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Furofuran lignans from the Simpson Desert species *Eremophila macdonnellii*☆

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ABSTRACT

The *Eremophila* plant family, which occurs in the arid zones of Australia, have witnessed extensive investigation, mostly inspired by Aboriginal traditional medicine. A wide and varied biological and phytochemical profile has been reported for over 18 individual species of Australian *Eremophila*, although *E. macdonnellii* from the Simpson Desert has not yet been investigated. Isolation and elucidation of one new and six known furofuran lignans are reported. The new lignan, epimethoxypiperitol, displayed moderate anti-cancer activity against the breast cancer cell line (MCF-7).

1. Introduction

The thriving diversity that has evolved to survive in extreme Australian arid landscapes has to-date only attracted meagre attention in terms of desert plant bioactive profiling and secondary metabolite discovery. Of those species that have been investigated thus far (e.g. *Acacia victoriae* [1–4], and *Myoporum deserti* [5,6]), the majority of investigations have focussed on the *Eremophila* family (i.e. *E. neglecta* [5,7,8], *E. serrulata* [9], *E. mitchellii* [10,11], *E. microtheca* [12], *E. longifolia* [13], *E. duttonii* [14–16], *E. maculata* [17,18], *E. sturtii* [19], *E. alternifolia* [20], *E. latrobei* [21], *E. freelingii* [22], *E. bignoniifloru* [23], *E. cuneifolia* [24], *E. dalyunu* [25], *E. fruseri* [26], *E. gilesii* [27], *E. foliosissima* [27], *E. georgei* [27], *E. paisley* [28]). Much of the inspiration behind these substantial efforts has been in the pursuit of evaluating biological activity as informed by Australian indigenous traditional medicine [7,9,10,12–14,16,18,19,20,22–29]. As such a wide variety of pharmacological properties have been identified (e.g. anticancer [1–4], antimicrobial [7,9], antibacterial [8,12–16,21,29], hepatoprotective [17], antiinflammatory [18,19], cardioactive [20], and antiviral [22]), along with many different secondary metabolite classes (e.g. sesquiterpenes [5,10,24,28], diterpenes [7–9,12,14,19,27,28], triterpenoids [3,17], glucosides [17,20,23,24], lignans [17,25] and flavonoids [26]).

Inspired by the wide variety of secondary metabolites being produced by *Eremophila* we chose to investigate *E. macdonnellii* collected from the Simpson Desert (i.e. Munga-Thirri National Park, Queensland) [30]. Herein, we report the isolation and elucidation of a new furofuran lignan epimethoxypiperitol (**1**) and six known furofuran lignans (+)-methoxypiperitol (**2**) [31], (+)-piperitol (**3**) [32], (+)-epieudesmin (**4**) [17,33], (+)-epiyangambin (**5**) [33], (+)-phillygerin (**6**) [17,34] and 3,4,5′-trimethoxy-3′,4′-methylenedioxy-7,9′:7′,9-diepoxylignan (**7**) [35] (Fig. 1) [36].

2. Results and discussion

A ^{1}H NMR analysis of several fractions revealed a number of aromatic and methoxy group signals, which attracted our attention. Further purification by HPLC provided compounds possessing from one to six methoxy groups, well-resolved aromatic protons, and several proton signals arising from oxygenated and benzylic positions. Additional analysis and structure elucidation using ^{13}C NMR, 2D NMR and ESIMS data confirmed the structures of the known natural products, **2–7** (Fig. 1).

Compound **1** displayed ^{1}H and ^{13}C NMR data similar to that of the lignan (+)-methoxypiperitol (**2**) (Table 1), but no match could be identified in the literature. A molecular ion at *m/z* 385.1306 $[M\text{-}H]^-$ in negative HRESIMS mode, and *m/z* 409.1259 in positive HRESIMS mode, provided a molecular formula of $C_{21}H_{22}O_7$ identical to **2**, which equated to the molecule containing eleven ring and double-bond equivalents (RDBE). According to ^{1}H NMR coupling constants [e.g. 6.88 ppm (d, 1.8 Hz), 6.82 ppm (dd, 8.1, 1.8 Hz) and 6.87 ppm (d, 8.1 Hz)] compound **1** also contained a 1,3,4-trisubstituted phenyl ring moiety. Additional close similarities were also observed in the ^{13}C NMR and DEPT spectra, which revealed 21 carbons consisting of two methyls, nine methines, seven quaternary carbons, three methylenes and

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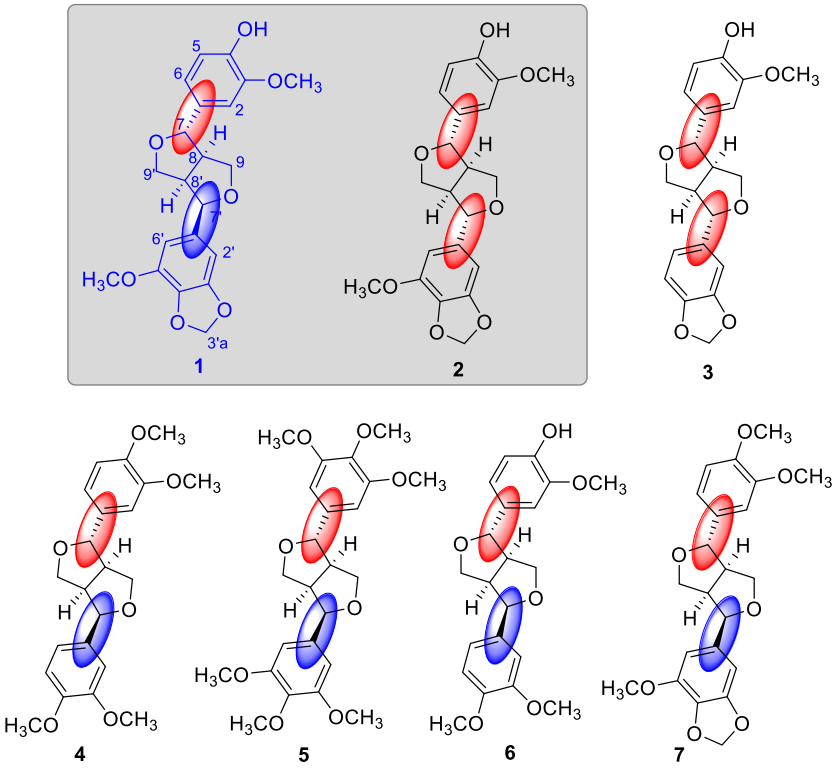

Fig. 1. Furofuran lignans **1**–**7** isolated from *Eremophila macdonnellii*.

Table 1
^{1}H and ^{13}C NMR data for lignans 1 and 2 in $CDCl_3$.

Lignan 1			Lignan 2	
Position	δ_C, type	δ_H (*J* in Hz)	δ_C, type	δ_H (*J* in Hz)
1	132.9, C		132.8, C	
1′	133.0, C		135.9, C	
2	108.5, CH	6.88 d (1.8)	108.6, CH	6.868 d (1.8)
2′	99.9, CH	6.49 dd (1.5, 0.7)	100.1, CH	6.51 dd (1.5, 0.7)
3	146.7, C		146.7, C	
3a	55.9 OCH_3	3.89 s	56.0, OCH_3	3.89 s
3′	148.8, C		149.1, C	
3′[a]	101.4, OCH_2O	5.95 m	101.5, OCH_2O	5.94 m
4	145.3, C		145.3, C	
4-OH		5.57 br. s		5.57 s
4′	134.1, C		134.6, C	
5	114.2, CH	6.87 d (8.1)	114.3, CH	6.870 d (8.1)
5′	143.5, C		143.7, C	
5′[a]	56.6, OCH_3	3.90 s	56.7, OCH_3	3.89 s
6	119.2, CH	6.82 dd (8.1, 1.8)	119.0, CH	6.80 dd (8.1, 1.8)
6′	104.9, CH	6.57 m	105.5, CH	6.53 m
7	87.7, CH	4.39 d (7.3)	85.9, CH	4.70 d (4.8)
7′	82.0, CH	4.80 d (5.5)	85.8, CH	4.69 d (5.1)
8	54.4, CH	2.87 m	54.1, CH	3.03 m
8′	50.1, CH	3.29 m	54.4, CH	3.07 m
9a	70.9, CH_2	3.81 dd (9.5, 6.2)[a]	71.7, CH_2	3.86 m
9b		4.09 d (9.5, 0.7)[b]		4.23 dd (7.0, 4.8)
9′[a]	69.6, CH_2	3.30 m[b]	71.8, CH_2	3.86 m
9′[b]		3.85 m[a]		4.24 m (6.8, 5.0)

[a] Proton is in the α position.
[b] Proton is in the β position.

one methylenedioxy C-3′a (δ_C 101.4 ppm) (Table 1).

HMBC correlations (Fig. 2B) for the methylenedioxy 3′a-H (δ_H 5.95 ppm) with C3′ (δ_C 148.8 ppm) and C4′ (δ_C 134.1 ppm), and the methoxy group 5′a-H (δ_H 3.90 ppm) with C5′ (δ_C 143.5 ppm) started to build the 3,4-methylenedioxy-5-methoxy fragment. Cross peaks connecting 7-H′ (δ_H 4.80 ppm) with C2′ (δ_C 99.9 ppm), C6′ (δ_C 104.9 ppm) and C9′ (δ_C 69.6 ppm), together with 6-H′ (δ_H 6.57 ppm) resonances with C4′ and C5′ confirmed the proposed fragment. Additional key HMBC interactions that confirmed the structural similarity between **1** and **2** consisted of correlations between Me-3a (δ_H 3.89 ppm) and C3 (δ_C 146.7 ppm), OH-4a (δ_H 5.57 ppm) with C5 (δ_C 114.2 ppm), and that of 7-H (δ_H 4.39 ppm) with C2 (δ_C 108.5 ppm), C6 (δ_C 119.2 ppm) and C9 (δ_C 70.9 ppm), together with 6-H (δ_H 6.82 ppm) to C4 (δ_C 145.3 ppm) and C5. COSY (Fig. 2B) cross peaked associated with the tetrahydrofurofuran fragment confirmed that the same planar structure existed for compounds **1** and **2**.

The main differences between these two compounds were emphasised in the chemical shift values and coupling constants, observed for positions 7 and 7′ (^{1}H and ^{13}C NMR, Table 1).

A survey of the furofuran lignan literature provided important stereochemical information that further assisted with the relative and absolute configuration determination. Biosynthetically furofuran lignans are formed by an enantioselective dimerisation of coniferyl alcohol, a cinnamyl alcohol derivative, to give the *cis*- fused *bis*-tetrahydrofuran (2,6-dioxa-[3,3,0]-bicyclooctane) unit [36]. This process proceeds in either enantiomeric series to afford the (+)- or (−)-enantiomers series having the 8*R*,8′*R* and 8*S*,8′*S* configuration respectively [38–40]. The configuration of the aryl groups within these systems have historically been described as *pseudo-axial* and *pseudo-equatorial* [37], which corresponds to an *exo*- and/or *endo*- relationship relative to the oxygen atom in the adjacent ring [33]. However, these stereochemical relationships are better described by the 7H,8H and 7′H,8′H protons, which are *cis*-positioned instead of *axial* and *trans*-positioned instead of *equatorial*. This notation has been used previously to avoid confusion when undertaken molecular modelling [41]. Studies directly related to furofuran lignan stereochemistry have been undertaken using ^{1}H and ^{13}C NMR spectroscopy [37,41], such that chemical shift and coupling constant data for the benzylic carbons and their corresponding protons (i.e. 7H,7′H) have been supported by quantum chemical calculations [41].

Based on the information gathered above the ^{1}H and ^{13}C NMR chemical shifts and proton coupling constants for the benzylic positions were summarised (see Table 2), by dividing all the isolated compounds