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Illilanceolide A, a unique *seco*-prezizaane sesquiterpenoid with 5/5/6 tricyclic scaffold from the fruits of *Illicium lanceolatum* A. C. Smith

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ABSTRACT

A unique *seco*-prezizaane sesquiterpenoid with 5/5/6 tricyclic skeleton, illilanceolide A (**1**), and two rare 10,14-cycloseco-prezizaane sesquiterpenoids, 2-oxo-6-dehydroxyneoanisatinic acid (**2**) and 3,4-anhydro-2-oxo-6-dehydroxyneoanisatinic acid (**3**), together with two known sesquiterpenoids, were isolated from the fruits of *Illicium lanceolatum*. Their structures and absolute configurations were elucidated on the basis of extensive ^{1}H, ^{13}C, and 2D NMR, and HRESIMS data, as well as single-crystal X-ray diffraction analysis. Compounds **2**–**4** enhanced the neurite outgrowth of NGF-mediated PC12 cells at a concentration of 10 μM with differentiation rates of 13.33%, 10.90%, and 11.76%, respectively. Moreover, compounds **2**–**4** were found to exhibit moderate neuroprotective effect against MPP^{+}-induced PC12 cell damage.

Introduction

Illicium sesquiterpenoids with highly oxidized polycyclic architecture occur exclusively in *Illicium* species and are usually classified into three skeletal classes, *seco*-prezizaane, anislactone, and allo-cedrane [1–3]. To date, more than 150 *Illicium* sesquiterpenoids have been isolated and characterized since the report of anisatin and pseudoanisatin from *I. anisatum* in 1968 by Yamada and co-workers [4]. Most of them belong to the *seco*-prezizaane-type sesquiterpenoids, which are further categorized into six major subgroups according to their lactonization pattern: anisatin, pseudoanisatin, majucin, minwanensin, pseudomajucin, and cycloparvifloralone subtypes (Fig. 1) [1]. In addition, *Illicium* sesquiterpenoids exhibit intriguing biological activities including neurotrophic, neurotoxic, antiviral, and anti-inflammatory activities [5–9]. Especially, jiadifenin, jiadifenolide, merrilactone A, and 11-debenzoyltashironin have been found to exhibit strong neurite outgrowth activity [8–11]. For decades, *Illicium* sesquiterpenoids have attracted much synthetic attention due to their fascinating polycyclic and complex structures and their promising activities [12–16].

Illicium lanceolatum A. C. Smith (Illiciaceae), an aromatic evergreen shrub, is a folk medicine with Chinese name "Mangcao" or "Hongduhui" and primarily distributed in southwestern China. Its bark and roots have historically been used to cure bruises, internal injuries, and rheumatoid arthritis [17–18]. Previous phytochemical investigations on this species have disclosed the presence of monoterpenoids, germacrane sesquiterpenoids, *Illicium* sesquiterpenoids, lignans, phenylpropanoids, and hexalactone derivatives [19–26]. In search for structurally unique and biologically active *Illicium* sesquiterpenoids, the chemical constituents from the fruits of *I.lanceolatum* were investigated, which led to the isolation of three new *seco*-prezizaane sesquiterpenoids, illilanceolide A (**1**), 2-oxo-6-dehydroxyneoanisatinic acid (**2**), and 3,4-anhydro-2-oxo-6-dehydroxyneoanisatinic acid (**3**), and two known sesquiterpenoids, pseudomajucin (**4**) [27] and 7-*O*-methylpseudomajucin (**5**) (Fig. 2) [28]. Structurally, compound **1** represented a new subtype *seco*-prezeaane sesquiterpenoid possessing a unique 5/5/6 tricyclic core and having an inversion of configuration at C-9 in contrast to other six major *seco*-prezizaane sesquiterpenoids. Compounds **2** and **3** were the second report of naturally occurring 10,14-cycloseco-prezizaane sesquiterpenoids [26]. The isolation and structural elucidation of **1**–**3** and biological activities of all isolated compounds are described herein.

Results and discussion

Compound **1** was obtained as colorless crystals, and its molecular formula was determined to be $C_{15}H_{22}O_6$ by negative HRESIMS ion peak at *m/z* 297.1346 $[M-H]^-$ (calcd 297.1344 for

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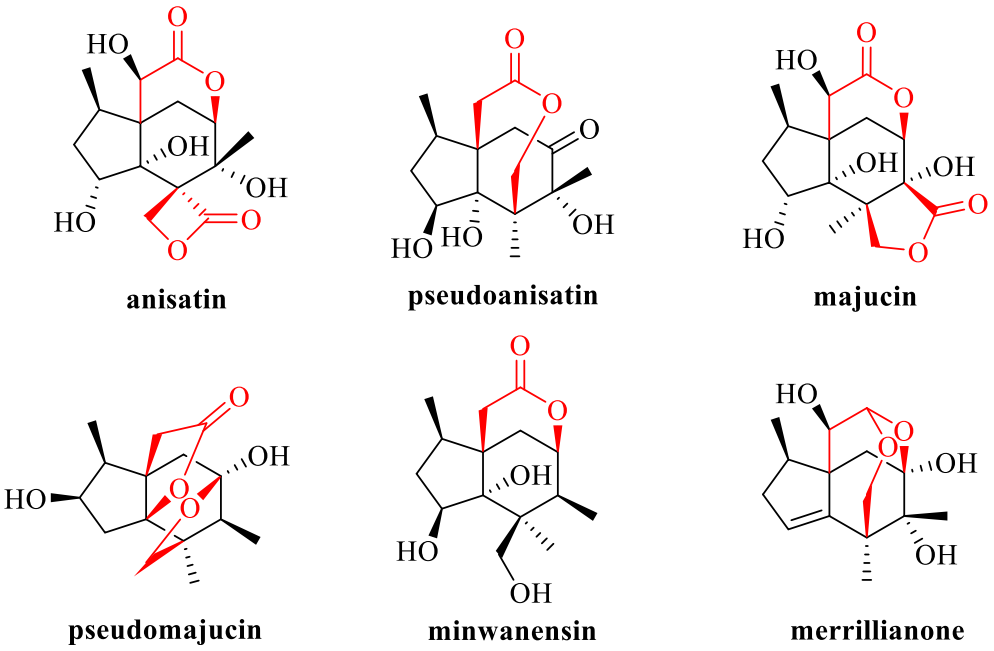

Fig. 1. Representative compounds of six major *seco*-prezizanne subtype sesquiterpenoids characterized by lactonization pattern.

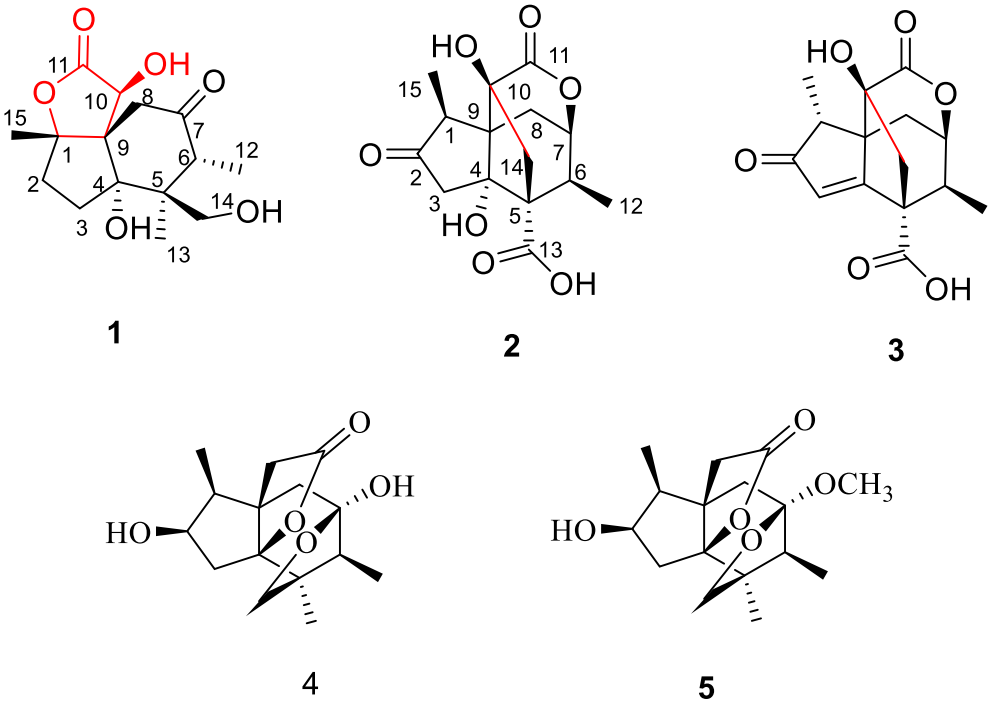

Fig. 2. Chemical structures of **1**–**5** from *I. lanceolatum*.

$C_{15}H_{21}O_6$), requiring five degrees of unsaturation. The IR spectrum showed the presence of hydroxy (3417 cm^{-1}) and carbonyl (1712 and 1753 cm^{-1}) groups. The ^1H NMR spectrum (Table 1) showed typical signals of one secondary methyl group at δ_H 0.92 (d, J = 6.6 Hz, H_3-12), two tertiary methyl groups at δ_H 1.00 (s, H_3-13) and 1.38 (s, H_3-15), an oxygenated methylene at δ_H 3.62 (s, H_2-14), and an oxymethine at δ_H 4.40 (s, H-10). The ^{13}C NMR and HSQC data of **1** displayed 15 carbon resonances assignable to three methyl groups, four methylenes (one oxygenated at δ_C 69.8), two methines (one oxygenated at δ_C 71.8), and four nonprotonated carbons (one oxygenated at δ_C 99.1, one ester carbonyl at δ_C 179.1, and one ketone carbonyl at δ_C 212.9). The presence of the ester and ketone carbonyls accounted for two of the five degrees of unsaturation, suggesting that compound **1** include a tricyclic ring system.

The structural elucidation of **1** was subsequently characterized by its 2D NMR spectroscopic data. HMBC correlations (Fig. 3) from H_2-2 (δ_H 2.05, dd, J = 14.1, 10.6 Hz; 2.48, ddd, J = 14.1, 10.6, 9.2 Hz) and H_2-3 (δ_H 2.68, dt, J = 13.6, 10.6 Hz; 2.12, dd, J = 13.6, 9.2 Hz) to C-1 (δ_C 99.1), C-4 (δ_C 86.6), and C-9 (δ_C 61.1) and from H_3-15 to C-1, C-2 (δ_C 37.0), and C-9, along with the ^1H–^1H COSY correlation of

Table 1
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data for **1** in methanol d_4 (δ in ppm, J in Hz).

Position	δ_H	δ_C
1		99.1
2α	2.48 (ddd, 14.1, 10.6, 9.2)	37.0
2β	2.05 (dd, 14.1, 10.6)	
3α	2.12 (dd, 13.6, 9.2)	35.5
3β	2.68 (dt, 13.6, 10.6)	
4		86.6
5		48.2
6	2.82 (q, 6.6)	47.4
7		212.9
8α	2.91 (d, 14.3)	39.5
8β	2.31 (d, 14.3)	
9		61.1
10	4.40 s	71.8
11		179.1
12	0.92 (d, 6.6)	8.3
13	1.00 s	14.4
14	3.62 s	69.8
15	1.38 s	24.4

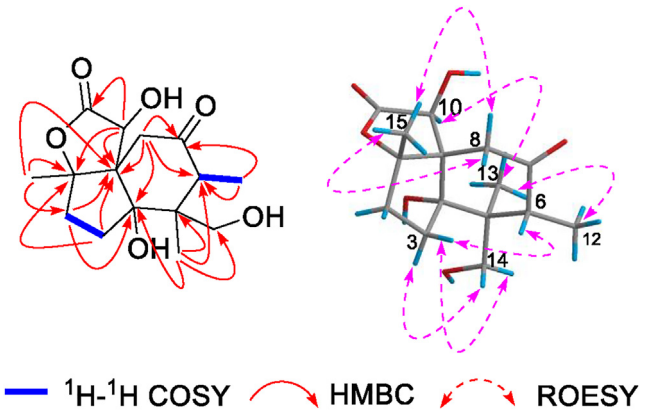

Fig. 3. The key 2D NMR correlations of **1**.

H_2-2 with H_2-3, were indicative of a five-membered carbon ring with a methyl and a hydroxy group at C-1 and C-4, respectively. Furthermore, HMBC correlations from H_2-8 (δ_H 2.31, d, J = 14.3 Hz; 2.91, d, J = 14.3 Hz) to C-4, C-6 (δ_C 47.4), C-7 (δ_C 212.9), and C-9, and from H_3-13 and H_2-14 to C-4, C-5 (δ_C 48.2), and C-6 indicated a six-membered carbon ring fused with the five-membered carbon ring through C-4/C-9 bond and featuring one hydroxymethylene and one methyl groups at C-5 and one ketone carbonyl at C-7. In addition, one secondary methyl group was placed at C-6 according to HMBC correlations from H_3-12 to C-6 and C-7, as well as the correlation between H-6 and H_3-12 in ^{1}H–^{1}H COSY spectrum. The remaining ester carbonyl group and downfield shift of C-1 (δ_C 99.1), combined with HMBC correlations from H-10 to C-1, C-9, and C-11 (δ_C 179.1), suggested a α-hydroxy-γ-lactone ring fused at C-1 and C-10 of the five-membered carbon ring. The above information led to the establishment of the planar structure of **1** with a unique 4-oxa-tricyclo[6.4.0^{1,5}.0^{1,8}]dodecane core.

The relative configuration of **1** was determined based on a ROESY experiment (Fig. 3). ROESY correlations of H_3-13 with H-10 and H_3-12 and of H_3-15 with H-8α and H-8β suggested the β-configurations of H-6, 10-OH, H_2-14, and H_3-15 and R^* configuration for C-9. 4-OH was assigned to be α-oriented by the cross-peaks of H_2-14 and H-6 with H-3β and of H_2-14 with H-3α in ROESY spectrum. Furthermore, suitable crystals of **1** were obtained from MeOH and X-ray crystallographic analysis using Cu Kα radiation unambiguously established its absolute configuration as 1*S*,4*S*,5*S*,6*R*,9*R*,10*S* (Fig. 4) [29]. Thus, the structure of **1** was characterized as shown in Fig. 2 and named as illilanceolide A.

Compound **2** gave a pseudomolecular ion peak at m/z 309.0984 [M−H]$^-$ in HRESIMS spectrum, corresponding to a molecular formula of $C_{15}H_{18}O_7$. IR spectrum displayed absorptions due to hydroxy group at 3464 cm^{-1} and carbonyls at 1701 and 1736 cm^{-1}. The ^{1}H and ^{13}C NMR spectroscopic data for **2** (Table 2) revealed the presence of two secondary methyl groups [δ_H 1.08 (d, J = 7.1 Hz, H_3-12) and 1.11 (d, J = 7.0 Hz, H_3-15); δ_C 13.3 (C-12) and 7.7 (C-15)], two methylenes, one oxymethine [δ_H 4.57 (q, J = 2.9 Hz, H-7); δ_C 80.2 (C-7)], two oxygenated tertiary carbons [δ_C 82.7 (C-4) and 78.3 (C-10)], one carboxylic carbon [δ_C 173.5 (C-13)], one ketone carbonyl carbon [δ_C 213.2 (C-2)], one ester carbonyl carbon [δ_C 176.8 (C-11)], and one quaternary carbon. A comparison of the ^{1}H and ^{13}C NMR data of **2** with those of 2α-hydroxyneoanisatinic acid [29] revealed that they possessed the same 5/5/6 tricyclic carbon skeleton. The main differences were the presence of a methine and the absence of an oxygenated tertiary carbon in **2** and that the C-2 hydroxy in 2α-hydroxyneoanisatinic acid was oxidized to ketone carbonyl group. These deductions were confirmed by HMBC correlations (Fig. 5) from H_3-15 to C-1 (δ_C 49.4), C-2, and C-9 (δ_C 56.2) and from H_3-12 to C-5 (δ_C 57.9), C-6 (δ_C 35.1), and C-7, as well as the correlation of H-6/H_3-12 in ^{1}H–^{1}H COSY spectrum. ROESY correlations (Fig. 5) of H-3β/H-14a and H_3-12/H-14b revealed the α-orientations of H-6, 4-OH, and 10-OH, and the R^* configuration for C-9. H_3-15 was determined to be β-oriented by the ROESY correlations of H-1/H-8α and H-8β/H_3-15. Colorless crystals of **2** were obtained from MeOH and then subjected to X-ray crystallographic using Cu Kα radiation [30], which defined unambiguously the absolute configuration of **2** as 1*S*,4*R*,5*S*,6*S*,7*R*,9*R*,10*S* (Fig. 6). Accordingly, the structure of **2** was constructed and named as 2-oxo-6-dehydroxyneoanisatinic acid.

Compound **3** was isolated as colorless crystals. Its molecular formula was determined to be $C_{15}H_{16}O_6$ based on the HRESIMS and ^{13}C NMR data. The ^{1}H and ^{13}C NMR data of **3** (Table 2) closely resembled those of **2**, except for the only difference being that a methylene and an oxygenated tertiary carbon were replaced by one trisubstituted double bond [δ_C 118.5 (C-3) and 186.0 (C-4)], suggesting that **3** was a dehydration derivative of **2**. The double bond between C-3 and C-4 was supported by the correlations between H-3 (δ_H 5.78) and C-1 (δ_C 45.7), C-2 (δ_C 212.4), C-4, and C-9 (δ_C 57.4) in HMBC spectrum. The relative configurations of C-4, C-5, C-6, C-9, and C-10 were identical to those of **2** by analysis of ROESY spectrum. The structure and absolute configuration (1*R*,5*S*,6*S*,7*R*,9*R*,10*S*) of **3** were verified unambiguously by X-ray crystallography study (Cu Kα) with a Flack parameter of [0.04(4)]

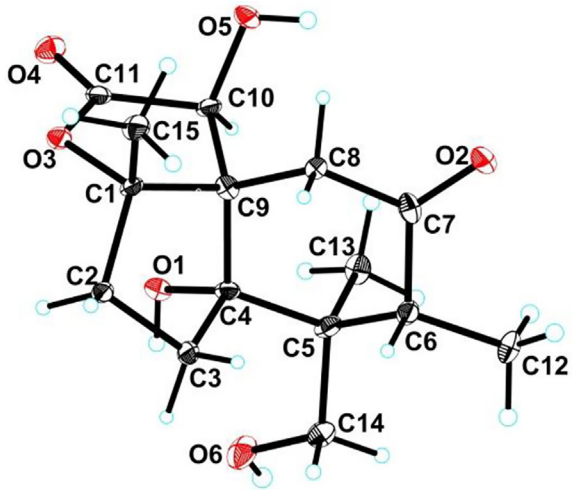

Fig. 4. X-ray crystallographic structure of **1**.

Table 2
^{1}H (600 MHz) and ^{13}C NMR (150 MHz) data for **2** and **3** (δ in ppm, J in Hz).

Position	**2**[a]		**3**[b]	
	δ_H	δ_C	δ_H	δ_C
1	2.45 (q, 7.0)	49.4	3.00 (q, 7.5)	45.7
2		213.2		212.4
3α	2.39 (d, 19.0)	47.2	5.78 s	118.5
3β	2.77 (d, 19.0)			
4		82.7		186.0
5		57.9		57.7
6	2.91(m)	35.1	2.64 (m)	41.8
7	4.57 (q, 2.9)	80.2	4.65 (q, 2.9)	79.3
8α	2.61 (dd, 13.8, 2.9)	32.9	1.85 (dd, 14.0, 2.9)	39.7
8β	1.94 (dd, 13.8, 2.9)		2.31 (dd, 14.0, 2.9)	
9		56.2		57.4
10		78.3		76.6
11		176.8		176.9
12	1.08 (d, 7.1)	13.3	1.19 (d, 7.0)	12.6
13		173.5		172.8
14a	2.34 (d, 13.7)	43.2	2.74 (d, 13.9)	45.1
14b	2.32 (d, 13.7)		2.13 (d, 13.9)	
15	1.11 (d, 7.0)	7.7	1.05 (d, 7.5)	9.5

[a] Recorded in acetone d_6;
[b] Recorded in methanol d_4.

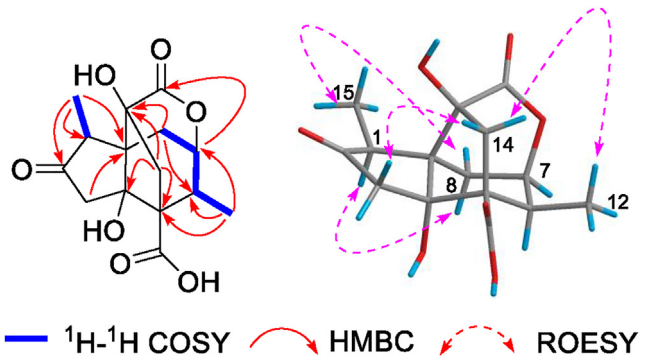

Fig. 5. The key 2D NMR correlations of **2**.

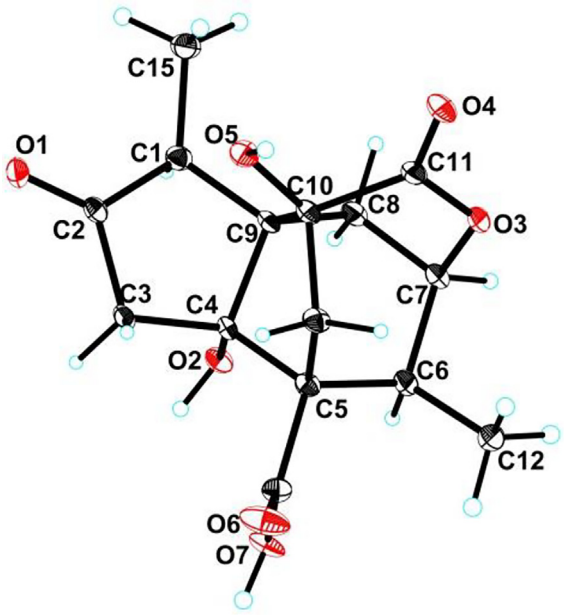

Fig. 6. X-ray crystallographic structure of **2**.

(Fig. 7) [31]. Thereby, the structure of **3** was assigned and named as 3,4-anhydro-2-oxo-6-dehydroxyneoanisatinic acid.

Some *Illicium* sesquiterpenoids have been reported to show noticeable neurotrophic and neuroprotective activities [8–11]. So, the current isolated compounds **1**–**5** were evaluated for their neurite outgrowth-promoting effect and neuroprotective activity against MPP^{+}(1-methyl-4-phenylpyridinium ion)-induced PC12 cell injury. As a result, compounds **2**–**4** showed remarkable neurotrophic activity at 10 μM with differentiation rates of 13.33%, 10.90%, and 11.76%, respectively, compared with 4.46% of 5 ng/mL NGF (Table S1). Furthermore, compounds **2**–**4** exhibited moderate neuroprotective activity against MPP^{+}-induced PC12 cell damage at 20 μM with cell survival rate of 72.92 ± 0.32%, 72.89 ± 0.40%, and 72.41 ± 0.48%, respectively, compared with 69.70 ± 0.33% for the model group (Table S2).

In conclusion, three new *seco*-prezizaane sesquiterpenoids (**1**–**3**) and two know sesquiterpenoids (**4** and **5**) were isolated from the fruits of *I. lanceolatum* A. C. Smith. The structures and absolute configurations of **1**–**3** were confirmed by single-crystal X-ray

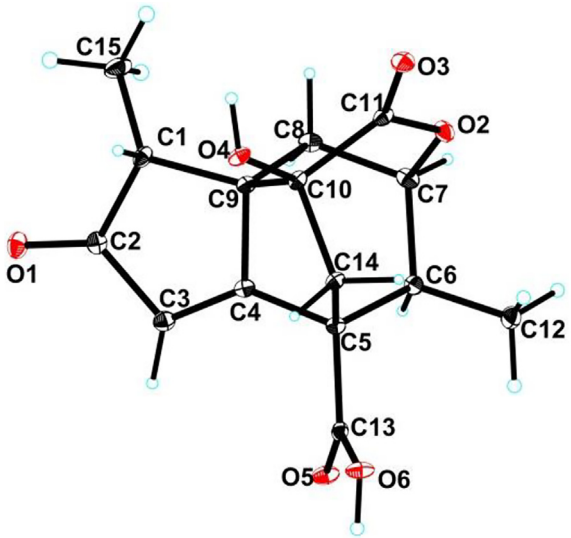

Fig. 7. X-ray crystallographic structure of **3**.

diffraction. To the best of our knowledge, compound **1** was a new subtype of *seco*-prezizaane sesquiterpenoid with a unique 4-oxa-tricyclo[6.4.0^{1,5}.0^{1,8}]dodecane core. Compounds **2** and **3** were the second report of naturally occurring 10,14-cycloseco-prezizaane type sesquiterpenoids. Compounds **2**–**4** exhibited noticeable neurite outgrowth-promoting effect and showed moderate neuroprotective activity. Thus, these bioactive compounds might be further developed as neurotrophic and neuroprotective agents for the treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153022.

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[29] Crystal data for 1: C15H22O6, M = 298.32, a = 6.6389(11) Å, b = 16.242(3) Å, c = 13.228(2) Å, α = 90°, β = 91.558(5)°, γ = 90°, V = 1425.8(4) Å3, T = 100(2) K, space group P1211, Z = 4, μ(Cu Kα) = 0.894 mm-1, 25661 reflections measured, 5202 independent reflections (Rint = 0.0607). The final R1 values were 0.1016 (I > 2σ(I)). The final wR(F2) values were 0.3088 (I > 2σ(I)). The final R1 values were 0.1059 (all data). The final wR(F2) values were 0.3145 (all data). The goodness of fit on F2 was 1.572. Flack parameter = 0.18(7). Crystallographic data for the structure of 2 have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 2063617).
[30] Crystal data for 2: C15H18O7•H2O, M = 328.31, a = 7.2983(4) Å, b = 12.6932(8) Å, c = 15.5603(9) Å, α = 90°, β = 96.461(2)°, γ = 90°, V = 1432.33(15) Å3, T = 100 (2) K, space group P1211, Z = 4, μ(Cu Kα) = 1.059 mm-1, 40298 reflections measured, 5616 independent reflections (Rint = 0.0557). The final R1 values were 0.0552 (I > 2σ(I)). The final wR(F2) values were 0.1562 (I > 2σ(I)). The final R1 values were 0.0553 (all data). The final wR(F2) values were 0.1563 (all data). The goodness of fit on F2 was 1.067. Flack parameter = 0.19(5). Crystallographic data for the structure of 2 have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 2063618).
[31] Crystal data for 3: C15H16O6•H2O, M = 310.29, a = 7.9661(2) Å, b = 12.0909(3) Å, c = 14.4646(4) Å, α = 90°, β = 90°, γ = 90°, V = 1393.19(6) Å3, T = 101(2) K, space group P212121, Z = 4, μ(Cu Kα) = 1.002 mm-1, 23990 reflections measured, 2755 independent reflections (Rint = 0.0359). The final R1 values were 0.0275 (I > 2σ(I)). The final wR(F2) values were 0.0726 (I > 2σ(I)). The final R1 values were 0.0275 (all data). The final wR(F2) values were 0.0726 (all data). The goodness of fit on F2 was 1.078. Flack parameter = 0.04(4). Crystallographic data for the structure of 2 have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 2063619).