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Chemical constituents of the lichen *Usnea baileyi* (Stirt.) Zahlbr

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ABSTRACT

Investigation of the chemical constituents of the lichen *Usnea baileyi* (Stirt.) Zahlbr led to the isolation of a new dimeric xanthone, bailexanthone (**1**), and a novel depsidone, bailesidone (**2**), along with twenty-five known metabolites (**3**–**27**). Their structures were established by means of extensive spectroscopic analysis and comparison with data reported in the literatures. Compound **1** derives from secalonic acid scaffold with C-8/8′ reduction and compound **2** represents the first example of menegazziaic acid derivative with an unprecedented B-ring moiety. Two new compounds **1**–**2** were evaluated for their cytotoxic activities against A549 (human lung carcinoma) and HT29 (human colorectal adenocarcinoma) cell lines. All of them showed weak or no activity against two cell lines.

Introduction

Lichens are fungal and algal/cyanobacterial symbioses, producing unique secondary metabolites which are endowed with various bioactivities.[1,2] Vietnamese lichens have been under-investigated with some recent phytochemical studies affording new bioactive metabolites.[3,4]

The fruticose lichen *Usnea baileyi* belongs to the *Usnea* genus, one of the most popular genera occurring in high-attitude Vietnam forests. Previous phytochemical studies on this lichen reported the presence of several metabolites as xanthones,[5] depsidones and depsides[6,7] along with the major component, usnic acid. Continuing our effort to explore the chemical diversity of Vietnam lichens and their biological effects, we carried out an investigation of the lichen *Usnea baileyi*.

In this paper, we reported the isolation, structural elucidation of a new bixanthone, bailexanthone (**1**) and a new depsidone, bailesidone (**2**) (Fig. 1) together with twenty-five known compounds (**3**–**27**) as well as the biogenetic considerations of the two new ones. Compound **1** derives from secalonic acid derivative with C-8/8′ reduction and compound **2** represents the first example of menegazziaic acid derivative with an unprecedented B-ring moiety. The cytotoxic activities against A549 (human lung carcinoma) and HT29 (human colorectal adenocarcinoma) cell lines were evaluated on the two new compounds.

Results and discussion

The *U. baileyi* thalli were collected on tree barks at Lam Dong province, Vietnam. A detailed chromatographic fractionation of its acetone extract led to the isolation of two new compounds (**1**–**2**), along with twenty-five known metabolites (**3**–**27**) (Fig. S3). These known compounds were elucidated as stictic acid (**3**),[8] constictic acid (**4**), cryptostictic acid (**5**),[9] hypoconstictic acid (**6**),[10] menegazziaic acid (**7**),[11] 8′-*O*-methylconstictic acid (**8**),[12] methylstictic acid (**9**), 8′-*O*-methylmenegazziaic acid (**10**),[13] virensic acid (**11**), 9′-*O*-methylprotocetraric acid (**12**), protocetraric acid (**13**),[14] barbatic acid (**14**),[15] diffractaic acid (**15**),[16] 4-*O*-demethylbarbatic acid (**16**),[17] atranorin (**17**),[18] (20*R*,24*R*)-ocotillone (**18**), (20*S*,24*R*)-ocotillone (**19**),[19] betulonic acid (**20**),[20] usnic acid (**21**),[21] dasypogalactone (**22**),[22] 7-hydroxy-5-methoxy-6-methylphthalide (**23**),[21] methyl 4-*O*-methylhaematomate (**24**)[23], methyl orcinolcarboxylate (**25**),[15] atranol (**26**),[23] and eumitrin A_2 (**27**).[5]

The two new compounds were elucidated as the following.

Compound **1**[24] was obtained as yellow crystals. The HRESIMS of **1** showed a protonated ion peak at *m*/*z* 611.2138, consistent with a molecular formula of $C_{32}H_{34}O_{12}$. The ^{1}H NMR spectrum of **1**

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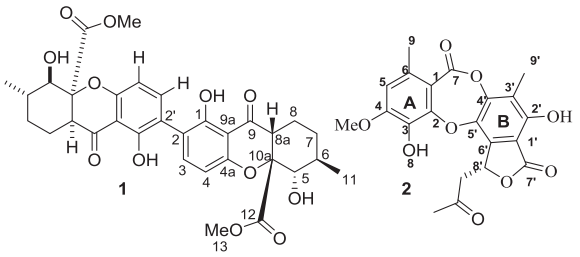


Fig. 1. Chemical structures of **1** and **2**.

showed the presence of one chelated hydroxy group (δ 11.86), two *ortho* aromatic protons at δ 7.50 and 6.62 with the coupling constant of 8.4 Hz, one oxymethine (δ 3.72, 1H, *d*, J = 10.8 Hz), one methoxy (δ 3.68, 3H, s), one *doublet* methyl (δ 1.11, 1H, *d*, J = 6.4 Hz) and six protons in the high-field range of 1.23–2.98 ppm. The ^{13}C NMR in accordance with the HSQC spectra of **1** revealed the existence of 16 carbon signals, comprising of one conjugated ketone carbon (δ 197.4), one ester carbonyl carbon (δ 169.3), two aromatic methines (δ 140.4 and 107.4), one methoxy group (δ 53.0), three methines (δ 34.3, 51.2, and 80.3), two methylenes (δ 31.2 and 20.4), one methyl (δ_C 18.5), and five quaternary carbons (δ 159.0 (2C), 117.6, 107.6 and 87.6).

In the HMBC spectrum, the methoxy protons at δ 3.68 correlated with the carbon at δ 169.3 defining the presence of a methyl ester moiety. The spectroscopic data characterized for the xanthone scaffold[25] with the molecular formula of $C_{16}H_{17}O_6$. Taking into account on the HRESIMS and NMR data, **1** was determined as a dimeric xanthone whose skeleton was similar to the reported ones such as secalonic acids A–D[25] or ergochromes BD, CD, and DD.[26]

The HMBC experiment of **1** showed correlations of protons 1-OH (δ 11.86), H-3 (δ 7.50), and H-4 (δ 6.62) to C-2 (δ 117.6), of 1-OH and H-4 to C-9a (δ 107.6) and C-4a (δ 159.0), of H-3 to C-1 (δ 159.0), C-4 (δ 107.4), and C-4a defining the first spin system of the A-ring. Long range HMBC cross-peak of H-4 to C-9 (δ 197.4) together with the presence of a chelated hydroxy group led to define the position of the ketone group at C-9.

In the C-ring, the spin system through C-8a–C-8–C-7–C-6–C-5 was unambiguously determined by ^{1}H–^{1}H COSY correlations and was further supported by HMBC correlations (Fig. 2). HMBC cross-peak of all protons H-8a (δ 2.98), H$_2$-8 (δ 2.17), and H-5 (δ 3.72) to C-10a and C-12 and of H-8a and H$_3$-13 (δ 3.67) to C-12 suggested the position of the methoxycarbonyl group at C-10a. If the NOESY correlations of methoxy protons of this group with H-4 as well as the oxygenation status of C-10a established the C-4a–O—C-10a connectivity between the two A- and C-rings, the HMBC cross peak of H-8a to C-9 was diagnostic for the connection of C-8a–C-9–C-9a. The absence of an enolic double bond at C-8/8′-C-8a/8a′ or the ketone group at C-8/8′ led to the conformational change of the fuse rings B and C (Fig. 2). This structural feature is highly evocative of eumitrins A$_2$, B and T isolated from the same biosource[27] and similar to egrochromes BD, CD, and DD.[28]

Altogether, the molecular formula and NMR data of **1** confirmed its homodimeric xanthone possessing either 2, 2′- or 4, 4′- linkages. HMBC correlations of 1-OH to three quaternary carbons C-1, C-2, and C-9a supported the 2,2′-linkage of **1** which further supported by NOESY correlations of H-4 to 1-OH and H$_3$-13 (Fig. 2).

The relative configuration of **1** was established by extensive analysis of ^{1}H NMR (Table S1) and NOESY correlations (Fig. 2). The *anti*-relationship of the methyl H$_3$-11 and the methoxy H$_3$-13 was often found in many naturally reported xanthone dimers such as secalonic acids or ergochromes and was defined by key NOESY correlation of H-6 to the methoxycarbonyl H$_3$-13.[26] In compound **1**, this was a *syn* correlation confirmed by the NOESY correlation of H$_3$-13 to H$_3$-11.

Moreover, the coupling constant of H-5 (δ 3.72, d, J = 10.8 Hz) was consistent with the corresponding one reported in secalonic acid A (J = 11.3 Hz)[25] or ergochrome BD (J = 11.3 Hz).[26] In addition, the NOE correlation of H-5 and H$_3$-11 (Fig. 2) indicated the axial positions of H-5 and H-6 and further defining the *trans* configuration of 5-OH and H$_3$-11. Moreover, the coupling constants of H-8a (δ 2.98, dd, J = 11.6, 4.8 Hz) in **1** were consistent with those of eumitrin A$_2$ (**27**) led to define the axial position of H-8a. In the case of eumitrin A2 (**27**), the NOESY correlations of H-5′/H-8a′ and of H$_3$-13′/H$_3$-15′ defined their *syn* relationships, respectively. These data confirmed the *anti*-relationship of H-8a and H$_3$-13 in **27**.

On the contrary, in **1**, strong NOE correlations of H-8a to H$_3$-11 and H$_3$-13 showed that the four groups H-5, H-8a, H$_3$-11, and H$_3$-13 were at the same side of the C-ring cyclohexane. Interestingly, the axial-equatorial relationship of H-8a and 10a-COOCH$_3$ represented the *cis*-decalin junction of the two (8a*S*, 10a*S*) or (8a*R*, 10a*R*) diastereomers, resulting in the highly unusual pattern of homodimer **1** among known xanthone dimers. Accordingly, the relative configuration of the C-ring was determined as shown in Fig. 2. Consequently, **1** was elucidated as shown and was named bailexanthone.

The absolute configuration of **1** was defined by ECD spectra. In many tetrahydroxanthone monomers or bixanthone, two distinct types of chromophores namely 1-arylpropenone (330 nm) and benzoyl (230 nm) were reported.[29,30] Lacking of the 1-arylpropenone feature in the C-ring of **1** and in the unit A of **27** (eumitrin A$_2$) led to the absence of Cotton effects (positive or negative) at around 330 nm in their ECD spectra (Fig. 3). The ECD curves of **1** and eumitrin A$_2$ (**27**) in the zone of 245–255 nm (negative Cotton effect) were somewhat different due to their atropimeric characteristics. Compound **1**, possessing the 2–2′-linkage, therefore its

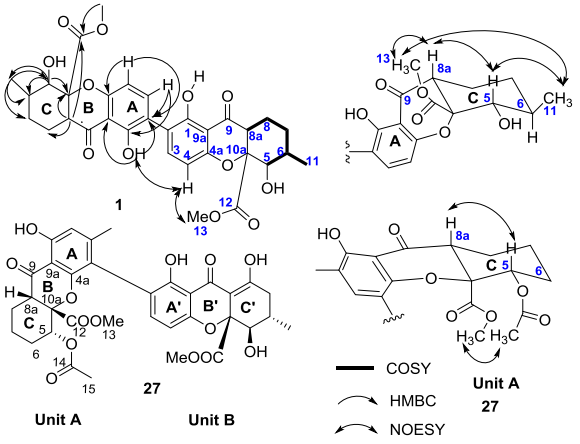


Fig. 2. Selected COSY, HMBC and NOESY correlations of **1** and **27**.

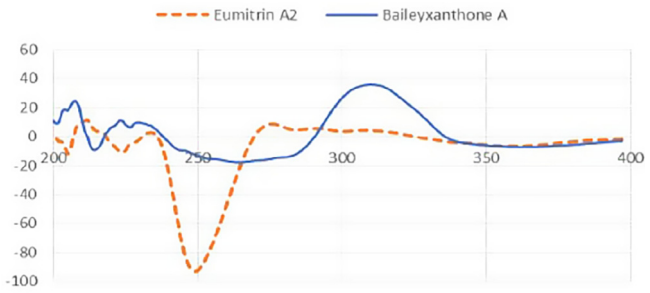


Fig. 3. The ECD spectra of **1** and eumitrin A$_2$ (**27**).

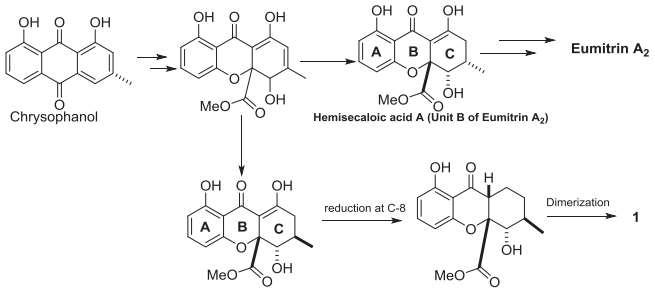
axial chirality was not well exhibited due to the rapid interconversion of two M- and P-helicity conformers as observed in versixanthone D[31] or blenolide G.[29] Compound **27** (Eumitrin A_2) with the 2–4′ linkage and bulky groups at C-10a' and C-5′ enabled its atropisomers resulting the stronger negative Cotton effect.[32] In addition, at the longer absorption (from 270 to 320 nm), the ECD spectrum of **1** showed strong positive Cotton effect at 311 nm while that of Eumitrin A_2 showed very weak one. Moreover, the monomer *cis*-dihydro-8-hydroxyblennolide H having the *anti* relationship of H-8a and H_3-13[33], similar to that of eumitrin A_2, lacked this corresponding Cotton effect and showed the strong positive Cotton effect at 276 nm. The difference in the ECD curves of **1** and eumitrin A_2 or monomer *cis*-dihydro-8-hydroxyblennolide H proposed the change of the *trans*-decalin conformer in **27** or *cis*-dihydro-8-hydroxyblennolide H to the *cis*-decalin conformer in **1**.

Similar to secalonic acid or eumitrin derivatives, the biosynthesis of bailexanthone (**1**) (Scheme 1) should begin with chrysophanol via an aryl epoxidation, Baeyer-Villiger oxidation, lactone hydrolysis, and 1,4-addition to afford the intermediate, methyl 1,4,8-trihydroxy-3-methyl-9-oxo-4,9-dihydro-4a*H*-xanthene-4a-carboxylate.[25,26,32] The selective reduction of the C-6–C-7 linkage of this intermediate produced hemisecalonic acid B possessing the *trans* orientation of the methyl CH_3-11 and the methoxycarbonyl 10a–$COOCH_3$ whilst this key step drove to another selective path to obtain the intermediate having the *cis* configuration of both these groups. The following step of this biosynthesis could be the selective reduction of the ketone C-8 after the tautomerization of the enolic double bond to afford the mono unit of **1** which could be dimerized to afford bailexanthone **1**. Due to the isolation from the same biosource of **1** and eumitrin A (**27**), the (5*R*, 10a*R*) absolute configurations of C-5 and C-10a were proposed. The combination with the *syn* orientations of H-8a, H_3-11, H_3-13, 5-OH, the absolute configuration of C-6 and C-8a were suggested as (6*R*, 8a*R*). Finally, the absolute configuration of bailexanthone (**1**) was proposed as (5*R*, 6*R*, 8a*R*, 10a*R*).

Compound **2**[34] was isolated as a white amorphous powder. The HRESIMS of the sodiated molecular ion peak $[M+Na]^+$ established a molecular formula of $C_{21}H_{18}O_9$. The ^{1}H NMR spectrum showed the presence of three methyls (δ 2.34, 2.20 and 2.15), one diastereotopic methylene (δ 3.65 and 3.03), one oxymethine (δ 5.90), one methoxy moiety (δ μ3.85), one aromatic methine (δ 6.87) and two phenolic hydroxy groups (δ 10.03 and 9.48).

The ^{13}C NMR and HSQC spectra of **2** accounted for 21 carbon resonances, comprising one ketone carbon (δ 204.3), two carboxyl carbons (δ 167.5 and 161.4), one methoxy carbon (δ 56.2), one methylene carbon (δ 45.8), two methines (δ 111.7 and 74.3), three methyls (δ 29.9, 19.9, and 9.3) and eleven aromatic quaternary carbons in the range of 108–167 ppm.

In the so-called A-ring, HMBC cross peaks of both H-5 (δ 6.87) and 4-OCH_3 (δ 3.85) to C-4 (δ 152.5), of both H-5 and H_3-8 (δ 2.34) to C-1 (δ 113.2) and C-6 (δ 132.8), and of H_3-8 to C-5 (δ 111.7) defined a first spin system through the C-1–C-6–C-5–C-4.



Scheme 1. Putative biosynthesis of **1** and **27**.

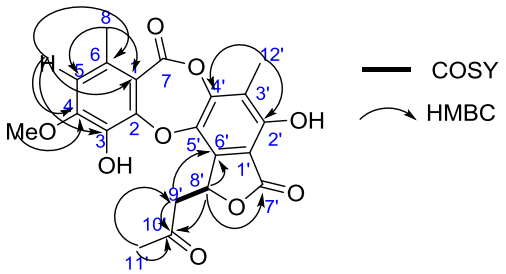


Fig. 4. Selected HMBC and NOESY correlations for **3** and **4**.

The chemical shifts of H_3-8 and C-7 in DMSO d_6 together with the long range HMBC cross-peak of H-5 to C-7 (δ 161.4)[14] defined the depsidone scaffold of **2** which was similar to known compounds isolated from the same biosource (Compounds **3**–**10**). However, proton H-5 gave a HMBC cross-peak to carbon signal at δ 134.7 (C-3) whose chemical shift could be surmised the presence of the hydroxy group at C-3. Altogether, the A-ring of **2** was determined as described in Fig. 4.

NMR data of **2** was highly reminiscent to those of menegazziaic acid[11] except for the signal patterns related to the lactone ring (C-ring). Firstly, the hemiacetal methine H-8′ (δ 6.47) in menegazziaic acid was replaced by an oxymethine (δ 5.90, d, J = 8.4 Hz) in **2** which coupled with two diastereomethylene protons H_2-9′ (δ 3.65, d, J = 16.4 Hz and 3.03, dd, 17.4, 9.4 Hz). The direct connection of C-8′ and C-9′ was further confirmed by the HMBC cross-peaks of both H-8′ and H_2-9′ to C-6′ as well as the ^{1}H–^{1}H COSY correlation between both groups (Fig. 4). The singlet methyl at δ 2.11 (H_3-11′) gave a HMBC cross peak to C-9′ whilst all H-8′, H_2-9′, and H_3-11′ showed HMBC correlation to C-10′ (δ 204.3) indicating the connectivity through C-6′–C-8′–C-9′–C-10′–C-11′. The ECD spectrum of **2** (Scheme S1, Supporting Information) showed negative Cotton effects (CEs) at ($\Delta\varepsilon$) 321 (−9.6), 302 (−12.2), 268 (−10.5), and 240 (−5.7) nm, similar to those of lobarientalone A [(CEs) at ($\Delta\varepsilon$) 320 (−1.2), 300 (−2.1), 283 (−2.5), and 250 (−1.2) nm] which possessed the *S* absolute configuration of the stereogenic acetal center of the α,β-unsaturated-γ-lactone moiety.[4] This similarity proposed the (8′*S*) configuration of **2**. Therefore, **2** was elucidated as shown and was named bailesidone.

The similarities between **2** and menegazzianic acid suggest that menegazzianic acid should be the precursor of **2** when both were isolated from the same biosource. A possible way to obtain **2** from menegazzianic acid would involve the formation of the non-lactone intermediate of menegazzianic acid under acid condition (i) with the process previously described by Le Dévéhat and co-workers (2007).[8] The next step of the biosynthesis would be the aldolization at 8′-CHO to obtain the aldol product having a side chain consisting of two acetate units (ii) as displayed in Scheme S1. This reaction could followed by the ring-closure of the 8′-OH to 7′-COOH via the esterification (iii). Depsidones possessing the same A-ring as menegazinic acid are quite rare from lichens, thus the presence of the unusual 4-carbon side chain in the B-ring of **2** makes our carbon skeleton unique, as far as can be ascertained.

Cytotoxicity

In this study, compounds **1** and **2** were tested for their cytotoxicity against A549 (human lung carcinoma) and HT29 (human colorectal adenocarcinoma) cell lines (Figs. S1 and S2). Both compounds **1** and **2** exhibited moderate activity against the A549 cell line with IC_{50} values of 81.11 and 92.94 μM, respectively and failed to reveal any cytotoxicity against HT29 cell line.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2018.02.007.

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24. Bailexanthone (1): yellow crystals; $[a]_D^{25}$. 137.7 (*c* 0.7, $CHCl_3$); ECD (0.1, $CHCl_3$) λ (Δε) 208 (+24.0), 214 (−9.2), 224 (+10.8), 265 (−17.5), 275 (−15.5) 311 (+36.0). HR-ESI-MS *m/z* 611.2138 $[M+H]^+$ (calcd for $C_{32}H_{34}O_{12}$+H, 611.21285). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (6H, *d*, 6.4 Hz, H-11, 11′), 1.23–1.96 (4H, m, H-7, 7′), 1.83 (2H, m, H-6, 6′), 2.15 (4H, m, H-8, 8′), 2.98 (2H, dd, 11.6, 4.8 Hz, H-8a, 8a′), 3.68 (6H, s, H-13, 13′), 3.72 (2 H, d, 10.8 Hz, H-5, 5′), 6.62 (1H, d, 8.4 Hz, H-4, 4′), 7.50 (2H, d, 8.4 Hz, H-3, 3′), 11.86 (2H, s, 1-OH, 1′-OH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.0 (C-1, 1′, 4a, 4a′), 117.6 (C-2, 2′), 140.4 (C-3, 3′), 107.4 (C-4, 4′), 159.0 (C-4a, 4a′), 80.3 (C-5, 5′), 34.4 (C-6, 6′), 31.2 (C-7, 7′), 20.4 (C-8, 8′), 51.2 (C-8a, 8a′), 197.4 (C-9, 9′), 107.6 (C-9a, 9a′), 87.6 (C-10a, 10a′), 18.5 (C-11, 11′), 169.3 (C-12, 12′), and 53.0 (C-13, 13′).
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34. Bailesidone (2): white amorphous powder; $[a]_D^{25}$. 47.4 (*c* 0.7, $CHCl_3$); ECD (0.25, MeOH) λ (Δε) 321 (−9.6), 302 (−12.2), 268 (−10.5), 240 (−5.7) nm. HR-ESI-MS *m/z* 437.0858 $[M+Na]^+$ (calcd for $C_{21}H_{18}O_9$+Na, 437.0848). ^{1}H NMR (DMSO-d_6, 400 MHz) δ 2.15 (3H, s, H-12′), 2.20 (3H, s, H-11′), 2.34 (3H, s, H-8), 3.03 (1H, dd, 17.4, 9.4 Hz, H-9′a), 3.65 (1H, d, 16.4 Hz, H-9′b), 3.85 (3H, s, 4-OMe), 5.90 (1H, d, 8.4 Hz, H-8′), 6.87 (1H, s, H-5), 9.48, 10.03 (2H, s, 3-OH, 2′-OH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 113.2 (C-1), 148.7 (C-2), 134.7 (C-3), 152.5 (C-4), 111.7 (C-5), 132.8 (C-6), 161.4 (C-7), 19.9 (C-8), 56.2 (4-OMe), 108.6 (C-1′), 151.8 (C-2′), 118.7 (C-3′), 148.3 (C-4′), 137.5 (C-5′), 137.0 (C-6′), 167.5 (C-7′), 74.4 (C-8′), 45.8 (C-9′), 204.3 (C-10′), 29.9 (C-11′), and 9.3 (C-12′).