Tetrahedron Letters 78 (2021) 153294

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Isolation of the 3′*R* and 3′*S* diastereomers of fasciculic acid C from the Australian mushroom *Hypholoma australianum*

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ARTICLE INFO

Article history:
Received 21 March 2021
Revised 30 June 2021
Accepted 12 July 2021
Available online 22 July 2021

Keywords:
Lanostane triterpene
Hypholoma australianum
Natural Product
Fungal Metabolite

ABSTRACT

Nine compounds including the new diastereomers (3′*R*)-fasciculic acid C (**1**) and (3′*S*)-fasciculic acid C (**2**), the triterpenes (**3**–**5**), the sesquiterpenes (**6**–**7**) and the diketopiperazines (**8**–**9**) were isolated from the Australian mushroom *Hypholoma australianum*. Several lanostane triterpenes have been isolated from the genus *Hypholoma* previously contain a 3-hydroxy-3-methylglutaric acid or a 3-hydroxy-3-methylglutaryl-glycine side chain. Only *Hypholoma* derived triterpenes possessing the *S*-configuration for these two side chains have been isolated previously. Compound **1** is the first example of a triterpene isolated from *Hypholoma* to have an *R*-configuration for the side chain.

Introduction

Mushrooms are an excellent source of bioactive metabolites. The genus *Hypholoma* (formerly *Naematoloma*) is a source of a variety of chemical classes including pyrones, sesquiterpenes and triterpenes [1–4]. *Hypholoma australianum* is native to Australian and New Zealand forests and has not previously had its secondary metabolites investigated. *Hypholoma australianum* (originally described as *H. australe*) is phylogenetically most closely related to *H. frowardii* (synonym = *Naematoloma frowardii*) from South America [5]. In overall morphology it closely resembles the Northern Hemisphere species *H. lateritium* (=*H. sublateritium*, *Naematoloma sublateritium*) but crosses between single-spore isolates of *H. australianum* and *H. lateritium* are not fertile [6]. Several of the fasciculols and the fasciculic acids described herein, as well as the related sublateriols, have previously been isolated from *H. lateritium* [2,4,7–12].Fig 1.

Consisting of a lanostane skeleton, the fasciculols and the fasciculic acids differ from each other primarily by the C-2 or C-3 side chain, which contains either a 3-hydroxy-3-methylglutaric acid or a 3-hydroxy-3-methylglutaryl-glycine. These triterpenes can further exist as their methyl-esters and vary by the extent and pattern of the hydroxyl substituents (C-12 and/or C-21) [2,4,7,8,10,11,13]. The fasciculols and the fasciculic acids have shown a variety of bioactivities including plant growth inhibition, weak antimicrobial activity, calmodulin inhibitory activities, weak antiproliferative activities and cytotoxicity [7,9–11,14,15].

The chemical investigation of *H. australianum* collected in Victoria, Australia led to the isolation of five triterpenoids including (3′*R*)-fasciculic acid C (**1**), (3′*S*)-fasciculic acid C (**2**), fasciculol C (**3**), fasciculol E (**4**) and fasciculol F (**5**) [8,11,13], as well as the isolation of the known sesquiterpenes fascicularone B and G (**6**–**7**) and the diketopiperazines cyclo-(Leu-Val) and cyclo-(Leu-Ile) (**8**–**9**) [16,17].

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https://doi.org/10.1016/j.tetlet.2021.153294
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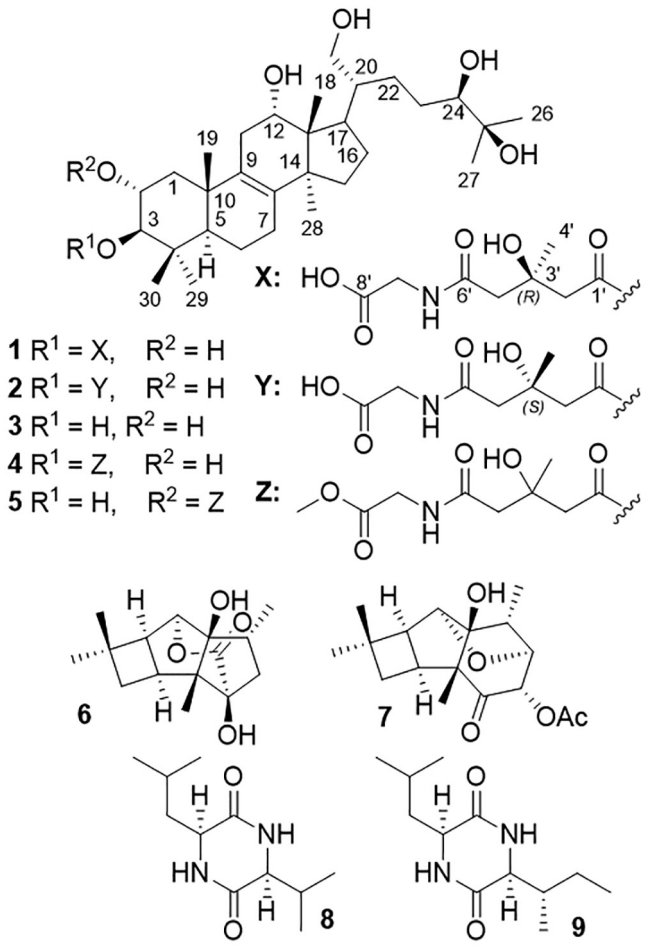

Figure 1. The lanostane triterpenes (3′*R*)-fasciculic acid C (**1**), (3′*S*)-fasciculic acid C (**2**), fasciculol C (**3**), fasciculol E (**4**) and fasciculol F (**5**). The sesquiterpenes fascicularone B and G (**6**–**7**) and the diketopiperazines cyclo (Leu-Val) and cyclo (Leu-Ile) (**8**–**9**).

Table 1
^{1}H (500 MHz) NMR data for (3′*R*)-fasciculic acid C (**1**) and (3′*S*)-fasciculic acid C (**2**) acquired in pyridine d_5.

Position	1 ^{1}H (δ, mult., J in Hz)	2 ^{1}H (δ, mult., J in Hz)
1α	1.60 (m)	1.62 (m)
1β	2.42 (dd, 12.7, 4.0)	2.42 (dd, 12.5, 4.1)
2β	4.23 (ddd, 11.0, 9.8, 4.0)	4.22 (ddd, 11.2, 9.8, 4.1)
3α	5.07 (d, 9.8)	5.10 (d, 9.8)
5	1.39 (m)	1.41 (m)
6β	1.53 (m)	1.54 (m)
6α	1.67 (m)	1.65 (m)
7α	2.09 (m)	2.09 (m)
7β	2.09 (m)	2.09 (m)
11α	2.45 (d, 19.0)	2.46 (d, 18.9)
11β	2.85 (dd, 19.0, 8.7)	2.86 (dd, 18.9, 8.4)
12α	4.29 (d, 8.7)	4.30 (d, 8.4)
15α	1.25 (m)	1.25 (m)
15β	1.77 (m)	1.77 (m)
16α	2.18 (m)	2.18 (m)
16β	1.55 (m)	1.56 (m)
17	2.90 (q, 9.4)	2.91 (q, 9.3)
18	0.73 (s)	0.73 (s)
19	1.11 (s)	1.10 (s)
20	1.62 (m)	1.62 (m)
21a	4.14 (bs)	4.14 (bs)
21b	4.14 (bs)	4.14 (bs)
22a	1.84 (m)	1.84 (m)
22b	2.36 (m)	2.38 (m)
23a	1.97 (m)	1.96 (m)
23b	1.97 (m)	1.96 (m)
24	3.87 (dd, 8.6, 3.8)	3.87 (dd, 9.4, 2.9)
26	1.52 (s)	1.52 (s)
27	1.55 (s)	1.54 (s)
28	1.37 (s)	1.38 (s)
29	1.06 (s)	1.07 (s)
30	1.03 (s)	1.04 (s)
2a'	3.15 (d, 13.9)	3.19 (d, 14.0)
2b'	3.21 (d, 13.9)	3.23 (d, 14.0)
4′	1.81 (s)	1.84 (s)
5a'	2.99 (d, 14.0)	3.06 (d, 14.0)
5b'	3.13 (d, 14.0)	3.13 (d, 14.0)
6′(NH)	8.91 (bs)	9.15 (t, 4.6)
7a'	4.41 (bs)	4.42 (dd, 17.7, 5.8)
7b'	4.41 (bs)	4.49 (dd, 17.7, 5.8)

Results and discussion

The aerial parts of *H. australianum* were extracted as described in the experimental section. A combination of reverse-phase and normal-phase chromatography led to the isolation of the new triterpene (3′*R*)-fasciculic acid C (**1**), and the four known triterpenes **2**–**5**, the sesquiterpenes **6**–**7** and the diketopiperazines **8**–**9**. The structures of all compounds were elucidated using a combination of NMR and HRESIMS. The proton and carbon chemical shifts of **3**–**9** were a close match with the published chemical shifts [8,11,13,16–19].

(3′*R*)-Fasciculic acid C **1** (Tables 1 and 2) was obtained as a yellow oil. The molecular formula was determined to be $C_{38}H_{63}NO_{11}$ from analysis of the molecular ion at *m*/*z* 710.4472 (calculated M + H^{+} 710.4472, Δ 0.27) in the positive HRESIMS. Analysis of the ^{13}C NMR data suggested nine of these carbons were non-protonated including three carbonyl carbons (δ_C 173.0 (C-8′), δ_C 172.7 (C-6′) and δ_C 172.2 (C-1′)), two olefinic carbons (δ_C 135.5 (C-8) and δ_C 134.1 (C-9)), two oxygenated quaternary carbons (δ_C 73.3 (C-25) and δ_C 71.5 (C-3′)) and four aliphatic quaternary carbons (δ_C 51.1 (C-14), δ_C 51.2 (C-13), δ_C 39.7 (C-4) and δ_C 38.7 (C-10)). Six ^{1}H–^{1}H spin systems (Fig. 2, bold bonds) were determined from analysis of the COSY data; these included CH_2-1 to CH-3, CH-5 to CH_2-7, CH_2-11 to CH-12, CH_2-15 to CH_2-21, CH_2-22 to CH-24, and NH-7′ to CH_2-7′.

The HMBC correlations (Fig. 2, arrows) between the pair of methyl singlets H_3-29 and H_3-30 and C-4, the oxygenated methine carbon C-3 and the aliphatic methine carbon at C-5 as well as the HMBC correlations between the methyl singlet H_3-19 and C-5, and the methylene carbon C-1 allowed the A-ring to be deduced. HMBC correlations between the methylene protons H_2-7 and the olefinic carbons C-8 and C-9 established a double bond between C-8 and C-9. The HMBC correlation between H_3-19 and C-9 allowed the B-ring to be determined. The HMBC correlations between H-11β and C-9 and C-13, between the methyl singlet H_3-18 and C-12, C-13 and C-14, and between the methyl singlet H_3-28 and C-8 allowed the C-ring to be deduced. The HMBC correlations between H_3-28 and C-15 and between H_3-18 and C-17 established the D-ring. The HMBC correlation between the oxygenated methylene H_2-21 and C-22 and the correlations between the pair of methyl singlets H_3-26 and H_3-27 and the oxygenated carbon C-24 and C-25 established the upper side chain. The carbon chemical shifts of C-2 (δ_C 67.3), C-12 (δ_C 73.7), C-21 (δ_C 61.7), C-24 (δ_C 79.6) and C-25 (δ_C 73.3) are consistent with hydroxy substitutions [11]. The HMBC correlations between 6′-NH and C-8′, C-7′ and C-6′, along with correlations between the methylene protons H_2-5′ and C-6′, C-4′, C-3′ and C-2′ and between the methylene protons H_2-2′ and the carbonyl carbon C-1′ allowed a 3-hydroxy-3-methyl-glutaryl-glycine fragment to be deduced. The HMBC correlation between H-3α and C-1′ established that the fragment is attached at the C-3 position. The deduced structure of **1** was consistent with

Table 2
^{13}C (125 MHz) NMR data for (3′*R*)-fasciculic acid C (**1**) and (3′*S*)-fasciculic acid C (**2**) acquired in pyridine d_5.

Position	1 ^{13}C (δ)	2 ^{13}C (δ)
1	44.9	44.6
2	67.3	67.4
3	85.7	85.7
4	39.7	39.7
5	50.8	50.8
6	19.0	19.0
7	27.1	27.1
8	135.5	135.3
9	134.1	134.1
10	38.7	38.7
11	33.6	33.6
12	73.7	73.3
13	51.2	51.2
14	51.1	51.2
15	32.8	32.8
16	28.9	28.9
17	39.1	39.2
18	17.7	17.7
19	20.7	20.7
20	44.6	44.6
21	61.7	61.7
22	28.7	28.7
23	30.3	30.2
24	79.6	79.6
25	73.3	73.6
26	26.6	26.6
27	26.5	26.5
28	24.6	24.6
29	29.2	29.2
30	18.4	18.4
1′	172.7	172.7
2′	47.7	47.7
3′	71.5	71.5
4′	29.2	29.1
5′	47.7	47.8
6′	173.0	173.2
7′	43.9	42.6
8′	174.6	173.6

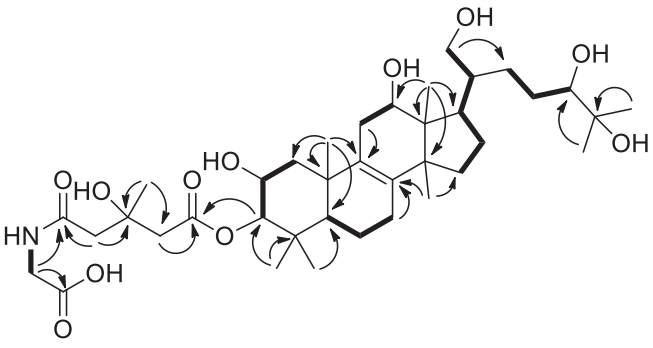

Figure 2. Key COSY (bold) and HMBC (arrows) correlations used to elucidate the structure of **1**.

that of the known lanostane triterpene fasciculic acid C however there were some clear differences in the NMR data previously reported and our data suggesting that we may have isolated a new diastereomer [11].

The relative configuration of **1** was determined from analysis of ^1H–^1H coupling constants and ROESY data. The large 10 Hz axial-axial coupling constant between H-2β and H-3α indicated that the 2-OH and the side chain attached at C-3 are both in equatorial configurations. The ROESY correlations between H-2β and both H_3-19 and H_3-30 indicated that both methyl groups are in an axial configuration, and that all of these protons are on the same face of the molecule (β). The ROESY correlations between H-5 and H-3, between H-3 and H-11α, between H-11α and H_3-28 and between H_3-28 and both H-16α and H-17 indicated that H-3, H-5, H-11α, H-17 and H_3-28 are all in axial configurations and on the α face of the molecule. The ROESY correlations between H_3-18 and H-12β and H-20 indicated that H-12β, 18-CH_3 and H-20 are on the β face of the molecule. The stereocenter at C-3′ could not be assigned based upon ROESY data alone. The relative configuration deduced for **1** was consistent with that of fasciculic acid C at all nine stereocenters in the triterpene moiety. Interestingly, the relative configuration of the C-3′ stereocenter in fasciculic acid C has not previously been assigned and so this suggested that the configuration at C-3′ was the point of difference between the published compound and **1** [11].

Other members of the fasciculol and the fasciculic acid series that contain a 3-hydroxy-3-methylglutaryl side chain and have had the absolute configuration of the C-3′ stereocenter determined have exclusively been reported to possess *S*-configuration [9,20]. Our initial assumption that the absolute configuration at C-3′ in **1** was therefore also *S* was challenged by the isolation of **2**. (3′*S*)-Fasciculic acid C **2** (Tables 1 and 2) was obtained as a yellow oil. The molecular formula was determined to be $C_{38}H_{63}NO_{11}$ from analysis of the molecular ion at *m*/*z* 710.4479 (calculated M + H^+ 710.4472, Δ −0.72) in the positive HRESIMS. Interpretation of a full set of NMR data (^1H, ^{13}C, COSY, HSQC and HMBC) resulted in the elucidation of the same constitutional structure as **1**. Furthermore, analysis of the ROESY data and ^1H–^1H coupling constants found that the configuration of the nine stereocenters associated with triterpene moiety in **2** are same as **1**.

Upon close inspection however, the proton chemical shifts of the 3-hydroxy-3-methylglutaryl-glycine side chain were distinctly different when the two compounds were compared, as was the proton chemical shift of H-2 of the terpene. These observations further supported the hypothesis that **1** and **2** are diastereomers at C-3′. The absolute configuration of the triterpene moiety has previously been determined and found to be the same both within *Hypholoma* species and in other mushrooms [13,21–23]. ROESY correlations were observed between H_3-29 and both H-2a′ and H-2b′ in **1**. ROESY correlations were observed between H_3-29 and H-2a′ and H-2b′ in **2**; weak ROESY correlations were also observed between H_3-29 and H-5a′ and H-5b′ and between H_3-30 and H-2a′ and H-2b′. These correlations suggested that the side chain was in proximity to 29-CH_3 and 30-CH_3 (Fig 3). H-2′a (δ_H 3.19, Δ 0.04 ppm) and H-5a' (δ_H 3.06, Δ 0.07 ppm) are on the same face of the molecule as the dimethyl and the deshielded chemical shifts of both protons can be explained by the deshielding effect of the dimethyl. ROESY correlations were only observed between H_3-29 and both H-2a′ and H-2b′ in **1**. The lack of ROESY correlations between H_3-29 and H-5a′ and H-5b′ and between H_3-30 and H-2a′ and H-2b′ in **2** suggested that the side chain was in a different configuration. The deshielded proton chemical shift of H-2 (δ_H 4.23, Δ 0.01 ppm) in **1** is a result of the proximity of the side chain. The carbon chemical shift of the carboxylic acid C-8′ (δ_C 174.6, Δ 1.0 ppm) in **1**, is further deshielded due to hydrogen bonds between the acid proton and amide carbonyl and C-2 hydroxyl. Based upon this evidence **1** has been assigned as 3′-*R* and **2** as 3′-*S*.

The absolute configuration at C-3′ in **1** was determined through ester hydrolysis and chiroptical analysis of the side chain fragment. To achieve this, **1** was subjected to alkaline hydrolysis in methanolic NaOH and RP HPLC purification yielded the side chain (**1a**, Fig. 4) and **3**. A negative Cotton effect in the experimental ECD spectra of **1a** at 210 nm showed a close match with that calculated using the TDDFT method for its 3′*R* enantiomer (Fig. 5). This confirmed that the absolute configuration at C3′ in **1** is *R* and by extension the absolute configuration at C-3′ in **2** is *S*.

A complete set of ^{13}C NMR data and a partial set of ^1H NMR data has previously been reported for fasciculic acid C, the ^{13}C and ^1H

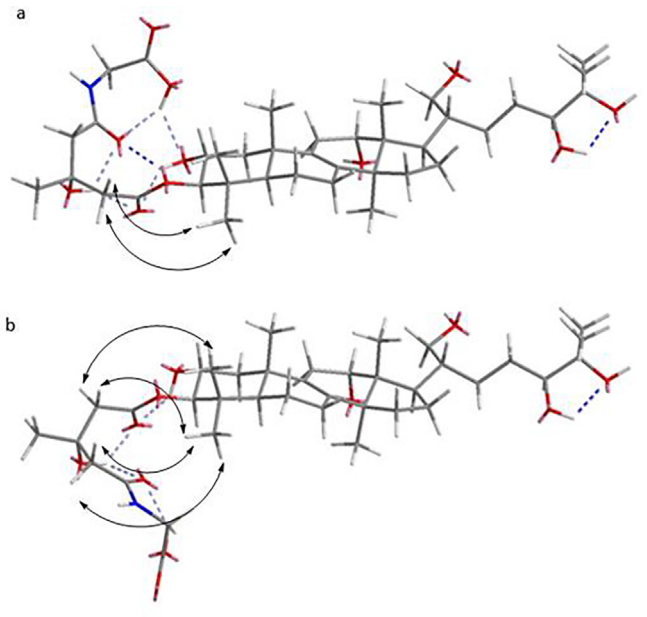

Figure 3. 3D images of **1** (a) and **2** (b) and key ROESY correlation (arrows) used to determine the configuration of the side chain. Dashed lines indicate hydrogen bonds.

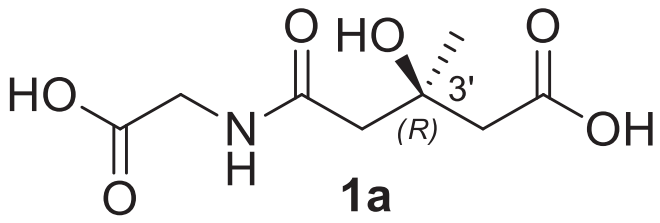

Figure 4. Structure of the side chain (**1a**).

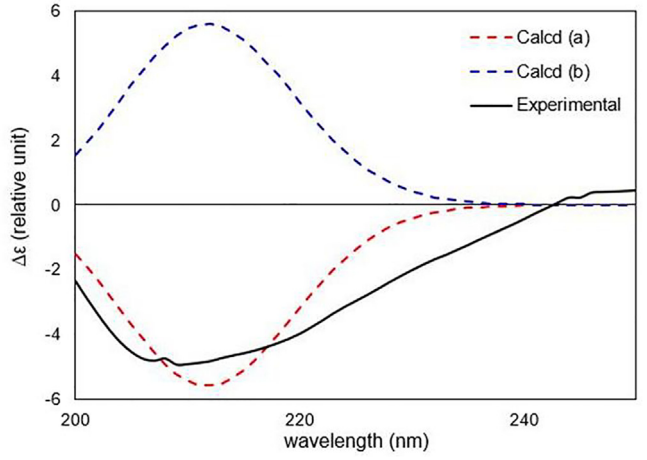

Figure 5. Comparison of experimental acquired between 200 and 250 nm (soild blank line) and TDDFT calculated ECD spectra of the (3′*R*) side chain (**1a,** calcd a, red dotted line) and the (3′*S*) side chain (calcd b, blue dotted line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

chemical shifts we observed for **2** more closely match the published data suggesting the that published compound is (3′*S*)-fasciculic acid C [11]. However, this assessment is tentative as there were numerus deviations between the published ^{13}C and ^{1}H NMR chemical shifts and our own. Only ^{13}C and ^{1}H spectra have been reported for the published compound **2** (without 2D NMR analysis) and its structure was assigned based upon comparison to other lanostane triterpenes [11]. The chemical shifts that we have assigned for **1** and **2** are supported by COSY, HSQC and HMBC spectra and these experiments suggest that several of the published ^{13}C and ^{1}H chemical shifts should be reassigned. Other discrepancies cannot be explained such as the published carbon chemical shift assigned to C-3 at δ_C 79.7 that we have definitively assigned to the resonance at δ_C 85.7, in both **1** and **2**. There was no resonance reported at δ_C 85.7 in the published data for **2** [11]. In the absence of published supporting information for fasciculic acid C the reason for these remaining discrepancies cannot be determined. We have therefore assigned **1** as a new diastereomer and **2** a known compound that has had its 3′ configuration determined for the first time. This is also the first time that a complete set of ^{1}H NMR data has been published for **2**.

The previous determination of the configuration at C-3′ has largely been limited to the triterpenes that contain 3-hydroxy-3-methylglutaric acid, and for compounds where the configuration has been determined, it was found exclusively to be the *S*-configuration [9,20]. However, it is noteworthy that the ester side chains of other mushroom derived lanostane triterpenoids have been reported to possess the *R*-configuration [23,24]. The configuration at C-3′ in triterpenes that have a methylglutaryl-glycine side chain has largely been neglected and most assignments have been based upon comparing ^{1}H NMR chemical shifts. However, this side chain has been shown to influence biological activity with the presence of a 3-hydroxy-3-methylglutaryl-glycine side chain resulting in selective cytotoxicity against SK-MEL-2 cells [9]. It is therefore not unreasonable to assume that the configuration of the side chain may also affect the biological activity.

Cytotoxicity has been thoroughly investigated for compounds in the fasciculol and the fasciculic acid series [9]. Fifteen of the lanostane triterpenes were screened for cytotoxicity towards the human cell lines A549 (non-small cell lung adenocarcinoma), SK-OV-3 (ovary malignant ascite), SK-MEL-2 (skin melanoma), and HCT-15 (colon adenocarcinoma) [9]. A structure activity relationship for these compounds identified two key features, the presence of the C-12 hydroxyl and both the presence and the type of side chain at either C-2 or C-3, that affected the potency and selectivity of the cytotoxicity. Compounds without either a C-2 or a C-3 side chain and the presence of a hydroxyl at C-12 showed cytotoxic activity against all four cell lines. The absence of a side chain and presence of a ketone at C-12 showed selective cytotoxicity against SK-OV-3 cells. Compounds with a hydroxy-3-methylglutaryl-glycine side chain at either position showed selective cytotoxicity against SK-MEL-2 cells, while compounds with a hydroxy-3-methylglutaryl side chain showed no or reduced activity against all four cell lines. Fasciculic acid C was not included in this study [9].

We therefore tested **1** to **4** for their cytotoxicity against HeLa (cervical cancer) and Vero (non-cancer monkey kidney) cells. At 70 μM some cytotoxic activity was observed for fasciculol C (**3**) (Fig. 6A) and fasciculol F (**4**) (Fig. 6B), but selective cytotoxicity was only noted for fasciculol C (Fig. 6A) confirming earlier reports that the presence of a 3-hydroxy-3-methylglutaryl-glycine side chain can introduce selective cytotoxicity [9]. The diastereomers of fasciculic acid C (Fig. 6C and D), both possessing a 3-hydroxy-3-methylglutaryl-glycine side chain, showed cytotoxicity already at lower concentrations (<10 μM). Moreover, the cancer specific cytotoxicity of only (3′*R*)-fasciculic acid C (**1**) (Fig. 6C) may indicate that the configuration of the side chain plays a role in selectivity [25,26].

Compounds **1** to **4** were also assessed for their ability to induce IL-6 and TNF-α expression in human macrophages, however at a

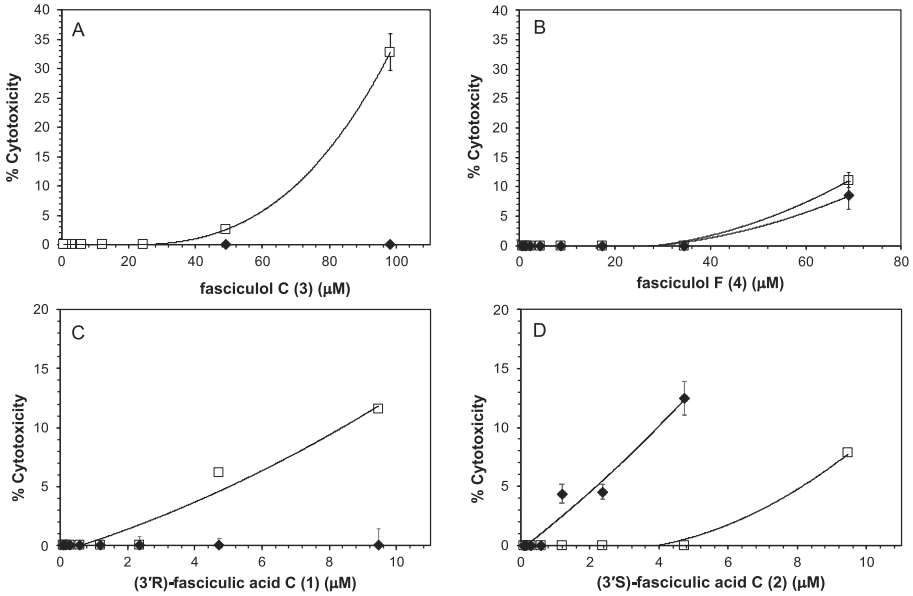

Figure 6. The cytotoxicity of fasciculol C (**A**), fasciculol F (**B**) and the diastereomers of fasciculic acid C (**C** and **D**) on HeLa (□) and Vero (◆) cells as determined using the MTT assay.

maximum concentration of 100 μM neither fasciculol C (**3**), fasciculol F (**4**), nor the diastereomers of fasciculic acid C (**1** and **2**) were able to stimulate the expression of cytokines IL-6 and TNF- α.

The same four compounds (**1**–**4**) were also tested for their antifungal and antibacterial activities against selected microorganisms. At a maximum concentration of 100 μM neither fasciculol C (**3**), fasciculol F (**4**), nor the diastereomers of fasciculic acid C (**1** and **2**) showed any antifungal activity against *Aspergillus fumigatus* (ATCC 13073). Similarly, **1** and **2** were inactive at 45 μM against a methicillin-susceptible *Staphylococcus aureus* (ATCC 25923), methicillin-resistant *S. aureus* (ATCC 43300) and *Pseudomonas aeruginosa* (ATCC 27853).

Conclusion

The isolation of the 3′*R* and 3′*S* diastereomers of fasciculic acid C highlights the importance of critically analyzing NMR data, as a difference in configuration may only be indicated by subtle differences in chemical shifts. Configuration is known to affect bioactivity, and our data shows that the configuration at C-3′ in the triterpene ester side chain affects the cytotoxic potency of the diastereoisomers **1** and **2**. Structural elucidation of new compounds should therefore carefully consider all structural features including the thorough analysis of the compound's stereochemistry.

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

The authors gratefully acknowledge Indy Siva and the Griffith University eResearch Services team for use of the 'Gowonda' High-Performance Computing (HPC) Cluster to perform ECD calculations for **1a**.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153294.

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