New Oxygenated *Cephalotaxus* Alkaloids from *Cephalotaxus harringtonia* var. *drupacea*

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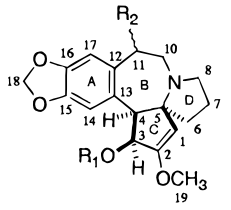
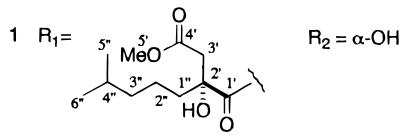
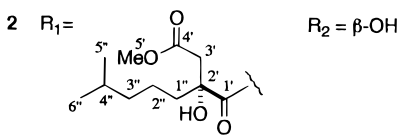
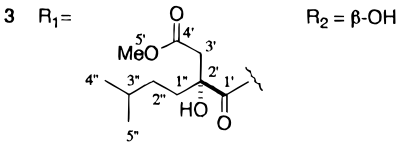
Three oxygenated cephalotaxine ester-type alkaloids, 11α-hydroxyhomodeoxyharringtonine (**1**), 11*β*-hydroxyhomodeoxyharringtonine (**2**) and 11*β*-hydroxydeoxyharringtonine (**3**) were isolated from *Cephalotaxus harringtonia* var. *drupacea*. Their structures were established by spectroscopic methods including 2D NMR and CD spectra, and their antileukemic activity was evaluated using P-388 leukemia cells.

The genus *Cephalotaxus* (Cephalotaxaceae) has long been known to contain the antileukemic ester alkaloids harringtonine and its congeners.[1,2] Although some oxygenated *Cephalotaxus* alkaloids, such as 11-hydroxycephalotaxine and drupacine,[3] have been isolated, there has been no report of the isolation of oxygenated ester-type congeners. We have isolated three 11-hydroxy derivatives of 11α-hydroxyhomodeoxyharringtonine (**1**), 11*β*-hydroxyhomodeoxyharringtonine (**2**), and 11*β*-hydroxydeoxyharringtonine (**3**) from *C. harringtonia* var. *drupacea*. (Sieb., & Zucc.) Koidzumi (Cephalotaxaceae). We report herein the isolation, characterization, and antileukemic activities of these alkaloids against P-388 leukemia cells.









The alkaloid fraction, prepared in the usual way,[4] from dried, cut leaves and stems of *C. harringtonia* was chromatographed repeatedly on ODS Si gel, which yielded compounds **1**−**3** along with such known *Cephalotaxus* alkaloids as deoxyharringtonine.

Compound **1** had the molecular formula $C_{29}H_{39}NO_9$ established by HRFABMS, indicating eleven degrees of unsaturation. The spectral data of **1** revealed the presence of a hydroxyl group (3522 cm^{-1}), two methoxyl groups (δ_H 3.56, δ_C 51.7 and δ_H 3.69, δ_C 57.3), an aromatic ring with two *para*-coupled protons (δ_H 6.55, δ_C 112.6 and δ_H 7.12, δ_C 104.3), a methylenedioxy group (δ_H 5.90 × 2, δ_C 100.9), and an AB-type methylene (δ_H 2.15, 2.31 ; δ_C 43.1). The X portion of an ABX system (δ_H 5.22, δ_C 67.4) was assignable to C-11, a carbon bearing both oxygen and aryl functions. In addition, the presence of two ester carbonyl groups (δ_C 170.9 and 173.8) and two terminal methyl groups (δ_H 0.84 × 2; δ_C 22.4, 22.6) indicated that **1** had an ester side-chain moiety. These spectral data were similar to those of deoxyharringtonine,[5,6] except for the presence of a hydroxyl group at C-11 on the seven-membered ring system and an additional methylene unit on the side-chain moiety. In the $^1H-^1H$ COSY spectrum, the partial structure $-CH(3)-CH(4)$, $-CH_2(6)-CH_2(7)-CH_2(8)$, $-CH_2(10)$ $-CH(11)$, and $-CH_2(1'')-CH_2(2'')-CH_2(3'')-CH(4'')-Me2(5''$ and $6'')$ was revealed. The HMBC[7] spectrum indicated the correlations H-1 to C-2 and C-5; H-3 to C-2, C-5, C-13, and C-1′; H-4 to C-2, C-5, C-12, C-13, and C-14; H-6 to C-5; H-10 to C-12; H-11 to C-12, C-13, and C-17; H-3′ to C-1′, C-2′, C-4′, and C-1″ for **1**. These spectral evidences suggested that **1** is the C-11 hydroxyl congener of deoxyharringtonine. The NOESY correlations between H-1 and H-8*β*, H-1 and H-10*β*, H-3 and H-4, H-4 and H-6α, H-4 and H-14, H-8α and H-10α, and the vicinal coupling constants of 10.2 Hz between H-10α and H-11 and of 7.0 Hz between H-10*β* and H-11 indicated the ring system shown in structure **1**. Furthermore, significant pyridine-induced solvent shifts[8] were observed for H-10α (δ pyridine − δ $CHCl_3$ = +0.4) and H-17 (+0.7). These deshielding effects suggested that these protons were situated vicinal to the hydroxyl group and were disposed towards the same side of the molecule. Therefore, it was evident that the secondary hydroxyl group attached to C-11 was in the α configuration. This is the first isolation of an 11α-hydroxy cephalotaxine derivative from *Cephalotaxus* spp.

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Compound **2** had the same molecular formula, as **1** ($C_{29}H_{39}NO_9$) established by HR FABMS. The ^{1}H- and ^{13}C-NMR data showed that **2** also had the same functional groups. The HMBC spectra also indicated the correlations H-1 to C-2 and C-5; H-3 to C-2, C-5, C-13, and C-1′; H-4 to C-2, C-5, C-12, C-13, and C-14; H-6 to C-5; H-10 to C-12; H-11 to C-12, C-13, and C-17; H-3′ to C-1′, C-2′, C-4′, and C-1″ for **2**. These spectral evidences showed that **2** is also the C-11 hydroxyl congener of deoxyharringtonine. NOESY correlations between H-1 and H-6β, H-3 and H-4, H-4 and H-6α, H-4 and H-14, and H-11α and H-17; vicinal coupling constants of 7.5 Hz between H-10α and H-11 and of 10.5 Hz between H-10β and H-11; and pyridine-induced solvent shifts for H-10β (+0.5) and H-17 (+0.3) were observed. Thus, the hydroxyl group at C-11 of **2** was revealed to be in the β configuration, that is, **2** is the C-11 diastereomer of **1**.

Comparison of the ^{1}H- and ^{13}C-NMR spectral data of **1** with those of **2** revealed significant differences in chemical shifts of some proton (H-1, H-4, H-6, H-8, and H-10) and carbon (C-1, C-4, C-5, C-6, C-7, C-8, C-10, and C-11) resonances, indicating conformational differences between these two diastereomers. Because the ^{1}H- and the ^{13}C-NMR chemical shifts of **1**, except for protons and carbons near C-11, were similar to those of deoxyharringtonine, the conformation of **1** was the same as that of deoxyharringtonine. The NOESY correlations between H-1 and H-8β, H-1 and H-10β were observed for **1** and deoxyharringtonine, and between H-1 and H-6β; H-11α and H-17 for **2**, which indicated that an orientational change on the nitrogen lone pair had occurred for **2**. These results were also supported by the ^{1}H- and ^{13}C-NMR chemical shift differences between **1** and **2**. High-field shifts were observed for H-8β ($\delta\Delta$ − 0.26) and H-10β ($\delta\Delta$ −0.41) of **1** compared with those of **2**, indicating that they are in the antiperiplanar position relative to the nitrogen lone pair, which is in the α orientation for **1**.[9−12] Also, the highfield shifts of H-8α ($\delta\Delta$ −0.21) in **2** compared with those of **1** indicated that the nitrogen lone pair of **2** is in the β orientation. Furthermore, the C-6 ($\delta\Delta$ +3.2), C-8 ($\delta\Delta$ +3.9), and C-10 ($\delta\Delta$ +8.4) resonances of **1** were observed at lower field than those of **2**. These data showed that **1** and deoxyharringtonine possess the *trans* B/D ring junction, and that **2** possesses the *cis* junction (Figure 1).

Compound **3** had the molecular formula $C_{28}H_{37}NO_9$ established by HR FABMS, indicating 11 degrees of unsaturation. The spectral data of **3** were very similar to those of **2**, except for lack of a methylene unit on the ester side chain. The ^{1}H−^{1}H COSY spectrum revealed the partial structure CH_2 (1″)−CH_2 (2″)−CH (3″)−2 × Me (4″ and 5″). Furthermore, in the HMBC spectra, the H-3 proton was correlated with the C-1′ carbonyl carbon, and the H-3′ methylene protons showed correlations with the C-1′, C-2′, C-4′, and C-1″ carbons. The above spectral evidence suggested that **3** is 11β-hydroxydeoxyharringtonine having an isopentyl branch instead of isohexyl branch of **2**. Because the ^{1}H- and ^{13}C-NMR chemical shifts, the NOESY correlations, and the vicinal coupling constants between H-10α and H-11 (7.5 Hz) and between H-10β and H-11 (10.5 Hz) were very similar to those of **2**, the ring conformation of **3** appears to be the same as **2** (Figure 1).

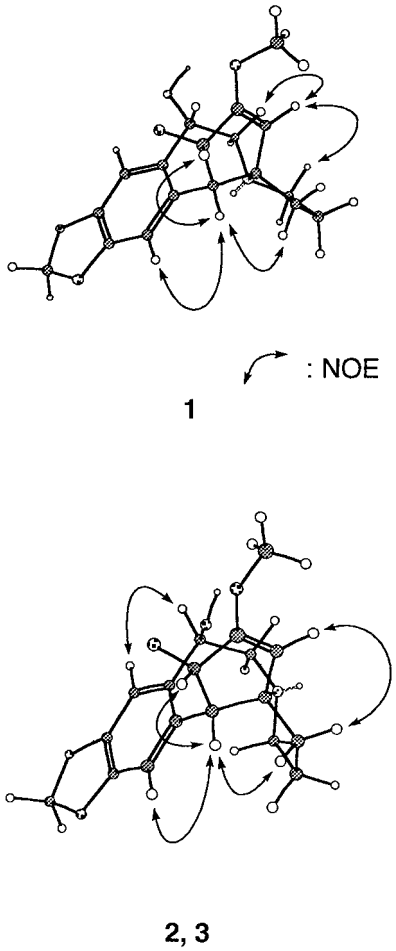

Figure 1. Selected NOESY correlations around the ring moiety of **1**−**3**. The ester side chains are omitted for clarity.

The absolute configurations of compounds **1**−**3** were established by using CD spectra. MeOH solutions of **1**−**3** showed negative Cotton effects (**1**: $[\theta]_{290}$ − 3600, **2**: $[\theta]_{290}$ −4400, and **3**: $[\theta]_{290}$ −3700) similar to that of deoxyharringtonine ($[\theta]_{290}$ −2600), whose absolute configuration was known. This indicated that the chirality between the two chromophores (the benzene ring and double bond on C ring system) of **1**−**3** were the same as that of **4** (3*S*,4*S*,5*R*). Brandänge *et al.* discussed the absolute configuration of some C-2′ alkyl diacids and found that the negative Cotton effects of the molybdate complex at 270 nm were characteristic for the *R* configuration.[13−15] The CD spectrum for the molybdate complex of the diacid derived from hydrolysis of **1**−**3** and deoxyharringtonine all showed negative Cotton effects; from **1** ($[\theta]_{270}$ −2900), **2** ($[\theta]_{272}$ −2500), **3** ($[\theta]_{270}$ −4100), and deoxyharringtonine ($[\theta]_{270}$ −12 800, known as 2′*R*), indicating that they all were 2′*R* configuration on the side-chain moiety. Therefore, the absolute configurations of **1**−**3** were revealed as 3*S*,4*S*,5*R*,11*S*, 2′*R* for **1**, 3*S*,4*S*,5*R*,11*R*, 2′*R* for **2**, and 3*S*,4*S*,5R,11*R*,2′*R* for **3**.

Compounds **1**−**3** showed antileukemic activities against P-388 leukemia cells.[16] The IC_{50} values were 0.38, 0.33, and 0.17 μg/mL, respectively, and they were less cytotoxic than deoxyharringtonine (0.0075 μg/mL).

Experimental Section

General Experimental Procedures. ^{1}H- and ^{13}C-NMR spectra: $CDCl_3$ and pyridine-d_5 with TMS as

internal standard. NOESY experiments were made with a mixing time of 0.40 s. FABMS: (positive), HPLC was performed with a CAPCELL PAK C_{18} UG 120A column (20 mm i.d. × 250 mm, Shiseido) packed with 5 μm ODS. TLC was conducted on precoated Kieselgel 60 F_{254}, and detection was achieved by UV light at 254 nm, exposure to I_2 vapor and/or spraying with Dragendorff's reagent.

Plant Material. The leaves and stems of *C. harringtonia* var. *drupacea* used in this experiment were collected in Yamanashi prefecture, Japan, in October 1994, and identified by Dr. Susumu Isoda (Showa University). Voucher specimens are deposited in the Herbarium of the Tokyo Metropolitan Research Laboratory of Public Health, Tokyo, Japan.

Extraction and Isolation. Dried, cut leaves and stems (10 kg) of the plants were extracted with MeOH (3 × 50 L) at 70 °C for 5 days to give the extract (1.1 kg). MeOH extract (800 g) was suspended in 3% tartaric acid (16 L) and extracted with EtOAc (3 × 8 L). Then the aqueous phase was basified with aqueous saturated Na_2CO_3 solution and extracted with $CHCl_3$ (3 × 8 L). The $CHCl_3$-soluble phase was concentrated to give crude extract (16 g). The extract was suspended in H_2O (100 mL) and subjected to ODS column (1.6 kg), which was conditioned with MeOH, H_2O, then 0.03M aqueous $(NH_4)_2CO_3$. Elution with 0.03 M aqueous $(NH_4)_2CO_3$−MeOH mixtures of increasing MeOH concentration (0 to 100%) gave 13 fractions, which were monitored by TLC and HPLC. Fractions eluted with 70% MeOH were combined and rechromatographed (ODS column, 0.03 M aqueous $(NH_4)_2CO_3$−MeCN) to give **1** (1.4 mg), **2** (1.8 mg), **3** (1.7 mg), and deoxyharringtonine (185.0 mg).

Molybdate Complex Preparation. One milligram each of **1**−**3** and deoxyharringtonine were hydrolyzed with 1 mL of 3 M HCl (reflux, 4 days). After cooling, the mixture was made basic with 3 M NH_4OH, and the alkaline phase was washed with $CHCl_3$. Excess NH_4OH was neutralized and evaporated under diminished pressure. The crude acids so obtained were used directly in preparation of CD solutions, which were 3.0 mM with respect to hydroxy acids and 2.7 mM with respect to sodium molybdate. HCl and NaOH solutions were added until pH 2.9−3.1 was reached. Measurements of the CD spectra were carried out in a 1-mm cell five days after the solutions had been prepared.

11α-Hydroxyhomodeoxyharringtonine (1): Oil; $[\alpha]^{25}_D$ −115° (c 0.07, MeOH); UV λ (MeOH) max (log ϵ): 290 (3.50) nm; IR (KBr) ν max KBr 3522 br (OH), 2952, 2929, 2872, 2804 (CH, aliphatic), 1742 (C=O, ester), 1652, 1503, 1484, 1456, 1439 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.12 (1H, s, H-17), 6.55 (1H, s, H-14), 5.95 (1H,d, J = 9.8 Hz, H-3), 5.90 (2H, brd, J = 1.4 Hz, H-18a and -18b), 5.22 (1H, br dd, J = 10.2, 7.0 Hz, H-11β), 5.02 (1H, s, H-1), 3.79 (1H, d, J = 9.8 Hz, H-4), 3.69 (3H, s, Me-19), 3.56 (3H, s, Me-5′), 3.07 (1H, m, H-8α), 2.91 (1H, dd, J = 10.4, 7.0 Hz, H-10β), 2.64 (1H, m, H-8β), 2.64 (1H, dd, J = 10.4, 10.2 Hz, H-10α), 2.31 (1H, d, J = 16.7 Hz, H-3′b), 2.15 (1H, d, J = 16.7 Hz, H-3′a), 2.03 (1H, brs, OH-11α), 2.01 (1H, m, H-6α), 1.90 (1H, m, H-6β), 1.76 (2H, m, H-7α and -7β), 1.48 (1H, m, H-4″), 1.29 (4H, m, H-1″a, -1″b, -3″a, and -3″b), 1.08 (2H, m, H-2″a and -2″b), 0.84 (3H, d, J = 6.5 Hz, Me-5″), 0.84 (3H, d, J = 6.5 Hz, Me-6″); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.8 (s, C-1′), 170.9 (s, C-4′), 157.8 (s, C-2), 147.1 (s, C-16), 146.0 (s, C-15), 136.9 (s, C-12), 125.1 (s, C-13), 112.6 (d, C-14), 104.3 (d, C-17), 100.9 (t, C-18), 99.9 (d, C-1), 74.9 (s, C-2′), 74.6 (d, C-3), 70.7 (s, C-5), 67.4 (d, C-11), 57.3 (q, C-19), 56.3 (t, C-10), 55.5 (d, C-4), 53.7 (t, C-8), 51.7 (q, C-5′), 43.1 (t, C-3′), 42.4 (t, C-6), 38.8 (t, C-1″), 38.8 (t, C-3″), 27.7 (d, C-4″), 22.6 (q, C-6″), 22.4 (q, C-5″), 20.5 (t, C-2″), 20.4 (t, C-7); HRFABMS (positive) m/z $[M + H]^+$ 546.2693 (calcd for $C_{29}H_{40}NO_9$: 546.2703); FABMS (positive) m/z $[M + H]^+$ 546 (55), $[M + H-H_2O]^+$ 528 (21), 314 (100) and 296 (64).

11β-Hydroxyhomodeoxyharringtonine (2): Oil; $[\alpha]^{25}_D$ −153° (c 0.10, MeOH); UV (MeOH) λ max (log ϵ) 290 (3.53) nm; IR (KBr) ν max 3370 br (OH), 2953, 2926, 2869, 2804 (CH, aliphatic), 1735 (C=O, ester), 1649, 1505, 1489, 1458, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.08 (1H, s, H-17), 6.51 (1H, s, H-14), 5.91 (1H,d, J = 1.5 Hz, H-18b), 5.87 (1H,d, J = 1.5 Hz, H-18a), 5.77 (1H,d, J = 8.1 Hz, H-3), 4.88 (1H, ddd, J = 10.8, 10.5, 7.5 Hz, H-11α), 4.75 (1H, s, H-1), 4.20 (1H, br d, J = 10.8 Hz, OH-11β), 3.68 (3H, s, Me-19), 3.68 (3H, s, Me-5′), 3.57 (1H, d, J = 8.1 Hz, H-4), 3.32 (1H, dd, J = 14.5,-10.5 Hz, H-10β), 3.24 (1H, dd, J = 14.5, 7.5 Hz, H-10α), 2.92 (1H, d, J = 16.5 Hz, H-3′b), 2.90 (1H, m, H-8β), 2.86 (1H, m, H-8α), 2.53 (1H, d, J = 16.5 Hz, H-3′a), 2.03 (1H, m, H-6β), 1.86 (1H, m, H-6α), 1.76 (1H, m, H-7α), 1.68 (1H, m, H-7β), 1.36 (1H, m, H-4″), 0.85 − 0.95 (6H, m, H-1″a, -1″b, -2″a, -2″b, -3″a, and -3″b), 0.81 (3H, d, J = 6.5 Hz, Me-6″), 0.79 (3H, d, J = 6.5 Hz, Me-5″); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.5 (s, C-1′), 172.6 (s, C-4′), 157.1 (s, C-2), 147.2 (s, C-16), 146.7 (s, C-15), 137.4 (s, C-12), 124.3 (s, C-13), 112.5 (d, C-17), 112.1 (d, C-14), 105.5 (d, C-1), 101.1 (t, C-18), 76.2 (s, C-2′), 76.0 (d, C-3), 73.2 (s, C-5), 72.3 (d, C-11), 58.0 (d, C-4), 57.2 (q, C-19), 52.0 (q, C-5′), 49.8 (t, C-8), 47.9 (t, C-10), 41.5 (t, C-3′), 39.1 (t, C-6), 38.6 (t, C-3″), 38.2 (t, C-1″), 27.2 (d, C-4″), 23.2 (t, C-7), 22.6 (q, C-6″), 22.4 (q, C-5″), 20.3 (t, C-2″); HRFABMS (positive) m/z $[M + H]^+$ 546.2691 (calcd for $C_{29}H_{40}NO_9$: 546.2703); FABMS (positive) m/z $[M + H]^+$ 546 (100), $[M + H - H_2O]^+$ 546 (67), 314 (65), and 296 (50).

11β-Hydroxydeoxyharringtonine (3): Oil; $[\alpha]^{25}_D$ −77° (c 0.085, MeOH); UV (MeOH) λ max (log ϵ) 290 (3.30); IR (KBr) ν max 3380 br (OH), 2953, 2870 (CH, aliphatic), 1736 (C=O, ester), 1649, 1506, 1490, 1458, 1438 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.07 (1H, s, H-17), 6.52 (1H, s, H-14), 5.92 (1H, d, J = 1.5 Hz, H-18b), 5.86 (1H, d, J = 1.5 Hz, H-18a), 5.78 (1H, d, J = 8.1 Hz, H-3), 4.88 (1H, ddd, J = 11.5, 10.5, 7.5 Hz, H-11α), 4.75 (1H, s, H-1), 4.16 (1H, br d, J = 11.5 Hz, OH-11β), 3.68 (3H, s, Me-19), 3.68 (3H, s, Me-5′), 3.57 (1H, d, J = 8.1 Hz, H-4), 3.32 (1H, dd, J = 14.5, 10.5 Hz, H-10β), 3.25 (1H, dd, J = 14.5, 7.5 Hz, H-10α), 2.91 (1H, m, H-8β), 2.91 (1H, d, J = 16.5 Hz, H-3′b), 2.87 (1H, m, H-8α), 2.53 (1H, d, J = 16.5 Hz, H-3′a), 2.03 (1H, m, H-6β), 1.87 (1H, m, H-6α), 1.77 (1H, m, H-7α), 1.68 (1H, m, H-7β), 1.27 (1H, m, H-3″), 1.21 (2H, m, H-1″ and -1″b), 0.87 (1H, m, H-2″b), 0.75 (3H, d, J = 6.5 Hz, Me-4″), 0.75 (3H, d, J = 6.5 Hz, H-5″), 0.73 (1H, m, H-2″a); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (s, C-1′), 172.6 (s, C-4′), 157.1 (s, C-2), 147.2 (s, C-15), 147.2 (s, C-16), 137.4 (s, C-12), 124.2 (s, C-13), 112.5 (d, C-17), 112.1 (d, C-14), 105.5 (d, C-1), 101.1 (t, C-18), 76.3 (s, C-2′), 76.0 (d, C-3), 73.2 (s, C-5), 72.3 (d, C-11), 58.0 (d, C-4), 57.2 (q, C-19), 51.9 (q, C-5′), 49.8 (t, C-8), 47.8 (t,

C-10), 41.6 (t, C-3′), 39.1 (t, C-6), 36.2 (t, C-1″), 31.3 (t, C-2″), 27.9 (d, C-3″), 23.3 (t, C-7), 22.3 (q, C-5″), 22.2 (q, C-4″); HRFABMS (positive) m/z $[M + H]^+$ 532.2520 (calcd for $C_{28}H_{38}NO_9$: 532.2547); FABMS (positive) m/z $[M + H]^+$ 532 (100), $[M + H - H_2O]^+$ 514 (86), 314 (35), and 296 (30).

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