



# Sesquiterpene lactones and bisbibenzyl derivatives from the neotropical liverwort *Frullania convoluta*<sup>☆</sup>

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## Abstract

The new germacranolide *epi-isocostunolide* and two new bisbibenzyls, 2'-(11-hydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydro-phenanthrene and 2'-(10,11-dihydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydro-phenanthrene, along with the known eudesmanolides,  $\alpha$ -cyclocostunolide, brothenolide, nepalensolide A and nepalensolide B, the bisbibenzyls, perrottetin E, perrottetin F, perrottetin G, 7',8'-dehydroperrottetin F, and the bibenzyls, lunularic acid and lunularin, have been isolated from the neotropical liverwort *Frullania convoluta*. Their structures were elucidated by NMR spectroscopy. © 1999 Elsevier Science Ltd. All rights reserved.

**Keywords:** *Frullania convoluta*; Frullaniaceae; Hepaticae; Sesquiterpene lactone; Germacrane; Eudesmane; Bibenzyl; Bisbibenzyl; Dihydrophenanthrene

## 1. Introduction

In the course of our evaluation of liverworts as a source for new bioactive natural products we have analysed the constituents of the neotropical species *Frullania convoluta*. This paper describes the isolation and characterization of a new germacranolide and two new bisbibenzyls with a dihydrophenanthrene moiety along with several known sesquiterpene lactones and bisbibenzyls.

## 2. Results and discussion

A combination of size exclusion chromatography, vacuum liquid chromatography and HPLC of the ether extract of the plant led to the isolation of the new (–)-germacranolide *epi-isocostunolide* (**1**). Furthermore, the following five eudesmanolides could be obtained: (–)- $\alpha$ -cyclocostunolide (**2**) (da Silva,

Garcia, Baker & Rabi, 1981; Conolly, 1990), (–)-*ent*- $\alpha$ -cyclodihydrocostunolide (**3**) (Nagashima, Tanaka, Takaoka, & Asakawa, 1997), (+)-brothenolide (**4**) (Takeda, Ohta, & Hirose, 1983), (+)-nepalensolide A (**5**) (Tori, Miyazaki, Kondo, Taira & Asakawa, 1990) and (+)-nepalensolide B (**6**) (Asakawa & Tori, 1993). These five lactones are known constituents of the *Frullania* species. The methanolic extract afforded two new bisbibenzyls with a dihydrophenanthrene substructure, 2'-(11-hydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydrophenanthrene (**7**) and 2'-(10,11-dihydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydrophenanthrene (**8**) together with the four bisbibenzyls perrottetin E (**9**), perrottetin F (**10**), perrottetin G (**11**) (Toyota et al., 1985) and 7',8'-dehydroperrottetin F (**12**) (Asakawa, 1995) as well as the common liverwort bibenzyls lunularin (**13**) (Huneck & Schreiber, 1976) and lunularic acid (**14**) (Huneck, 1976). Their structures were deduced from NMR and mass spectral data.

Compound **1** was obtained as colourless needles with a molecular formula of C<sub>15</sub>H<sub>20</sub>O<sub>2</sub> as calculated from the EI mass spectrum (*m/z* 232.3, [M]<sup>+</sup>). <sup>13</sup>C NMR ( $\delta_C$  170.3) and IR data (absorption at 1780

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$\text{cm}^{-1}$ ) indicated the presence of a  $\gamma$ -lactone. The  $^1\text{H}$ -NMR and  $^{13}\text{C}$  NMR spectra displayed the signals of an exomethylene group ( $\delta_{\text{H}}$  6.25, 5.50,  $\delta_{\text{C}}$  139.0, 121.5) and two methine protons, each belonging to a double bond ( $\delta_{\text{H}}$  4.97, 4.86,  $\delta_{\text{C}}$  119.5, 140.0 and 121.5, 138.0). Based on their chemical shifts the signals at  $\delta_{\text{H}}$  5.15 and  $\delta_{\text{H}}$  3.02 could be assigned to the bridgehead protons of a *cis*-lactone ring (Bohlmann, Jacupovic & Schuster, 1983; Zdero & Bohlmann, 1989) with the corresponding carbons at  $\delta_{\text{C}}$  77.3 and  $\delta_{\text{C}}$  39.0, respectively. The similarity of the spectroscopic data to  $\alpha$ -costunolide (Ming, Mayer, Zimmermann & Rücker, 1989) and its 7-epimer with 6,7-*cis*-lactone ring (Zdero & Bohlmann, 1989) coupled with the molecular formula showed that **1** was a germacrane type sesquiterpene lactone. However, the data suggested a different position of the double bonds within the germacrane ring. The location of the two double bonds could be deduced from the HMBC and HSQC spectra. The *E*-configuration of the 4-double bond and the *Z*-configuration of the double bond between C-9 and C-10 could be determined from NOESY correlations of H-6 to H-15 and H-9 to H-14 (Fig. 1). Furthermore, the *cis*-configuration of the lactone ring has been confirmed by cross peaks between H-6 and H-7 in the NOESY spectrum as depicted in Fig. 1. Thus, **1** should be *epi*-isocostunolide, the 7-epimer of isocostunolide (Bapat & Kulkarni, 1971).

Compound **7** was obtained as a yellow oil with the molecular formula  $\text{C}_{29}\text{H}_{26}\text{O}_6$  as indicated by the EI mass spectrum ( $m/z$  470.4  $[\text{M}]^+$ ). The IR spectrum displayed absorption bands characteristic of hydroxyl groups ( $3400\text{ cm}^{-1}$ ) and aromatic rings ( $1515\text{ cm}^{-1}$ ). The  $^{13}\text{C}$  NMR spectrum showed the presence of 29 carbons in the molecule. The  $^1\text{H}$ -NMR spectrum of **7** displayed the signals of four benzylic methylenes at  $\delta_{\text{H}}$  2.69 and  $\delta_{\text{H}}$  2.74 corresponding to the  $^{13}\text{C}$  NMR signals at  $\delta_{\text{C}}$  36.7, 37.7, 29.6 and 21.6 which are characteristic for bisbibenzyls. The  $^1\text{H}$ -NMR spectrum displayed also eleven aromatic protons. These signals

appearing in the range of  $\delta_{\text{H}}$  6.36 to 7.44 were attributed to the four benzene rings A–D of a bisbibenzyl. According to their multiplicity and their coupling constants the two aromatic proton signals at  $\delta_{\text{H}}$  6.90 (d,  $J = 8.5\text{ Hz}$ , H-3, H-5) and  $\delta_{\text{H}}$  6.69 (d,  $J = 8.5\text{ Hz}$ , H-2, H-6) could be assigned to the AA'BB' spin system of the 1,4-substituted ring A. Furthermore, chemical shift and multiplicity of four signals each integrating to one proton at  $\delta_{\text{H}}$  6.36 (s),  $\delta_{\text{H}}$  6.60 (dd),  $\delta_{\text{H}}$  6.70 (not resolved) and  $\delta_{\text{H}}$  7.08 (t), indicated the presence of a 1,3-substituted benzene ring (ring B). This was proven by the similarity of  $^{13}\text{C}$ -NMR data of ring A and B to the data of lunularin (Kunz & Becker, 1992). The HMBC spectral data displayed a correlation between H-13' in ring D and C-3' in ring C (Fig. 2). This correlation is explicable if a dihydrophenanthrene substructure is assumed for these two benzene rings. The NOESY spectrum confirmed the presence of a dihydrophenanthrene moiety by a correlation between H-2 and H-13', caused by the sterical fixing of ring D (Fig. 3). Two *ortho* doublets at  $\delta_{\text{H}}$  6.54 (d,  $J = 8.5\text{ Hz}$ , H-12') and 7.44 (d,  $J = 8.5\text{ Hz}$ , H-13') indicated the substitution pattern of ring D. The remaining singlet at  $\delta_{\text{H}}$  6.54 corresponded to H-5'. Therefore, **7** should be 2'-(11-hydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydro-phenanthrene.

Compound **8** was isolated as a brownish oil with a molecular formula  $\text{C}_{29}\text{H}_{26}\text{O}_7$  calculated from the EI-mass spectrum ( $m/z$  486.3  $[\text{M}]^+$ ). The IR and  $^1\text{H}$ -NMR spectrum of compound **8** were very similar to **7**. A difference of 16 mass units in the mass spectrum compared to **7** indicated the presence of an additional hydroxyl group in **8**. The location of this oxygenation could be deduced from the  $^1\text{H}$ -NMR spectrum. Since the singlet at  $\delta_{\text{H}}$  6.36 (H-10) of **7** was missing in the spectrum of **8**, a substitution at position 10 had to be assumed. The fragmentation pattern of **8** in the mass spectrum confirmed the location of an additional hydroxyl group in position 10. The spectrum displayed a fragment of  $m/z$  123 for ring B. The EI-MS of **7**

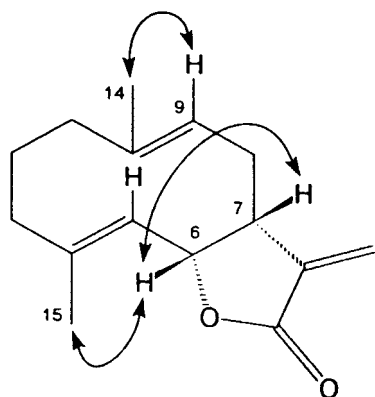


Fig. 1. Significant NOESY couplings of **1**.

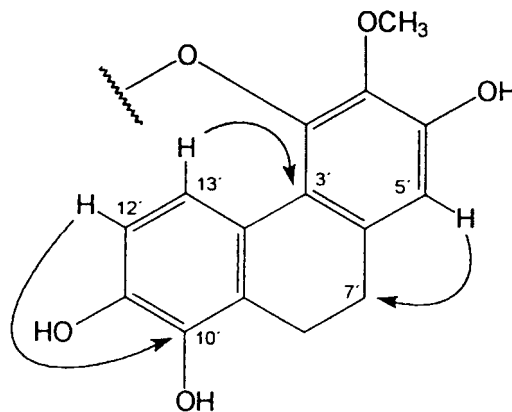
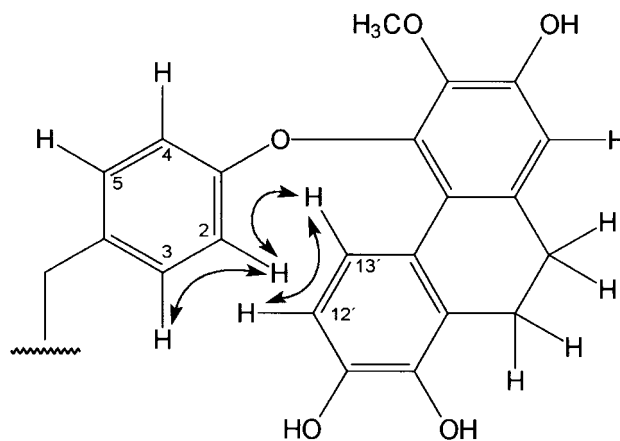


Fig. 2. Significant HMBC couplings of **7**.

Fig. 3. Significant NOESY couplings of **7**.

showed a fragment of  $m/z$  107. The difference of 16 mass units can be attributed to the second hydroxy-group in ring B. Accordingly, **8** is 2'-(10,11-dihydroxy-1-bibenzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydrophenanthrene.

So far, only a similar dihydrophenanthrene type bisbibenzyl (shancilin) is known as a constituent of the tubers of the orchid *Pleione bulbocodioides* (Bai, Yamaki & Takagi, 1996). However, its structure is different to **7** and **8** since in shancilin bibenzyl and the phenanthrene moiety are linked via an ether bridge between positions 1 and 6'. As similar compounds in liverworts only two biphenanthrenes are reported (Adam & Becker, 1994).

Based on a tentative chemosystematic classification of the genus *Frullania* (Toyota, Nagashima & Asakawa, 1988), only around 30 (Asakawa, 1995; Kraut, Mues & Sim-Sim, 1994; Nagashima et al., 1997) of the estimated 1250 species (Kron, 1988) have been thoroughly investigated, the present *Frullania convoluta* can be assigned to the group that forms both bisbibenzyls and sesquiterpene lactones.

### 3. Experimental

Solvents used for spectral measurements:  $\text{CDCl}_3$  [ $^1\text{H}$  NMR: 400 MHz;  $^{13}\text{C}$  NMR: 100 MHz for 1D and 500 MHz and 125 MHz for 2D techniques, respectively. Chemical shifts are given in  $\delta$  values (ppm) from TMS,  $\text{CHCl}_3$  (UV, optical rotation).

#### 3.1. Plant material

*Frullania convoluta* (L.) Lindenberg & Hampe was collected in Páramo el Angel, Ecuador in October 1988 and identified by Professor Dr. R. Mues and Professor Dr. S. R. Gradstein. A voucher specimen is

deposited at the Botanical Institute of the University (Herbarium SAAR, No. 5671).

#### 3.2. Extraction and isolation

The extraction scheme followed the standard procedures of our group (Adam & Becker, 1994; Bungert, Gabler, Adam, Zapp & Becker, 1998; Cullmann, Adam, & Becker, 1993). Powdered air dried plant material (750 g) was subsequently extracted with  $\text{Et}_2\text{O}$  and MeOH. The  $\text{Et}_2\text{O}$  extract (10.9 g) was chromatographed on Sephadex LH-20 (150  $\times$  2.5 cm i.d.) with  $\text{MeOH}-\text{CH}_2\text{Cl}_2$  (1:1) as eluent to give four fractions (I–IV). Fraction IV (1.5 g) was separated by VLC (silica gel 15  $\mu\text{m}$ , 60  $\times$  35 mm i.d., stepwise with an  $n$ -hexane– $\text{EtOAc}$  gradient) and gave the fractions IV-1 (100%  $n$ -hexane, 50 mg), IV-2 (0.5–3%  $\text{EtOAc}$ , 34

Table 1

$^1\text{H}$  NMR spectral data of compounds **7** and **8** ( $\text{CDCl}_3$ ). Coupling constants ( $J$  in Hz) in parentheses

| H   | <b>7</b>           | <b>8</b>          |
|-----|--------------------|-------------------|
| 2   | 6.69 d (8.5)       | 6.70 d (8.5)      |
| 3   | 6.90 d (8.5)       | 6.98 d (8.5)      |
| 5   | 6.90 d (8.5)       | 6.98 d (8.5)      |
| 6   | 6.69 d (8.5)       | 6.70 d (8.5)      |
| 7   | 2.75 <sup>a</sup>  | 2.74 <sup>a</sup> |
| 8   | 2.75 <sup>a</sup>  | 2.74 <sup>a</sup> |
| 10  | 6.36 s             | —                 |
| 12  | 6.60 dd (8.0, 2.3) | 6.63 <sup>b</sup> |
| 13  | 7.08 t (8.0)       | 6.62 <sup>b</sup> |
| 14  | 6.70 <sup>b</sup>  | 6.58 <sup>b</sup> |
| 5'  | 6.73 s             | 6.70 s            |
| 7'  | 2.69 <sup>a</sup>  | 2.67 <sup>a</sup> |
| 8'  | 2.68 <sup>a</sup>  | 2.73 <sup>a</sup> |
| 12' | 6.54 d (8.5)       | 6.54 d (8.5)      |
| 13' | 7.44 d (8.5)       | 7.43 d (8.5)      |
| 15' | 3.77 s             | 3.73 s            |

<sup>a</sup> Signals overlapped.

<sup>b</sup> Signals not resolved.

Table 2  
<sup>13</sup>C NMR spectral data of compounds **7** and **8** (CDCl<sub>3</sub>)

| C   | 7       | 8       |
|-----|---------|---------|
| 1   | 155.7 s | 155.7 s |
| 2   | 114.8 d | 114.9 d |
| 3   | 129.4 d | 129.3 d |
| 4   | 134.9 s | 135.4 s |
| 5   | 129.4 d | 129.3 d |
| 6   | 114.8 d | 114.9 d |
| 7   | 36.7 t  | 35.3 t  |
| 8   | 37.7 t  | 32.0 t  |
| 9   | 143.5 s | 128.6 s |
| 10  | 115.7 d | 142.4 s |
| 11  | 155.5 s | 143.8 s |
| 12  | 112.8 d | 112.8 d |
| 13  | 129.4 d | 119.8 d |
| 14  | 120.7 d | 121.4 d |
| 1'  | 138.7 s | 138.8 s |
| 2'  | 147.8 s | 147.8 s |
| 3'  | 121.5 s | 121.4 s |
| 4'  | 135.2 s | 135.2 s |
| 5'  | 111.6 d | 111.7 d |
| 6'  | 144.7 s | 144.7 s |
| 7'  | 29.6 t  | 29.6 t  |
| 8'  | 21.6 t  | 21.5 t  |
| 9'  | 124.9 s | 124.9 s |
| 10' | 140.5 s | 140.6 s |
| 11' | 142.2 s | 142.4 s |
| 12' | 112.5 d | 112.3 d |
| 13' | 119.8 d | 119.5 d |
| 14' | 125.2 s | 124.9 s |
| 15' | 61.2 q  | 61.2 q  |

mg), IV-3 (3.5–4% EtOAc, 178 mg), IV-4 (4.5–6% EtOAc, 410 mg), IV-5 (7–10% EtOAc, 122 mg), IV-6 (11–20% EtOAc, 115 mg) and IV-7 (20–100% EtOAc, 131 mg). The fractions IV-3, IV-4 and IV-5 were further purified by HPLC on silica gel LiChrospher Si 60, 5 µm, 4 × 250): *n*-hexane–EtOAc (193:7) for **2** (9.6 mg), **3** (18 mg) and **4** (17 mg), *n*-hexane–*t*-BME (94:6) for **6** (41 mg) and **5** (50 mg) and *n*-hexane–EtOAc (95:5) for **1** (6.5 mg).

The methanolic extract was evapd *in vacuo* and distributed between EtOAc and H<sub>2</sub>O. The organic layer was chromatographed on Sephadex LH-20. For the EtOAc soluble fraction of the methanol extract MeOH–CH<sub>2</sub>Cl<sub>2</sub> (4:1) was used as eluent to yield 3 frs.

Fr. I (370 mg) was chromatographed on diol-modified silicagel via VLC with an *n*-hexane–EtOAc-gradient to give the fractions I-1 (30–45% EtOAc, 113 mg) and I-2 (45–55% EtOAc, 83 mg). I-1 was further purified by HPLC on diol-modified silica gel with *n*-hexane–EtOAc (85:15) as eluent to give lunularin (32.9 mg), lunularic acid (5.1 mg), perrottetin E (**9**) (7.5 mg) and perrottetin G (**10**) (23.8 mg). HPLC of I-2 gave perrottetin F (**11**) (*n*-hexane–EtOAc 45:55, 7.0 mg). Fr. II was chromatographed as described above to give II-1 (45–60% EtOAc, 66.1 mg). The HPLC-purification

on diol-modified silicagel yielded **7** (*n*-hexane–EtOAc 45:55, 15.6 mg). The VLC of fr. III afforded III-1 (45–80% EtOAc, 115 mg). III-1 was purified via HPLC on diol-modified silicagel (*n*-hexane–EtOAc 37:63) to give 7',8'-dehydroperrottetin F (**12**) (1.7 mg) and **8** (22.0 mg).

### 3.3. Epi-isocostunolide (**1**)

[α]<sub>D</sub><sup>20</sup> –56° (CHCl<sub>3</sub>; *c*0.33); EI-MS *m/z* (rel. int.): 232.3 [M]<sup>+</sup> (30), 217 (20), 203 (19), 199 (12), 185 (18), 176 (41), 161 (27), 145 (31), 136 (39), 131 (54), 121 (68), 105 (73), 93 (82), 91 (98), 82 (100); IR ν<sub>max</sub><sup>KBr</sup> cm<sup>–1</sup>: 1780 (γ-lactone); <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ<sub>H</sub> 6.25 (1H, d, *J* = 3.4 Hz, H-13α), 5.50 (1H, d, *J* = 3.4 Hz, H-13β), 5.15 (1H, dd, *J* = 8.9, 10.4 Hz, H-6), 4.97 (1H, d, *J* = 10.4 Hz, H-5), 4.86 (1H, m, H-9), 3.02 (1H, m, H-7), 2.42 (1H, ddd, H-8α), 2.27–2.18 (2H, m, H-1α, H-1α), 2.14 (1H, m, H-8β), 2.01 (1H, m, H-3β), 1.75 (1H, m, H-1β), 1.68 (1H, m, H-2α), 1.64 (3H, s, H-14), 1.61 (1H, m, H-2β), 1.52 (3H, s, H-15); <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ<sub>C</sub> 170.3 (C-12), 140.0 (C-4), 139.0 (C-11), 138.0 (C-10), 121.5 (C-9, C-13), 119.5 (C-5), 77.3 (C-6), 41.7 (C-3), 39.0 (C-7), 30.5 (C-1), 29.7 (C-8), 23.3 (C-14), 20.7 (C-2), 15.8 (C-15)

### 3.4. 2'-(11-hydroxy-1-benzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydro-phenanthrene (**7**)

IR ν cm<sup>–1</sup>: 3400, 2940, 1580, 1470, 1290, 1210, 1170; UV λ nm: 280; <sup>1</sup>H NMR: Table 1; <sup>13</sup>C NMR: Table 2; EI-MS *m/z* (rel. int.): 470.4 [M]<sup>+</sup> (100), 363 (51), 246 (20), 226 (38), 214 (54), 107 (74).

### 3.5. 2'-(10, 11-dihydroxy-1-benzyl-oxy)-1'-methoxy-6',10',11'-trihydroxy-7',8'-dihydrophenanthrene (**8**)

IR ν cm<sup>–1</sup>: 3400, 2940, 1580, 1470, 1290, 1210, 1170; UV λ nm: 280; <sup>1</sup>H NMR: Table 1; <sup>13</sup>C NMR: Table 2; EI-MS *m/z* (rel. int.): 486.3 [M]<sup>+</sup> (100), 470 (13), 363 (73), 242 (26), 107 (88)

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