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# Sesquiterpene evoninate alkaloids from *Tripterygium hypoglaucum*

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**Abstract**

Esters of three new (hyponines D–F) and two known macrocyclic sesquiterpene pyridine alkaloid esters have been isolated from the root bark of *Tripterygium hypoglaucum*. The structures of the new alkaloids were elucidated as 7- (acetyloxy)-$O^2$-nicotinoyl-$O^2$-deacetyl-$O^5$-benzoyl-$O^5$-deacetyl-7-deoxo-evonine, 7- (nicotinoyloxy)-$O^5$-furanoyl-$O^5$-deacetyl-7-deoxo-evonine and 7- (acetyloxy)-$O^2$-furanoyl-$O^2$-deacetyl-7-deoxo-evonine by spectroscopic means. 

*Keywords:* *Tripterygium hypoglaucum*; Celastraceae; Root bark; Sesquiterpenes; Pyridine alkaloids; Hyponine

## 1. Introduction

In the last 30 years, many dihydroagarofuran sesquiterpenes have been isolated from Celastraceae plants (Brüning & Wagner, 1978). We have studied the sesquiterpene constituents of the Celastraceae and have described the isolation and structure determination of some of these compounds (Takaishi, Aihara, Tamai, Nakano & Tomimatsu, 1992; Takaishi, Oshima, Nakano, Tomimatsu & Tokuta, 1993). Dihydroagarofuran sesquiterpenes exhibit insect antifeedant and/or insecticidal activities (Tu, Wu, Zhou, Chen & Pan, 1990; Wakabayashi et al. 1988). Recently, we have found antitumor and antiviral activities (Hayashi, Hayashi, Ujita & Takaishi, 1996; Takaishi et al., 1993; Ujita et al., 1993) associated with these sesquiterpenes.

As a continuation of our previous studies in this area, we have examined the alkaloid components of *Tripterygium hypoglaucum* (Celastraceae) and reported seven new sesquiterpene alkaloids, hyponines A, B, C and hypoglaunines A, B, C and D (Duan, Kawazoe & Takaishi, 1997; Duan & Takaishi, 1998). In the present study, three new sesquiterpene evoninate alkaloids, named hyponines D (**1**), E (**2**) and F (**3**), along with two known sesquiterpene alkaloids, neoeunoymine (**4**) and forrestine (**5**) were isolated by repeated column chromatography of the ethyl acetate soluble fraction from methanol extracts of the root bark of *T. hypoglaucum*.

## 2. Results and discussion

Hyponine D (**1**) was obtained as an amorphous solid and its mass spectrum showed the molecular ion peak at $m/z$ 930. The IR spectrum showed hydroxy and ester carbonyl bands (3436 and 1746 $cm^{-1}$) and its UV absorption spectrum revealed the presence of an aromatic moiety (226 and 264 nm). It contained four acetyl groups ($\delta_H$1.77, 1.91, 2.17, 2.26), one nicotinoyl (Nic) group [$\delta_H$ 9.24 (s), 8.31 (d, $J$ = 8.0 Hz), 7.40 (dd, $J$ = 4.2, 8.0 Hz), 8.77 (d, $J$ = 4.2 Hz)], one benzoyl group (Bz) [$\delta_H$ 8.25 (2H, d, $J$ = 7.5 Hz), 7.43 (2H, dd, $J$ = 7.3, 7.5 Hz), 7.53 (1H, t, $J$ = 7.3 Hz)], two sets of methylene groups [$\delta_H$ 4.39, 5.37 (each 1H, d, $J$ = 13.5 Hz); 3.57, 5.99 (each 1H, d, $J$ = 11.5 Hz)] and seven methine protons [$\delta_H$ 2.47, 4.80, 5.39, 5.51, 5.53, 5.68 and 7.15]. It also contained one 2, 3-disub-

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stituted pyridine [$\delta_H$ 7.99, 7.20, 8.64], two secondary methyl groups [$\delta_H$ 1.16 and 1.37] and two methine protons [$\delta_H$ 2.55 and 4.66] which were coupled to each other. It was assumed that compound **1** was a sesquiterpene pyridine alkaloid derived from dihydroagarofuran polyol esters such as hyponine A, B and C (Duan, Kawazoe & Takaishi, 1997). The $^{13}C$ NMR spectral data of **1** revealed the presence of eight methyl carbons, two methylene carbons attached to an oxygen function, six methine carbons attached to an oxygen function, two methine carbons, eight ester carbonyl carbons, four quaternary carbons, one benzoyl group [$\delta_C$165.8 (s), 129.5 (s), 130.4 (d), 128.9 (d), 133.7 (d)], one nicotinoyl group [$\delta_C$163.7 (s), 151.2 (d), 125.0 (s), 137.5 (d), 123.7 (d), 154.2 (d)] and an evonic acid moiety [$\delta_C$9.6 (q), 11.9 (q), 36.4 (d), 45.1 (d), 165.3 (s), 125.2 (s), 137.7 (d), 121.2 (d), 151.6 (d), 168.7 (s, –COO–), 173.9 (s, –COO–)]. This evidence indicates the molecular formula of **1** to be $C_{47}H_{50}O_{18}N_2$, which was supported by HR mass spectral data. The macrocyclic structure, including a dihydroagarofuran moiety and an evonic acid, was deduced by comparing the $^{13}C$ NMR spectral data with those of hyponine A (Duan et al., 1997). From the $^1H$– $^1H$ COSY spectrum of **1**, two sets of separate spin–spin systems (1-H/2-H/3-H and 6-H/7-H/8-H) revealed their connections in the dihydroagarofuran core. The remaining proton signal at $\delta_H$ 7.15 (5-H) was correlated with the carbon signals at $\delta_C$ 50.5 (C-6), 52.3 (C-9), 93.7 (C-10) and 84.4 (C-13) in the HMBC spectrum. On the other hand, the proton signal at $\delta_H$ 5.99 (15-H″) was correlated with the carbon signals at $\delta_C$ 84.4 (C-13) and 168.7 (C-12′); the proton signal at $\delta_H$ 4.80 (3-H) with the carbon signal at $\delta_C$ 173.9 (C-11′); the proton signal at $\delta_H$ 2.55 (8′-H) with the carbon signals at $\delta_C$ 165.3 (C-2′), 36.4 (C-7′) and 173.9 (C-11′). From this evidence, it was possible to assign the attachment points of evoninic acid to the sesquiterpene unit to positions 3 and 15.

The long range correlations of the carbonyl carbon signal at $\delta_C$ 163.7 with the proton signals at $\delta_H$ 5.53 (2-H), 9.24 (Nic, 2″-H), 8.31 (Nic, 4″-H) indicated that the position of one nicotinoyl group was at C-2. The benzoyl group could be located at C-5 due to the same long range correlations of the carbonyl carbon signal at $\delta_C$ 165.8 with the proton signals at $\delta_H$ 7.15 (5-H) and 8.25 (Bz, ortho). In the case of the acetyl groups, the proton signals at $\delta_H$ 5.68 (1-H) and 1.77 (Ac) were correlated with the carbonyl carbon signal at $\delta_C$ 169.1, the proton signals at $\delta_H$ 5.39 (8-H) and 1.91 (Ac) with the carbon signal at $\delta_C$ 169.0; the proton signals at $\delta_H$ 4.39 (11-H′) and 2.17 (Ac) with the carbon signal at $\delta_C$ 170.2. Therefore, these three acetyl groups were assigned at positions C-1, C-8 and C-11, respectively. Finally, the only remaining acetyl group could be assigned to the last ester linkage site, C-7. In the NOESY spectrum, the proton signal at $\delta_H$ 7.15 (5-H) was correlated with proton signals at $\delta_H$ 4.39 (11-H′) and 1.57 (12-$H_3$), the proton signal at $\delta_H$ 5.39 (8-H) with the $\delta_H$ 5.51 (7-H) and 5.68 (1-H), the proton signal at $\delta_H$ 5.68 (1-H) with $\delta_H$ 5.39 (8-H) and 5.53 (2-H). This evidence indicated that the relative stereochemistries of the ester groups have 1, 2, 7, 8$\beta$ and 5$\alpha$ configurations. $^1H$ and $^{13}C$ NMR assignments were also revealed by 2D NMR spectra as shown in Tables 1 and 2. Therefore, the structure of hyponine D was determined as **1**.

Table 1
$^1H$ NMR chemical shifts for compounds **1**–**3**[a]

| Proton | 1 | 2 | 3 |
|---|---|---|---|
| 1-H | 5.68 (d, 5.0) | 5.65 (d, 4.0) | 5.61 (d, 5.0) |
| 2-H | 5.53 (dd, 2.2, 5.0) | 5.51 (dd, 2.1, 4.0) | 5.40 (dd, 2.2, 5.0) |
| 3-H | 4.80 (d, 2.2) | 4.78 (d, 2.1) | 4.77 (d, 2.2) |
| 5-H | 7.15 (s) | 7.09 (s) | 6.99 (s) |
| 6-H | 2.47 (d, 3.9) | 2.43 (d, 3.8) | 2.32 (d, 4.3) |
| 7-H | 5.51 (dd, 3.9, 6.5) | 5.49 (dd, 3.8, 5.3) | 5.49 (dd, 4.3, 6.1) |
| 8-H | 5.39 (d, 6.5) | 5.37 (d, 5.3) | 5.36 (d, 6.1) |
| 11-H′ | 4.39 (d, 13.5) | 4.37 (d, 13.5) | 4.24 (d, 13.5) |
| 11-H″ | 5.37 (d, 13.5) | 5.35 (d, 13.5) | 5.43 (d, 13.5) |
| 12-$H_3$ | 1.57 (s) | 1.55 (s) | 1.54 (s) |
| 14-$H_3$ | 1.66 (s) | 1.66 (s) | 1.65 (s) |
| 15-H′ | 3.57 (d, 11.5) | 3.59 (d, 11.5) | 3.67 (d, 11.5) |
| 15-H′ | 5.99 (d, 11.5) | 5.99 (d, 11.5) | 5.93 (d, 11.5) |
| 4′-H | 7.99 (dd, 1.5, 7.7) | 7.98 (dd, 1.4, 7.7) | 8.03 (dd, 1.3, 7.6) |
| 5′-H | 7.20 (dd, 4.6, 7.7) | 7.21 (dd, 4.8, 7.7) | 7.23 (dd, 4.8, 7.6) |
| 6′-H | 8.64 (dd, 1.5, 4.6) | 8.64 (dd, 1.4, 4.8) | 8.65 (br d, 4.4) |
| 7′-H | 4.66 (q, 7.0) | 4.57 (q, 6.9) | 4.61 (q, 7.1) |
| 8′-H | 2.55 (q, 7.1) | 2.53 (q, 7.1) | 2.55 (q, 7.2) |
| 9′-$H_3$ | 1.37 (d, 7.0) | 1.36 (d, 6.9) | 1.35 (d, 7.1) |
| 10′-$H_3$ | 1.16 (d, 7.1) | 1.15 (d, 7.1) | 1.16 (d, 7.2) |
| 1-Ac | 1.77 (s) | 1.76 (s) | 1.77 (s) |
| 2-Ac | – | 2.26 (s) | – |
| 5-Ac | – | – | 2.12 (s) |
| 7-Ac | 2.26 (s) | – | 2.17 (s) |
| 8-Ac | 1.91 (s) | 1.90 (s) | 1.93 (s) |
| 11-Ac | 2.17 (s) | 2.13 (s) | 2.30 (s) |

[a] **1**. 2-Nic:9.24 (s), 8.31 (d, 8.0), 7.40 (dd 4.2, 8.0), 8.77 (d, 4.2); 5-Bz: 8.25 (2H, d, 7.5), 7.43 (2H, dd, 7.3, 7.5), 7.53 (t, 7.3). **2**. 5-Fu: 7.39 (br s), 6.85 (d, 1.0), 8.30 (s); 7-Nic: 9.24 (s), 8.31 (d, 7.4), 7.41 (dd, 4.0, 7.4), 8.77 (d, 4.0). **3**. 2-Fu: 7.45 (br s), 6.82 (d, 0.8), 8.24 (s).

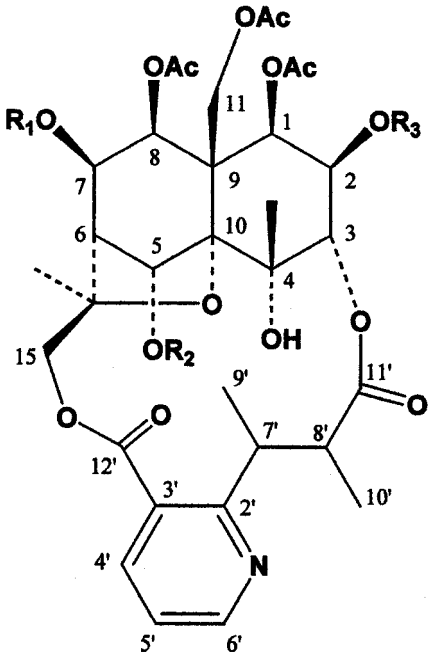
Hyponine E (**2**), $C_{45}H_{48}O_{19}N_2$, was shown to be a macrocyclic sesquiterpene pyridine alkaloid which contained four acetyl groups [$\delta_H$ 1.76, 1.90, 2.13 and 2.26], one furanoyl group [$\delta_H$ 7.39, 6.85 and 8.30] and one nicotinoyl group [$\delta_H$ 9.24, 8.31, 7.41 and 8.77] by comparing the $^1H$ and $^{13}C$ NMR spectral data with those of hyponine D (**1**). Its nicotinate derivative unit in the macrocycle was also evonic acid which was linked to the dihydroagarofuran core at positions 3 and 15, the same as for compound **1**. To determine the positions of the ester groups, the 2D NMR spectra were obtained and analysed. In the HMBC spectrum of **2**, the proton signal at $\delta_H$ 7.09 (5-H) was correlated with the carbonyl carbon signal at $\delta_C$ 162.0, which was

Table 2
. $^{13}C$ NMR chemical shifts for compounds **1**–**3**[a]

| Carbon | 1 | 2 | 3 |
|---|---|---|---|
| 1 | 73.2 | 73.2 | 73.3 |
| 2 | 69.8 | 69.9 | 68.8 |
| 3 | 75.8 | 75.8 | 75.7 |
| 4 | 70.5 | 70.7 | 70.6 |
| 5 | 74.8 | 74.1 | 73.8 |
| 6 | 50.5 | 50.5 | 50.7 |
| 7 | 69.1 | 69.1 | 69.0 |
| 8 | 70.7 | 70.7 | 70.8 |
| 9 | 52.3 | 52.2 | 52.2 |
| 10 | 93.7 | 93.8 | 94.2 |
| 12 | 23.3 | 23.4 | 23.3 |
| 13 | 84.4 | 84.4 | 84.3 |
| 14 | 18.5 | 18.8 | 18.7 |
| 15 | 70.0 | 70.0 | 70.0 |
| 2′ | 165.3 | 165.2 | 165.5 |
| 3′ | 125.2 | 125.4 | 125.2 |
| 4′ | 137.7 | 137.7 | 137.9 |
| 5′ | 121.2 | 121.3 | 121.3 |
| 6′ | 151.6 | 151.7 | 151.7 |
| 7′ | 36.4 | 36.6 | 36.6 |
| 8′ | 45.1 | 45.1 | 45.1 |
| 9′ | 11.9 | 12.0 | 12.0 |
| 10′ | 9.6 | 9.2 | 9.9 |
| 11′ | 173.9 | 174.0 | 174.0 |
| 12′ | 168.7 | 169.0 | 168.6 |
| 1-Ac | 20.5 | 20.5 | 20.5 |
| | 169.1 | 169.2 | 169.2 |
| 2-Ac | – | 21.4 | – |
| | – | 170.6 | – |
| 5-Ac | – | – | 21.0 |
| | – | – | 170.2 |
| 7-Ac | 21.3 | – | 21.8 |
| | 170.4 | – | 170.0 |
| 8-Ac | 20.5 | 20.6 | 20.6 |
| | 169.0 | 169.1 | 169.1 |
| 11-Ac | 21.1 | 21.2 | 21.4 |
| | 170.2 | 170.3 | 170.9 |

[a] **1**. 2-Nic: 163.7, 151.2, 125.0, 137.5, 123.7, 154.2; 5-Bz: 165.8, 129.5, 130.4, 128.9, 133.7. **2**. 5-Fu: 162.0, 144.4, 109.9, 119.0, 149.8; 7-Nic: 163.8, 151.4, 125.4, 137.6, 123.8, 154.4. **3**. 2-Fu: 161.0, 144.4, 110.0, 118.5, 148.9.

assigned to the furanoyl group and the proton signals at $\delta_H$ 5.49 (7-H) and 9.24 (2′-H, Nic) with the carbon signal at $\delta_C$ 163.8. This evidence indicated that the furanoyl and nicotinoyl groups should be assigned positions C-5 and C-7, respectively. The three acetyl groups were assigned to C-1, 8 and 11 due to long range correlations of the proton signals at $\delta_H$ 5.65 (1-H) and 1.76 (Ac) correlated with the carbon signal at $\delta_C$ 169.2; the proton signals at $\delta_H$ 5.37 (8-H) and 1.90 (Ac) with the carbon signal at $\delta_C$ 169.1; the proton signals at $\delta_H$ 4.37 (11-H′) and 2.13 (Ac) with the carbon signal at $\delta_C$ 170.3, respectively. Except for the macrocycle linkage sites of C-3 and C-15, the remaining acetyl group should be located at the last ester linkage site, C-2. The remaining proton and carbon signals




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| **1** | Ac | Bz | Nic |
| **2** | Nic | Fu | Ac |
| **3** | Ac | Ac | Fu |
| **4** | Ac | H | Ac |
| **5** | Ac | Ac | Bz |

Fig. 1. Structures of compounds 1–5.

were assigned as shown in Tables 1 and 2 by using 2D NMR, including NOESY spectroscopy. Thus, hyponine E was determined as **2**.

Hyponine F (**3**), $C_{41}H_{47}O_{19}N$, contained five acetyl groups [$\delta_H$ 1.77, 1.93, 2.12, 2.17 and 2.30] and one furanoyl (Fu) group [$\delta_H$ 7.45, 6.82 and 8.24]. It was also a macrocyclic sesquiterpene alkaloid and the nicotinated moiety was evoninic acid, which was again linked to the dihydroagarofuran core at positions 3 and 15. According to the long-range correlation of the proton signal at $\delta_H$ 5.40 (2-H) with the carbonyl carbon signal at $\delta_C$ 161.0 (furanoyl group), the furanoyl group was located at C-2. The other acetyl groups were assigned as shown in Fig. 1, in the same manner as described above. Therefore, hyponine F (**3**) was determined as shown.

Compounds **4** and **5** were identified from literature spectral comparison as neoeuonymine (**4**) (Yamanda, Sugiura, Shizuri, Wada & Hirata, 1977) and forrestine (**5**) (Cheng, Liu & Wu, 1992), respectively.

## 3. Experimental

NMR spectra were run on a Brüker ARX-400 instrument, $^1$H NMR: 400 MHz with TMS as int. standard, $^{13}$C NMR: 100 MHz. MS was obtained on a JEOL JMSD-300 instrument. Chromatography column: silica, HPLC: ODS (INERTSIL PREP ODS, 20.0 × 250 mm, GL Sciences Inc.).

### 3.1. Plant material

The root bark of *Tripterygium hypoglaucum* (Levl.) Hutch was purchased in 1995 from Kunming of Yunnan Province, China and identified by Prof. Dr. DaoFeng Cheng (Shanghai Medical University, China). A voucher specimen is deposited in Faculty of Pharmaceutical Sciences, University of Tokushima, Japan.

### 3.2. Extraction and isolation

Fractionation of *Tripterygium hypoglaucum* root bark solubles was described previously (Duan & Takaishi, 1998). Fr.14.2.4 (2 g) was dissolved in MeOH–$H_2O$ (8:2) and the dissolved portion was chromatographed using HPLC (ODS, MeOH–$H_2O$, 8:2) to give compound **1** (42 mg) and fr.14.2.4.1–14.2.4.10. Fr.14.2.4.8 (52 mg) was further chromatographed using HPLC (ODS, MeOH–$H_2O$, 7:3) to give **2** (16.5 mg). Fr.14.1 was chromatographed using HPLC (ODS, MeOH–$H_2O$, 8:2) to give **5** (102 mg) and fr.14.1.1–14.1.6. Fr.14.1.2 was further chromatographed using ODS (MeOH–$H_2O$, 7:3) to give **4** (19 mg). Fr.14.1.5 was chromatographed using ODS (MeOH–$H_2O$, 7:3) to give **3** (69 mg).

### 3.3. Hyponine D (*1*)

Amorphous powder, $[\alpha]_D^{25}$ + 5.2° (MeOH, *c* 1.1). IR $\nu_{MAX}^{KBr}$ cm$^{-1}$: 3652, 3631, 3436, 1746, 1638, 1459, 1372, 1252, 1166, 1117, 715, 602. UV $\lambda_{MAX}^{MeOH}$ (log $\epsilon$ : 226 (4.39), 264 (3.83). $^1$H NMR: $\delta$ ($CDCl_3$), see Table 1, $^{13}$C NMR: $\delta$ ($CDCl_3$), see Table 2. EI-MS: *m*/*z* (rel. int.) 930[M]$^+$ (1), 305 (2), 276 (2), 260 (5), 229 (8), 213 (9), 204 (15), 185 (13), 174 (19), 159 (28), 146 (25), 130 (35), 122 (35), 117 (25), 105 (100), 91 (18), 83 (10), 77 (45), 60 (15), 55 (9), 51 (20), 43 (77). HR-EIMS: *m*/*z* 930.3059 [M]$^+$, $C_{47}H_{50}O_{18}N_2$, required 930.3059.

### 3.4. Hyponine E (*2*)

Amorphous powder, $[\alpha]_D^{25}$ –4.2° (MeOH, *c* 1.0). IR $\nu_{MAX}^{KBr}$ cm$^{-1}$: 3652, 3631, 3449, 2363, 1746, 1639, 1590, 1372, 1229, 1162, 1118, 759, 603. UV $\lambda_{MAX}^{MeOH}$ (log $\epsilon$): 222 (4.25), 263 (3.79). $^1$H NMR: $\delta$ ($CDCl_3$), see Table 1, $^{13}$C NMR: $\delta$ ($CDCl_3$), see Table 2. EI-MS: *m*/*z* (rel. int.) 920 [M]$^+$ (2), 582 (5), 289 (4), 262 (12), 245 (10), 229 (13), 217 (16), 206 (93), 201 (15), 187 (28), 178 (48), 160 (64), 146 (46), 130 (74), 123 (45), 117 (49), 105 (83), 95 (43), 78 (48), 64 (44), 55 (17), 51 (27), 43 (100). HR-EIMS: *m*/*z* 920.2794, [M]$^+$, $C_{45}H_{48}O_{19}N_2$, required 920.2851.

### 3.5. Hyponine F (*3*)

Amorphous powder, $[\alpha]_D^{25}$ + 7.0° (MeOH, *c* 1.0). IR $\nu_{MAX}^{KBr}$ cm$^{-1}$: 3652, 3464, 2363, 1746, 1639, 1570, 1433, 1371, 1307, 1232, 1162, 1119, 1060, 875, 757, 603. UV $\lambda_{MAX}^{MeOH}$ (log $\epsilon$): 227 (4.00), 260 (3.58). $^1$H NMR: $\delta$ ($CDCl_3$), see Table 1, $^{13}$C NMR: $\delta$ ($CDCl_3$), see Table 2. EI-MS: *m*/*z* (rel. int.) 857 [M]$^+$ (100), 798 [M–$OCOCH_3$]$^+$ (16), 686 (12), 299 (11), 220 (15), 206 (93), 178 (66), 160 (22), 134 (18), 107 (54), 95 (37), 57 (13), 43 (23). HR-EIMS: *m*/*z* 857.2731 [M]$^+$, $C_{41}H_{47}O_{19}N$, required 857.2742.

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