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ALKALOIDS FROM *CEPHALOTAXUS HARRINGTONIA*

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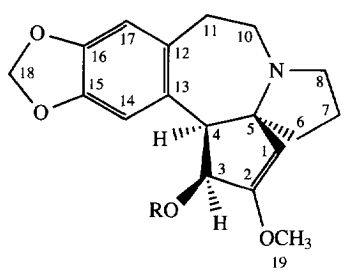
Key Word Index—*Cephalotaxus harringtonia*; Cephalotaxaceae; harringtonine; alkaloids.

Abstract—Four alkaloids, 5′-des-*O*-methylharringtonine, 3′*S*-hydroxy-5′-des-*O*-methylharringtonine, 5′-des-*O*-methylhomoharringtonine and 5′-des-*O*-methylisoharringtonine, were isolated from the leaves and stems of *C. harringtonia* var. drupacea. Their structures were established by ^{1}H and ^{13}C NMR spectroscopic studies, chemical conversions to known alkaloids and applying the advanced Mosher's method for the secondary alcohol moiety.

INTRODUCTION

Since cephalotaxine (**1**) was reported from *Cephalotaxus harringtonia* [1], many kinds of alkaloids have been isolated from *Cephalotaxus* spp. [2–9]. In particular, ester-type *Cephalotaxus* alkaloids, such as harringtonine (**2**), homoharringtonine (**3**), isoharringtonine (**4**) and deoxyharringtonine (**5**), are well known for their remarkable antitumour activity against experimental P388 and L-1210 leukaemia in mice [10,

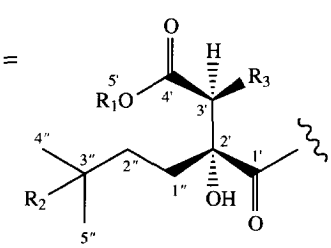


19

1 R = H

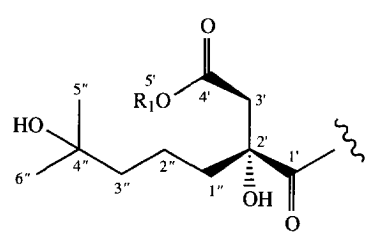
	R_1	R_2	R_3
2	Me	OH	H
4	Me	H	OH
5	Me	H	H
6	H	OH	H
7	H	OH	OH
9	H	H	OH
10	Me	OH	OH

R =



	R_1
3	Me
8	H

R =



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11]. Further investigations in the People's Republic of China have shown that **2** and **3** are also effective in the treatment of human cancers [12, 13]. Recently, we have isolated four ester-type *Cephalotaxus* alkaloids having a free carboxylic acid, 5′-des-*O*-methylharringtonine (**6**), 3′*S*-hydroxy-5′-des-*O*-methylharringtonine (**7**), 5′-des-*O*-methylhomoharringtonine (**8**) and 5′-des-*O*-methylisoharringtonine (**9**), from the methanol extract of the title species. We report herein, the characterization of these alkaloids.

RESULTS AND DISCUSSION

The methanol extract from dried cut leaves and stems was partitioned with ethyl acetate and 3% tartaric acid. The acidic aqueous phase was then made basic to pH 8.5, by the addition of saturated aqueous sodium carbonate solution and extracted with chloroform. The crude chloroform extract was chromatographed on ODS silica gel and reverse-phase preparative HPLC, which yielded **6–9** along with the five known *Cephalotaxus* alkaloids **1–5**.

Compound **6** was obtained as a white amorphous solid. It gave positive iodine and Dragendorff's reagent tests for alkaloids. The FAB-mass spectrum exhibited as a quasi molecular ion peak $[M+H]^+$ at *m/z* 518, which suggested the molecular formula $C_{27}H_{35}NO_9$. The EI-mass spectrum showed fragment ion peaks at *m/z* 298 (100), 284 (90), 266 (27), 214 (15) and 150 (25), which were characteristic of those of **1** [14]. The IR spectral data showed the presence of hydroxyl groups (3390 cm^{-1}), an ester carbonyl group (1740 cm^{-1}), a carboxylic acid with an intermolecular hydrogen bond (1660 cm^{-1}) and an aromatic ring (1590 and 1500 cm^{-1}). In the ^1H NMR (DMSO-d_6), two methyls (δ 0.96 *s* and 1.01 *s*), a methoxy (δ 3.58 *s*), seven sets of methylenes, a methine proton (δ 380 *d*), a vinyl proton (δ 5.13 *s*), a carbinyl proton (δ 5.77 *d*), methylene dioxide protons (δ 5.76 *d* and 5.92 *d*), two aromatic protons (δ 6.53 *s* and 6.65 *s*) were observed (Table 1). In the ^{13}C NMR (DMSO-d_6), three methyls, nine methylenes, five methines, eight quaternary and two carbonyl carbons (δ 171.0 and 172.8) were observed (Table 2). These resonances were assigned with the aid of 2D-NMR (^1H–^1H COSY, HMQC [15], HMBC [16] and NOESY) techniques. Although the NMR data of **6** were very similar to those of **2** [17], it lacked the ester methoxyl resonance. Methylation of **6** with TMSi-diazomethane [18] gave **2**, which was confirmed by comparison (TLC, $[\alpha]_D$ and ^1H NMR) with the authentic sample [10]. Thus, this alkaloid was concluded to be 5′-des-*O*-methylharringtonine.

Compound **7** was obtained as a white amorphous solid. The HRFAB-mass spectrum suggested the molecular formula $C_{27}H_{35}NO_{10}$. In the ^1H and ^{13}C NMR (DMSO-d_6) spectra, the chemical shifts of **7** showed

Table 1. ^1H NMR spectral data on compounds **6–9*** (500 MHz, DMSO-d_6)

H	**6**	**7**	**8**	**9**
1	5.13 *s*	5.17 *s*	5.14 *s*	5.20 *s*
3	5.77 *d* (9.7)	5.76 *d* (9.5)	5.70 *d* (9.5)	5.76 *d* (9.5)
4	3.80 *d* (9.7)	3.86 *d* (9.5)	3.82 *d* (9.5)	3.88 *d* (9.5)
6α	1.82 *m*	1.92 *m*	1.87 *m*	1.92 *m*
6β	1.81 *m*	1.90 *m*	1.85 *m*	1.91 *m*
7α	1.69 *m*	1.76 *m*	1.70 *m*	1.78 *m*
7β	1.57 *m*	1.63 *m*	1.58 *m*	1.64 *m*
8α	2.55 *m*	2.70 *m*	2.57 *m*	2.71 *m*
8β	2.83 *ddd* (8.8, 8.6, 3.9)	2.95 *m*	2.85 *ddd* (9.3, 9.1, 3.7)	2.99 *m*
10α	2.71 *ddd* (13.4, 11.6, 7.0)	2.81 *m*	2.73 *ddd* (12.9, 11.3, 7.0)	2.83 *m*
10β	2.54 *m*	2.69 *m*	2.57 *m*	2.70 *m*
11α	2.35 *dd* (14.2, 7.0)	2.38 *m*	2.37 *dd* (13.4, 7.0)	2.40 *dd* (14.2, 7.0)
11β	3.02 *ddd* (14.2, 13.4, 7.0)	3.15 *m*	3.01 *ddd* (13.4, 12.9, 7.0)	3.14 *m*
14	6.53 *s*	6.57 *s*	6.54 *s*	6.59 *s*
17	6.66 *s*	6.66 *s*	6.65 *s*	6.67 *s*
18a	5.92 *d* (1.4)	5.89 *s*	5.92 *d* (1.1)	5.89 *s*
18b	5.76 *d* (1.4)	5.79 *s*	5.78 *d* (1.1)	5.80 *s*
19	3.58 *s*	3.62 *s*	3.59 *s*	3.63 *s*
3′a	1.88 *d* (15.3)	3.06 *s*	1.89 *d* (15.8)	3.12 *s*
3′b	1.61 *d* (15.3)	—	1.67 *d* (15.8)	—
1″a	1.45 *ddd* (12.4, 12.1, 8.7)	1.51 *m*	1.26 *m*	1.43 *ddd* (13.4, 13.1, 4.3)
1″b	1.09 *dd* (12.4, 8.7)	1.39 *m*	1.26 *m*	1.27 *m*
2″a	1.35 *m*	1.24 *m*	1.02 *m*	1.04 *m*
2″b	1.35 *m*	0.99 *m*	0.96 *m*	0.71 *m*
3″a	—	—	1.18 *m*	1.27 *m*
3″b	—	—	1.18 *m*	—
4″	0.96 *s*	0.96 *s*	—	0.76 *d* (6.7)
5″	1.01 *s*	1.00 *s*	1.01 *s*	0.78 *d* (6.7)
6″	—	—	1.02 *s*	—

* Assignments from C/H correlation experiments.

Table 2. ^{13}C NMR spectral data of compounds **2** and **6–9*** (125 MHz, $CDCl_3$ for **2**, DMSO-d_6 for **6–9**)

C	2	6	7	8	9
1	100.4	100.3	99.2	100.3	99.1
2	157.5	157.4	158.7	157.6	158.7
3	74.5	73.1	73.1	73.1	73.2
4	55.6	54.9	54.0	54.7	53.9
5	70.7	69.9	70.5	70.2	71.7
6	43.0	42.8	42.3	42.6	41.2
7	20.1	20.1	19.7	20.1	19.7
8	53.7	53.0	52.8	53.0	52.8
10	48.4	47.7	47.4	47.6	47.1
11	31.1	30.6	28.9	30.4	29.8
12	133.0	133.4	132.8	133.2	132.5
13	128.0	129.0	127.9	128.8	127.9
14	112.6	112.3	112.9	112.3	112.9
15	146.7	145.7	145.9	145.8	145.9
16	145.8	144.9	145.0	145.0	145.1
17	109.6	109.2	109.5	109.3	109.6
18	100.7	100.6	100.3	100.4	100.4
19	57.2	56.9	57.1	57.2	57.1
1′	173.7	172.8	171.6	172.9	171.5
2′	74.6	74.3	78.6	74.4	78.7
3′	42.6	42.9	73.6	42.4	73.5
4′	170.2	171.0	172.9	171.1	172.9
5′	51.4				
1″	33.0	33.5	29.9	40.0	32.7
2″	36.7	36.5	36.1	17.9	31.1
3″	69.9	68.2	68.4	43.9	27.8
4″	28.7	28.3	28.5	68.7	22.2
5″	29.3	30.0	30.0	28.9	22.8
6″				29.3	

*Assignments from C/H correlation experiments.

good agreement with those of **6**, except around the C-3′ position. Although the H-3′ protons of **6** resonated at δ 1.61 and 1.88 as an AB type doublet (J = 15.3 Hz), the same proton was observed at δ 3.06 as a singlet on **7**. In addition, the C-3′ resonance was observed 30 ppm lower field than **6**, which indicated that **7** had one more hydroxyl group at the C-3′ position. A vicinal coupling (J = 9.5 Hz) between H-3 (δ 5.76 *d*) and H-4 (δ 3.86 *d*), the NOESY correlations of H-4 with H-3, H-6 α (δ 1.92 *m*) and H-14 (δ 6.57 s), H-11 α (δ 2.38 *m*) with H-17 (δ 6.66 *s*) suggested that **7** had the same configuration as **6**. There were two asymmetric centres on the side-chain moiety (2′, 3′) in **7**. It is known that there is a marked tendency for the ^1H NMR chemical shifts at H-3 and H-3′ with the configurations on C-2′ and C-3′ among **4** and its diastereomers at these positions [19–22]. These resonance of **10**, obtained by methylation of **7**, showed good agreement with the corresponding data for **4** (determined as the *erythro*-configuration). This result suggested that the C-2′ and C-3′ configuration of **7** was also *erythro* (Table 3). To confirm this spectral evidence and to determine the absolute configuration at C-3′, we used the advanced Mosher's method [23]. The (*S*)-MTPA ester of **10** (**11**) and the (*R*)-MTPA ester of **10** (**12**) were prepared; the selected chemical shift differences $\Delta\delta$ values ($=\delta_S - \delta_R$, 500 MHz) are shown in Fig. 1. In

Table 3. ^1H NMR chemical shifts of compounds **4** (2′*R*, 3′*S*) and **10** (500 MHz, $CDCl_3$)

H	4	10
3	6.04 d (9.5)	6.02 *d* (9.5)
14	6.54 *brs*	6.57 *brs*
17	6.65 *s*	6.65 *s*
18a	5.86 *d* (1.5)	5.88 *brs*
18b	5.81 *d* (1.5)	5.83 *brs*
19	3.69 *s*	3.72 *s*
3′	3.35 *s*	3.37 *s*
5′	3.61 *s*	3.60 *s*
4″	0.85 *d* (6.7)	1.15 *s*
5″	0.87 *d* (6.7)	1.16 *s*

an MTPA ester moiety with the absolute configuration shown in Fig. 1, protons on the right side of the MTPA plane should have negative $\Delta\delta$ values, because of the anisotropic effects of the phenyl groups of the (*S*)- and the (*R*)-MTPA esters. As a result, the 5′ methoxyl resonance of **10** indicated $\Delta\delta > 0$ and 1″, 2″ methylene protons indicated $\Delta\delta < 0$. Thus, the absolute configurations of C-3′ in **10** was determined to be *S*, and C-2′ as *R* (*erythro*). Therefore, **7** was elucidated as 3′*S*-hydroxy-5′-des-*O*-methylharringtonine. This result was supported by the model experiment for **4**, which had already determined it to be 2′*R*3′*S* by CD [24]. The (*S*)-MTPA ester of **4** (**13**) and the (*R*)-MTPA ester of **4** (**14**) gave the same result as in the case of **10**.

Compound **8** was obtained as a white amorphous solid, the HRFAB-mass spectrum suggesting the molecular formula $C_{28}H_{37}NO_9$. Since methylation of **8** gave **3**, the structure of **8** was concluded to be 5′-des-*O*-methylhomoharringtonine. Although **8** has been reported as a major metabolite of **3** in liver microsomes of rats and rabbits [25], this is the first time it has been isolated from a natural source.

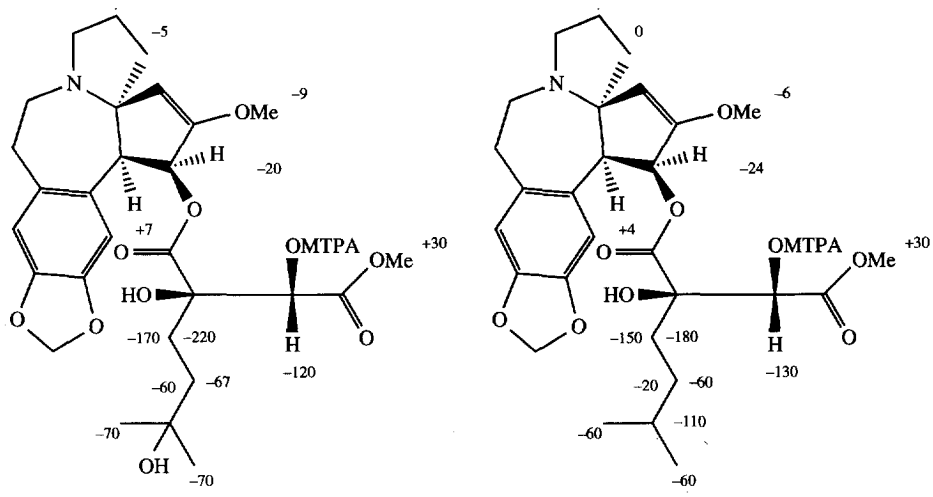
Compound **9** was obtained as a white amorphous solid, with the molecular formula $C_{27}H_{35}NO_9$. Since methylation of **9** gave **4**, the structure of **9** was concluded to be the 5′-des-*O*-methylisoharringtonine. Although this compound had been reported previously as isoharringtonic acid from *C. hainanensis* [26], this is the first report of its occurrence in *C. harringtonia*.

The IC_{50} values of compounds **6**, **7**, **8** and **9** against P-388 leukaemia cells were 1.0, 65.0, 4.6 and 0.41 μg ml^{-1}, respectively; they are much less cytotoxic than **2** (0.032 μg ml^{-1}) and **4** (0.018 μg ml^{-1}).

EXPERIMENTAL

General. ^1H and ^{13}C NMR: DMSO-d_6 or $CDCl_3$ with TMS as int. standard. NOESY expts were made with a mixing time of 0.40 s. HPLC was performed with a CAPCELL PAK C18 UG 120A column (250 mm × 20 mm i.d., Co., Shiseido) packed with 5 μm ODS. TLC was conducted on Kieselgel 60 F_{254} and detection was achieved by UV light at 254 nm, exposure to I_2 vapour and/or spraying with Dragendorff's reagent.

Materials. Leaves and stems of *C. harringtonia* var.



11 (S)-MTPA
12 (R)-MTPA

13 (S)-MTPA
14 (R)-MTPA

Fig. 1. $\Delta\delta$ [$=\delta_S - \delta_R$ (Hz)] values for the MTPA esters of compounds **10** (**11** and **12**) and **4** (**13** and **14**).

drupacea (Sieb. & Zucc.) Koizumi were collected in Yamanashi Prefecture, Japan, in October 1994 and identified by Dr S. Isoda (Showa University). Voucher specimens are deposited in the Herbarium of the Tokyo Metropolitan Research Laboratory of Public Health, Tokyo, Japan.

Extraction and isolation of **1–9**. Dried cut leaves and stems (2 kg) were extracted with MeOH (15 l × 3) at 70° for 2 days to give an extract (300 g). This extract was suspended in 3% tartaric acid (2 l) and extracted with EtOAc (1 l × 3). Then the aq. phase was basified with satd Na_2CO_3 soln and extracted with $CHCl_3$ (1 l × 3). The $CHCl_3$-sol. phase was concd to give a crude extract (6 g). This was suspended in H_2O (100 ml) and fractionated on an ODS column (500 g) conditioned with MeOH, H_2O, then 0.03 M $(NH_4)_2CO_3$. Using 0.03 M $(NH_4)_2CO_3$–MeOH mixts of increasing MeOH conc (0 to 100%) 13 frs were obtained which were monitored by TLC and HPLC. Frs eluted with 30% MeOH were combined and processed on ODS columns or by reverse-phase HPLC using a 0.03 M $(NH_4)_2CO_3$–MeCN solvent system to give **1** (48 mg), **2** (90 mg), **3** (950 mg), **4** (25 mg), **5** (40 mg), **6** (15 mg), **7** (22 mg), **8** (20 mg) and **9** (10 mg).

Methylation of **6–9**. Each compound (*ca* 5 mg) was treated with TMSi-diazomethane in MeOH benzene (2:7) at room temp. for 30 min. The reagents and solvents were evapd off and the residue subjected to prep. TLC [Kiesel gel PF_{254}, $CHCl_3$–MeOH (17:3)] to afford the Me derivatives (*ca* 3 mg). R_f **2**; 0.35, **10**: 0.10, **3**: 0.42 and **4**: 0.31.

*5′-Des-*O*-methylharringtonine* (**6**). Amorphous solid. $[\alpha]_D$ −113° (DMSO; *c* 0.43). FABMS *m/z* (rel. int.): 518 $[M+H]^+$ (100), 298 $[M+H-C_9H_{16}O_6]^+$ (40). (HRFABMS, found: $[M+H]^+$, 518.2417. $C_{27}H_{36}NO_9$ requires $[M+H]^+$, 518.2390). EIMS *m/z* (rel. Int.): 517 (1), 499 (0.6), 315 (90), 298 (100), 284 (90), 266 (27), 254 (35), 214 (15), 150 (25). IR ν max KBr cm^{-1}: 3390 *br*, 2970, 2930, 1740, 1660, 1590, 1500, 1490. UV λMeOH max nm: 289 (log ε 3.56). ^1H NMR: Table 1. ^{13}C NMR: Table 2.

*3′S-Hydroxy-5′-Des-*O*-methylharringtonine* (**7**). Amorphous solid. $[\alpha]_D$ −91° (DMSO; *c* 1.00). FABMS *m/z* (rel. int.): 534 $[M+H]^+$ (90), 298 $[M+H-C_9H_{16}O_7]^+$ (100). (HRFABMS, found: $[M+H]^+$, 534.2350. $C_{27}H_{36}NO_{10}$ requires $[M+H]^+$, 534.2339). EIMS *m/z* (rel. int.): 533 (1), 517 (1), 386 (3), 315 (90), 298 (100), 284 (85), 272 (18), 266 (16), 254 (25), 229 (27), 214 (30). IR ν max KBr cm^{-1}: 3390 *br*; 2970, 2930, 1740, 1650, 1620, 1510, 1490. UV λMeOH max nm: 288 (log ε 3.52). ^1H NMR: Table 1. ^{13}C NMR: Table 2.

Methyl ester of **7** (**10**). Oil, $[\alpha]_D$ −88° (MeOH; *c* 0.05) ^1H NMR: Table 3.

Preparation of (R)- *and* (S)-*MTPA esters of* **10** *and* **4**. To a soln of **10** (2.7 mg) in pyridine (0.2 ml) was added (−)-MTPA Cl (10 mg) and *N,N*-dimethylaminopyridine (1.5 mg). The mixt. was allowed to stand at room temp. for 13 hr. The residue obtained after evapn of solvent was applied to a silica gel column [$CHCl_3$–MeOH, 4:1] to give the (*S*)-MTPA ester of **10** (**11**) (3 mg). HRFABMS *m/z* calcd for $C_{38}H_{45}NO_{12}F_3$ ($[M+H]^+$) 764.2894, found 764.2899. Other esters were prepared by the same method. (R)-*MTPA ester of* **10** (**12**). HRFABMS *m/z* calcd for $C_{38}H_{45}NO_{12}F_3$ ($[M+H]^+$) 764.2894, found 764.2904. (S)-*MTPA ester of* **4** (**13**). HRFABMS *m/z* calcd for $C_{38}H_{45}NO_{11}F_3$ ($[M+H]^+$) 748.2944, found 748.2937.

(R)-*MTPA* ester of **4** (**14**). HRFABMS *m/z* calcd for $C_{38}H_{45}NO_{11}F_3$ ($[M+H]^+$) 748.2944, found 748.2935.

5′-*Des*-O-*methylhomoharringtonine* (**8**). Amorphous solid. $[\alpha]_D$ −172° (MeOH; *c* 0.50). FABMS *m/z* (rel. int.): 532 $[M+H]^+$ (100), 298 $[M+H-C_{10}H_{18}O_6]^+$ (50). (HR FABMS, found: $[M+H]^+$, 532.2567. $C_{28}H_{38}NO_9$ requires $[M+H]^+$, 532.2546). EIMS *m/z* (refl. int.): 531 (6), 513 (1), 500 (2), 315 (35), 298 (100), 282 (67), 266 (23), 214 (14), 150 (22). IR *ν* max KBr cm^{-1}: 3400 *br*, 2960, 2930, 2850, 1740, 1650. UV *λ* MeOH max nm: 290 (log *ε* 3.55). ^1H NMR: Table 1. ^{13}C NMR: Table 2.

5′-*Des*-O-*methylisoharringtonine* (**9**). Amorphous solid. $[\alpha]_D$ −113° (DMSO; *c* 0.33). FABMS *m/z* (rel. int.): 518 $[M+H]^+$ (100), 298 $[M+H-C_9H_{16}O_6]^+$ (75). (HRFABMS, found: $[M+H]^+$, 518.2418. $C_{27}H_{36}NO_9$ required $[M+H]^+$, 518.2390). EIMS *m/z* (rel. int.): 517 (7), 486 (2), 298 (100), 282 (55), 266 (21), 214 (10), 150 (16). IR *ν* max KBr cm^{-1}: 3370 *br*, 2950, 2930, 2860, 1730, 1650. UV *λ* MeOH max nm: 289 (log *ε* 3.73). ^1H NMR: Table 1. ^{13}C NMR: Table 2.

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