and confirm the novelty of the diterpene framework of the barekoxides. The tricyclic entity of *trans*-decalin fused to cycloheptane is extremely rare in nature and is only encountered in strobal[3] and strobic acid (**4**).[4] Significantly, the configuration of the C(5), C(9) and C(10) atoms in **1** and **3** is the same as in **4**. Clearly, all three metabolites arise by a similar stereoselective biogenetic pathway. Bromination or protonation of geranyllinalool (**5**) creates a steroid-like tetracyclic array affording **1** or **3**, whereas proton-initiated cyclization followed by oxidation of the C(19) methyl group, 1,3 methyl shift, and elimination accounts for **4** (Scheme 1).

Notes and references

† *Crystal data* for **1**: $C_{20}H_{33}OBr$, M = 369.4, orthorhombic, $P2_12_12_1$, Z = 4, a = 7.6677(6), b = 11.419(1), c = 21.001(1) Å, U = 1838.8(2) Å^3, $F(000)$ = 784, μ(Cu-Kα) = 3.029 mm^{-1}, D_c = 1.334 g cm^{-3}, T = 200 K, 2651 measured reflections, of which 2141 were observable ($|F_o| > 4\sigma(F_o)$). R_{int} for equivalent reflections 0.022. Data were corrected for Lorentz and polarization effects, and for absorption ($T_{min,max}$ = 0.4460, 0.5262). The structure was solved by direct methods and refined (on F) by full matrix least squares. The absolute configuration was determined (Flack parameter x = 0.02(3)).[5] R = 0.031, wR = 0.030 for 255 variables and 2141 contributing reflections. Non-Me hydrogen atoms were observed and refined with a fixed value of isotropic displacement parameters (U = 0.05 Å^2); Me-hydrogen atoms were refined with restraints on bond lengths and bond angles (free rotation) and blocked in the final cycles. Calculations were carried out using the XTAL system.[6] CCDC 182/1646. See http://www.rsc.org/suppdata/cc/b0/b002530p/ for crystallographic files in .cif format.

‡ 3-Bromobarekoxide (**1**, 6 mg) was treated with tributyltin hydride (50 µL) and AIBN (3 mg) in DMSO (0.2 mL) at room temperature overnight. The reaction mixture was worked up in the usual manner and the product purified by HPLC (Lichrosorb Si60, hexane/AcOEt, 10:1) to yield **3** (4.2 mg, 88%).

§ Some of the proton signals cited in ref. 2 for **2** were incorrectly assigned. Our assignments for semi-synthetic **3** (formerly **2**) are as follows: ^{1}H NMR (C_6D_6) δ 2.59 (t, J = 7.5 Hz, H-14), 1.88 (dd, J = 14.0, 8.0 Hz, H-12), 1.71 (dd, J = 13.5, 6.0 Hz, H-15), 1.58 (m, H-1), 1.55 (m, H-2), 1.55 (m, H-6), 1.50 (m, H-11), 1.42 (br t, J = 13.0 Hz, H-12), 1.38 (m, H-1), 1.35 (m, H-2), 1.30 (m, H-3), 1.29 (m, H-7), 1.25 (m, H-6), 1.22 (m, H-15), 1.22 (s, H-16), 1.15 (m, H-11), 1.10 (m, H-3), 1.02 (m, H-7), 0.86 (s, H-17), 0.84 (s, H-18), 0.80 (s, H-19), 0.70 (s, H-20), 0.60 (m, H-9), 0.58 (m, H-5).

¶ We thank Professor Y. Kashman and Dr A. Rudi of Tel Aviv University, Israel, for kindly measuring the optical rotation ($[\alpha]_D$) of an old, stored sample of sponge-derived barekoxide which they found to be 13.9.

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