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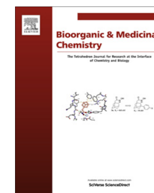

Antiproliferative homoscalarane sesterterpenes from two Madagascan sponges ☆

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Dereplication of the antiproliferative ethyl acetate fraction of the Madagascan sponge *Carteriospongia* sp. led to the detection and isolation of the two known homoscalarane-type sesterterpenes **1** and **2**. Investigation of a similar sponge containing closely related compounds afforded the four new antiproliferative homoscalarane sesterterpenes (**3** and **5**–**7**). The structures of all isolated compounds were elucidated by spectroscopic methods, including UV, IR and 1D and 2D NMR. Compounds **1**, **3** and **5** displayed submicromolar antiproliferative activity against the A2780 ovarian cell line with IC_{50} values of 0.65, 0.26 and 0.28 μM, respectively, while compounds **6** and **7** showed moderate activity (4.5 and 8.7 μM, respectively). Compounds **3** and **5** also displayed anti-proliferative activity against the H522-T1 non-small cell lung and A2058 human melanoma cancer cell lines.

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1. Introduction

Despite the improvement of pharmaceuticals and good responses to initial chemotherapy, surgery and radiation therapy, epithelial ovarian cancer is still one of the leading causes of gynecological cancer mortality. In the United States alone, 22,240 new cases and 14,030 deaths are estimated for 2013.[1] One of the reasons for the increase of these numbers is chemoresistance, and so the search for new and selective pharmaceuticals is as important as it is challenging. One of the aims of the Madagascar international cooperative biodiversity group (ICBG) program is the discovery of potential anticancer natural products from Madagascar. Sponges are well known to contain bioactive secondary metabolites, and the recent introduction of eribulin mesylate (Halaven™, Eisai) into clinical use demonstrates that even a synthetically challenging drug can be developed successfully. Eribulin is a synthetic analogue of the sponge derived compound halichondrin B, and it has been approved by the food and drug administration for treatment of patients with metastatic breast cancer who have failed at least two prior rounds of anthracycline- and taxane-based chemotherapy.[2] Madagascan sponges (*Lendenfeldia* sp., and *Phyllospongia* sp.) are rich sources of a variety of scalarane-type sesterterpenes which have a broad range of biological activities, including anticancer activity.[3]

2. Results and discussion

2.1. Isolation and structure elucidation of bioactive sesterterpenes

In the expectation of finding bioactive ingredients, we have been carrying out chemical investigations of ethanol extracts from a variety of Madagascan marine organisms. Preliminary bioassay of the extracts received using the A2780 human ovarian cell line demonstrated that extracts of a sponge identified as a *Carteriospongia* sp. and of an unidentified marine sponge both showed good antiproliferative activity with IC_{50} values of 3.3 and 3 μg/mL, respectively. The activity of the extract of the *Carteriospongia* sp. was found to be concentrated in the EtOAc fraction (IC_{50} 2.4 μg/

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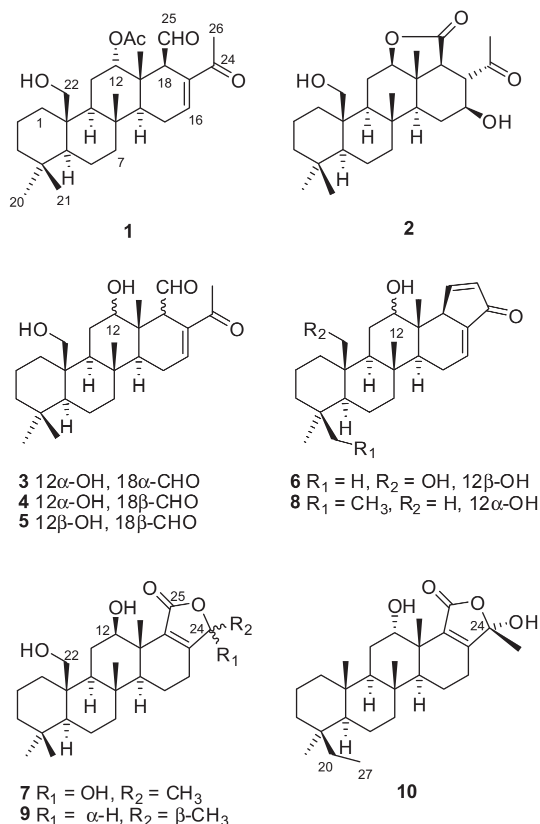
mL) obtained from a liquid–liquid partition. Chromatography of the EtOAc fraction on a size exclusion column gave an active fraction with improved activity (IC_{50} 1.3 μg/mL). About 2 mg of this active fraction was subjected to dereplication using HPLC followed by off-line bioassay, Electrospray Ionization Mass Spectrometry, ^{1}H NMR and analysis using the ^{1}H NMR search features of MarinLit and the dictionary of natural products. These studies identified the known compound 12α-acetoxy-22-hydroxy-24-methyl-24-oxoscalar-16-en-25-al (**1**) as the most active constituent (IC_{50} 0.65 μM), together with the weakly active 16β,22-dihydroxy-24-methyl-24-oxoscalaran-25,12β-olactone (**2**).[4] HPLC/UV analysis of the bioactive EtOAc soluble fraction (IC_{50} 0.45 μg/mL) of the EtOH extract of the second sponge extract showed a very similar HPLC profile to that of the *Carteriospongia* sp. extract, suggesting that this sponge was also a *Carteriospongia* sp. Size exclusion chromatography of this second extract on Sephadex LH-20 followed by further purification by HPLC and silica gel column chromatography of the most active fraction afforded the four bioactive homoscalarane compounds **3** and **5**–**7**.



Compound **3** had the molecular formula $C_{26}H_{40}O_4$ as determined by positive-ion high resolution electrospray ionization (HRESI) mass spectrometry [m/z 439.2819 $[M+Na]^+$ (calcd for $C_{26}H_{40}O_4Na$, 439.2824)], which displayed a quasi-molecular ion peak at m/z 439.2819 $[M+Na]^+$. Its IR spectrum showed absorption bands at 3436, 1713, and 1653 cm^{-1}, suggestive of hydroxyl, saturated carbonyl and α,β-unsaturated carbonyl functions. The ^{1}H NMR spectroscopic data of **3** (Table 1) exhibited signals for five methyl singlets, four on sp^3 carbons (δ 0.80, 0.86, 0.90, 1.11) and one on an sp^2 carbon (δ 2.27), one hydroxymethylene group (δ 3.82 and 4.00, each d, J = 11.9 Hz), one oxygen-bearing methine (δ 3.30, overlapped with the solvent protons), one olefin methine (δ 7.30, dd, J = 4.8, 2.8 Hz) and an aldehyde proton (δ 9.89, d, J = 2.4 Hz). Inspection of the ^{13}C NMR spectrum revealed signals for quaternary methyl groups, aldehyde (δ_C 200.3, C-25) and methyl ketone (δ_C 205.5, C-24) carbonyl groups, two olefin carbons at δ_C 136.8 and 146.1 ppm (C-17 and C-16), a C-22 hydroxymethylene group (δ_C 62.2), and an oxymethine carbon at δ_C 77.6; this carbon was coupled to the C-12 proton at δ 3.30 as observed in an HSQC spectrum. The above data suggested that compound **3** was a type II homoscalarane sesterterpene which was oxygenated at C-12, C-22, C-24 and C-25.[5] The NMR data of **3** were very similar to those of the homoscalarane sesterterpene **4** previously isolated from a *Lendenfeldia* sp.[6] Comparison of the ^{1}H and ^{13}C NMR data of **3** with those of **4** indicated that the difference between the two compounds was only in their stereochemistry at C-12 and/or C-18. 2D NMR experiments were then carried out to confirm the planar structure of **3** and to clarify the orientation of the substitutions at C-12 and C-18. In an HMBC spectrum, long-range correlations were observed from the oxymethylene proton signals at δ 3.82 and 4.00 and C-1, C-5, C-9 and C-10, the oxygen-bearing methine at δ 3.30 and C-9, C-14, and C-23, the aldehyde proton signal at δ 9.89 and C-13, C-17, and C-18; the olefin methine signal at δ 7.30 and C-14, C-18 and the methyl ketone at C-24 (δ 205.5). The α-orientations of the hydroxyl group at C-12 and the aldehyde at C-18 were determined by interpretation of a NOESY spectrum. As illustrated in Figure 1, NOESY correlations were observed between H-12 δ 3.30) and CH_3-19 (δ 1.11), between CH_3-19 and CH_3-23 (δ 0.90), between CH_3-23 and H-18 (δ 3.70) and between H-18 and CH_3-26 (δ 2.27). The relative stereostructure of **3** was thus determined to be 12α,22-dihydroxy-24-methyl-24-oxoscalar-16-en-25α-al.

Compound **5** had the same molecular formula as **3** ($C_{26}H_{40}O_4$) as deduced by positive-ion HRESIMS (m/z 439.2819 $[M+Na]^+$, requires 439.2824 Similarly to **3**, the IR spectrum showed absorption bands for hydroxyl, saturated carbonyl and α,β-unsaturated carbonyl functions. In addition the ^{1}H and ^{13}C NMR data of **5** (Table 1) were almost superimposable with those of **3**, indicating that compounds **3** and **5** must share the same planar structure. Comparison of the ^{13}C NMR data of **3** with those of **5** revealed that the major differences between the two compounds were the chemical shifts of C-12, C-18 and C-23, signals at δ_C 83.0, 63.0 and 10.1 (C-12, C-18 and C-23, respectively) were observed in 5 instead of δ_C 77.6, 57.3 and 16.1 in **3**. Interestingly, the ^{1}H and ^{13}C NMR chemical shifts of the aldehyde group of **5** were the same as those of **3**, and the chemical shift of H-12 appeared at δ 3.40 as a doublet of doublets (J = 13.8, 6.7 Hz), suggesting that the proton at C-12 was axially oriented. Thus, the only possible differences between the two compounds must be the orientation of the hydroxyl group at C-12 and/or the aldehyde group at C-18. The assignment of the carbons in the structure of **5** and the determination of the orientation of the substitutions at C-12 and C-18 were made by 2D NMR experiments including HSQC, HMBC and NOESY. The planar structure was confirmed to be 12,22-dihydroxy-24-methyl-24-oxoscalar-16-en-25-al by interpretation of the HSQC, COSY and HMBC spectra, which displayed similar correlations with those observed in the spectra of **3**. The β-orientations of the hydroxyl group at C-12 and the aldehyde at C-18 were determined by the interpretation of the NOESY spectrum. As depicted in Figure 2, NOESY correlations were observed between H-12 (δ 3.40) and H-18 (δ 3.68), between H-19 (δ 1.13) and H-23 (δ 0.77), between H-23 and the aldehyde proton H-25 (δ 9.87), and between H-25 and H-26 (δ 2.24). The relative stereostructure of **5** was thus assigned as 12β,22-dihydroxy-24-methyl-24-oxoscalar-16-en-25β-al.

The molecular formula of compound **6** was determined to be $C_{26}H_{38}O_3$ by positive-ion HRESIMS analysis (m/z 399.2916 $[M+H]^+$, requires 399.2899). Its IR spectrum displayed absorption bands of hydroxyl group at 3432 cm^{-1} and a carbonyl group at 1693 cm^{-1}, consistent with a cyclopentenone with additional

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