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# A NEW TRIMERIC HYDROLYZABLE TANNIN, OENOTHERIN $T_2$, ISOLATED FROM AERIAL PARTS OF *OENOTHERA TETRAPTERA* CAV. †

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**Abstract –** A new hydrolyzable tannin, oenotherin $T_2$, was isolated from the aerial parts of *Oenothera tetraptera* Cav., together with 15 known polyphenolic compounds. The trimeric structure of oenotherin $T_2$ was elucidated based on spectroscopic data and chemical correlation with oenotherin $T_1$.

## INTRODUCTION

Plants of *Oenothera* species (Onagraceae) produce oligomeric hydrolyzable tannins with unique macrocyclic structures, such as oenotheins A (**1**)[1] and B (**2**).[2] These tannins were first isolated as the major constituents of *Oenothera erythrosepala* Borbas and *O. biennis* L., and were later found in species of Lythraceae.[1,2] We then isolated oenotherin $T_1$ (**3**), structurally related to **1**, from the aerial parts of *O. tetraptera* Cav.[3] This compound was also obtained as a product of callus tissues induced from a leaf of *O. laciniata* Hill.[3] Among the hydrolyzable tannins examined, oligomeric ones with macrocyclic structures showed potent antitumor effects.[4,5] These tannins also showed antiviral effects on herpes simplex virus (HSV)[6] and human immunodeficiency virus (HIV).[7,8] Thus, we further investigated on the constituents of *Oenothera* species and isolated an additional trimeric hydrolyzable tannin named oenotherin $T_2$ (**4**) from *O. tetraptera*. This report describes the elucidation of the structure of this trimeric tannin and the isolation of the accompanied known polyphenolics.

## RESULTS AND DISCUSSION

### Isolation of polyphenolic compounds

Dried leaves and stems of *O. tetraptera* were homogenized in 70% acetone, and the concentrated filtrate

from the homogenate was fractionated by Diaion HP-20 column chromatography.[3] The eluate containing 40% MeOH from the column was purified by column chromatography on Toyopearl HW-40, MCI-gel CHP-20, and ODS-gel, and also by preparative HPLC, to yield the new compound, oenotherin $T_2$ (**4**), as well as 15 known polyphenolic compounds: (+)-catechin,[9] quercetin 3-*O*-β-D-glucuronide,[10] myricetin 3-*O*-β-D-glucuronide,[11] 1,2,6-tri-*O*-galloyl-β-D-glucose,[12,13] gemin D,[14] tellimagrandin I,[15,16] tellimagrandin II,[15,16] geraniin,[17] heterophylliin A,[18] oenotherin $T_1$ (**3**),[3] oenothein A (**1**),[1] oenothein B (**2**),[2] woodfordin E (**5**),[19] woodfordin F (**6**),[19] and woodfordin I (**7**).[19]

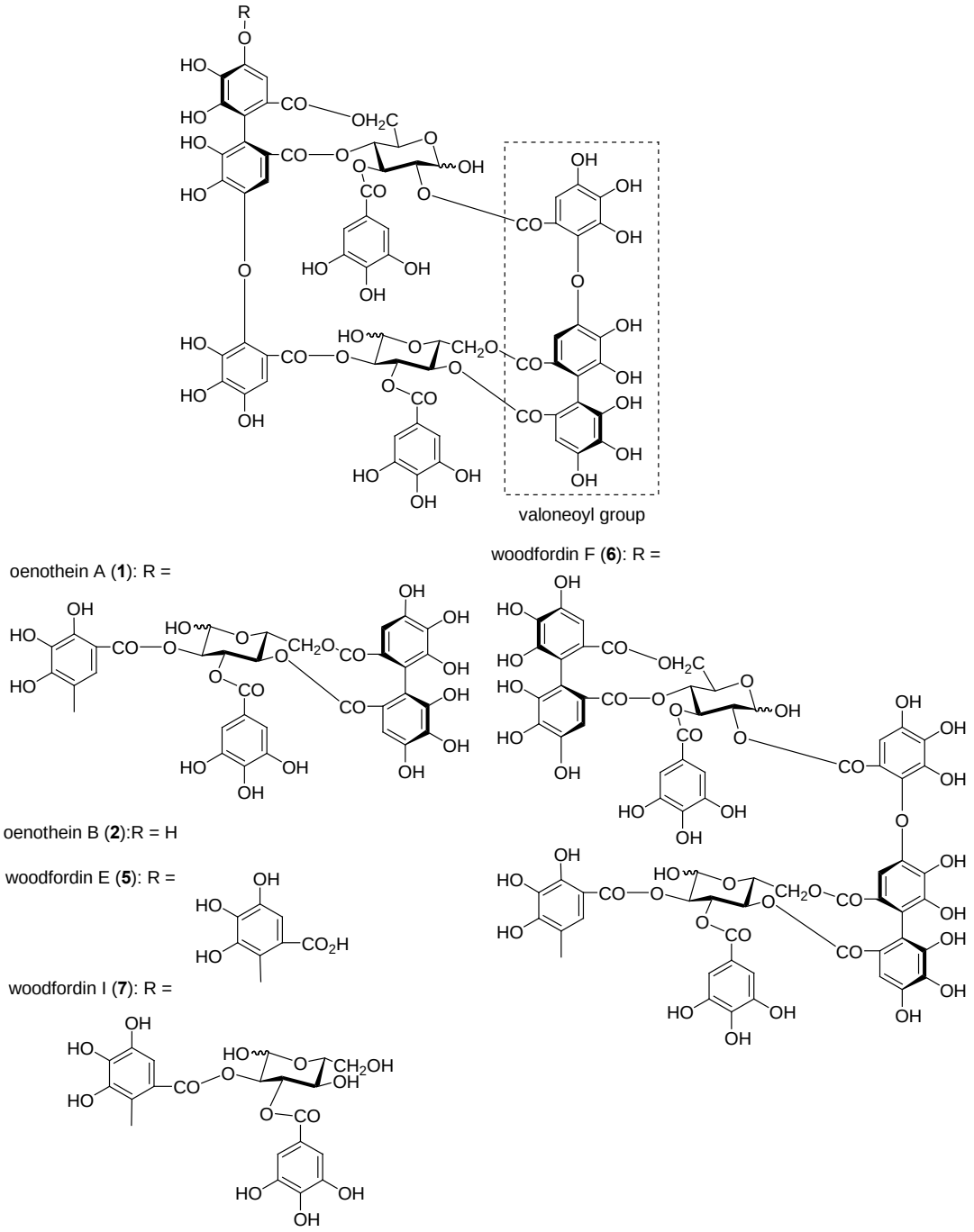
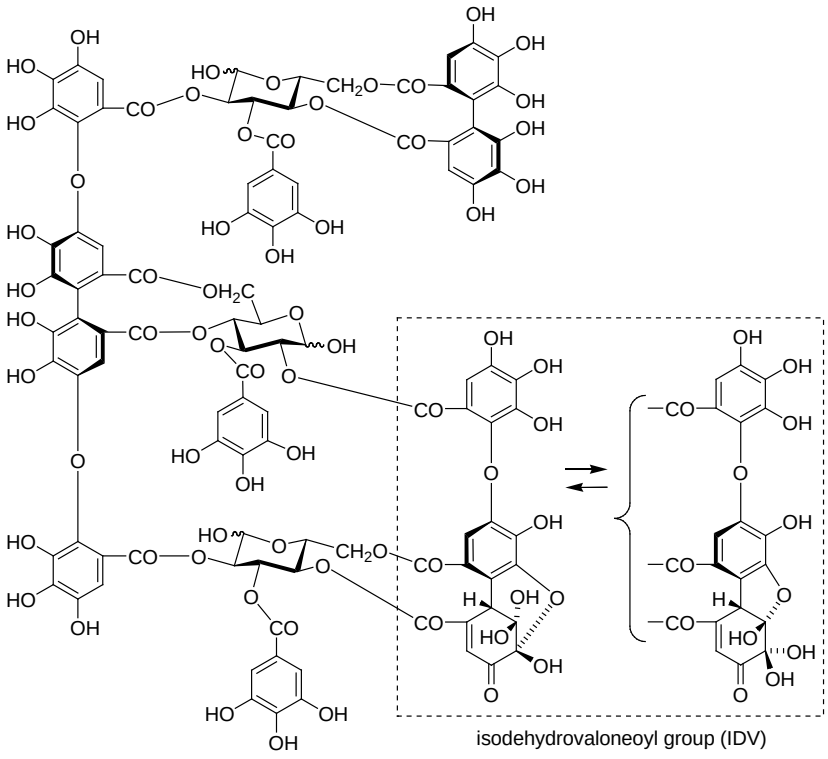



**Figure 1.** Structures of known oligomeric hydrolyzable tannins isolated from the aerial part of *Oenothera tetraptera*.




**3**

**Figure 2**. Structure of oenotherin $T_1$ (**3**), previously isolated from the aerial part of *Oenothera tetraptera*.

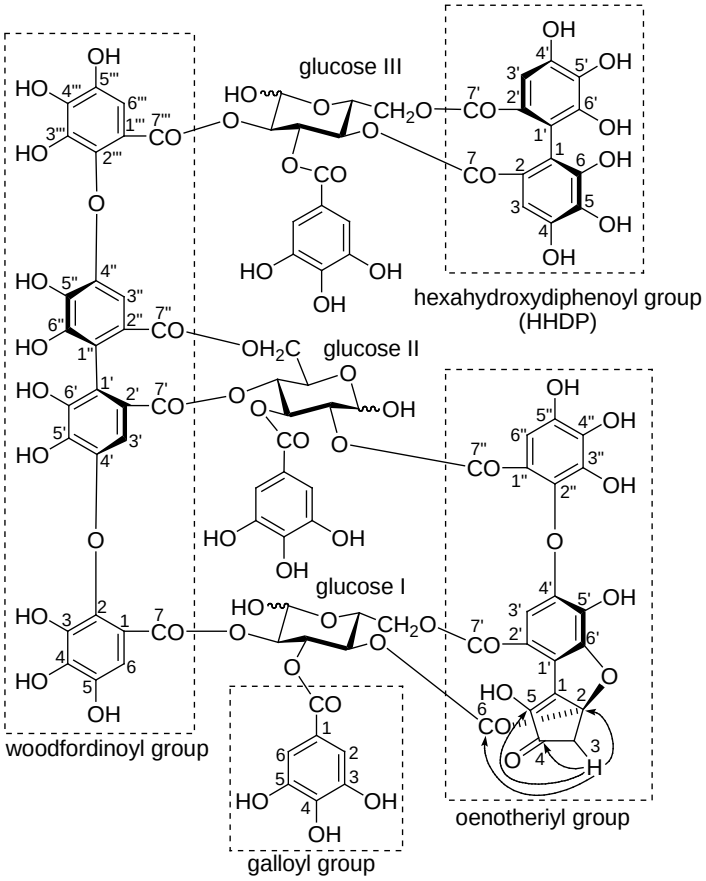
**Structure of oenotherin $T_2$**

Oenotherin $T_2$ (**4**) was obtained as a pale yellow amorphous powder. The trimeric molecular formula, $C_{101}H_{70}O_{65}$, was indicated by the $[M + NH_4]^+$ ion peak at *m*/*z* 2340 in the electrospray-ionization (ESI)-MS. The $^1$H-NMR spectrum of **4** (in acetone-$d_6$ + $D_2O$) was complicated by the appearance of four sets of signals due to the α,β-anomerization of the glucose cores. The spectrum showed signals from eight aromatic protons [δ 5.91–6.20 (2H), 6.34–6.41 (1H), 6.46–6.48 (1H), 6.59–6.66 (1H), 7.00–7.04 (1H), 7.23–7.28 (2H in total)] in addition to the protons of three galloyl groups [δ 6.92–6.98 (2H), 7.03–7.06 (2H), 7.16–7.19 (2H in total)]. The spectrum also displayed glucose protons, which overlapped heavily with each other, and also characteristic doublets of methylene protons [δ 2.84, 2.86, 2.88, (1H), 3.05, 3.12, 3.29, 3.30 (1H in total), oenotheriyl H-3] other than the glucose protons in the aliphatic region.

The presence of three glucose cores was indicated by the anomeric protons at δ 6.03, 6.00 (glucose-I, α-anomer), 4.28, 4.26 (glucose-II, β-anomer), 5.42, 5.31 (glucose III, α-anomer), 5.05, and 4.98 (glucose III, β-anomer), which were correlated with the anomeric carbons at δ 91.2 (glucose-I, α-anomer), 96.9 (glucose-II, β-anomer), 90.8, 90.6 (glucose III, α-anomer), 94.9, and 94.8 (glucose III, β-anomer), in the

$^{1}$H-$^{13}$C heteronuclear single-quantum correlation (HSQC) spectrum.

Combined with the $^{1}$H-NMR spectral data, the presence of three galloyl groups, one hexahydroxydiphenoyl (HHDP), and one woodfordinoyl group in **4** was indicated by the $^{13}$C-NMR data (see experimental section). Although the $^{13}$C-NMR spectrum of oenotherin $T_2$ (**4**) was similar to that of oenothein A (**1**),[1] signals attributable to a new acyl group (named the oenotheriyl group) instead of those of the valoneoyl group in **1** were observed in the spectrum of **4** as follows: an oxygen-bearing quaternary carbon (δ 76.4–76.9, oenotheriyl C-2), a conjugated quaternary carbon (δ 128.3, 128.5, oenotheriyl C-2'), an oxygenated aromatic carbon (δ 147.8, oenotheriyl C-5), an ester carbonyl carbon (δ 171.5–171.7, oenotheriyl C-6), and a conjugated carbonyl carbon (δ 194.1–194.4, oenotheriyl C-4).

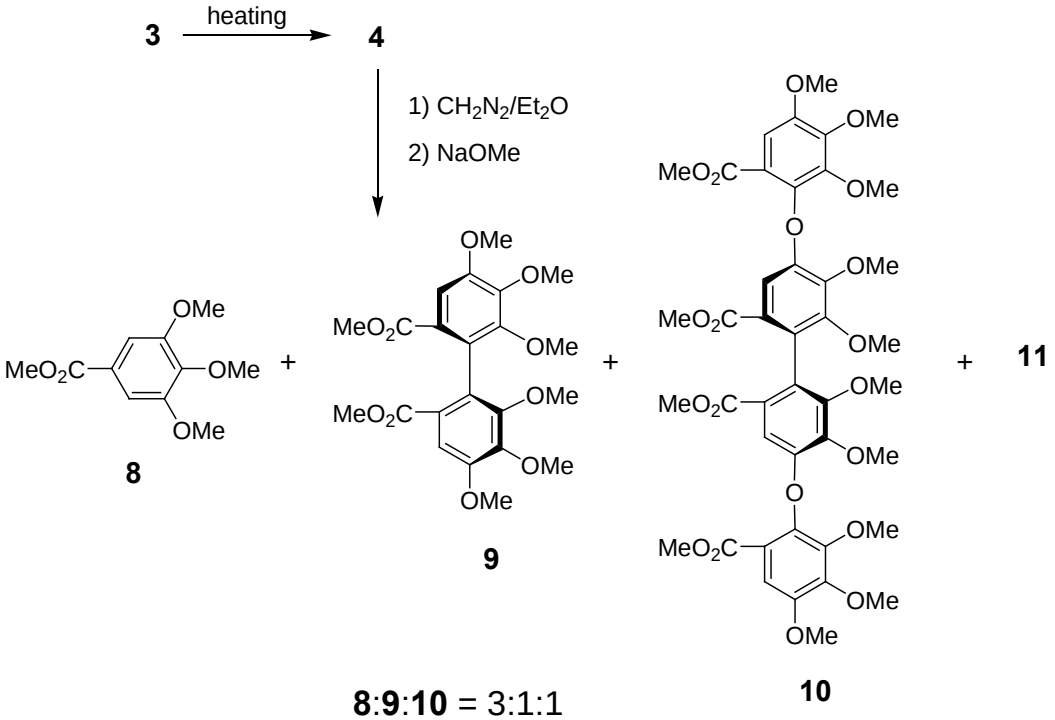



**4**

**Figure 3.** Structure of oenotherin $T_2$ (**4**) and important HMBC correlations (H→C) observed for **4**.

The heteronuclear multiple-bond correlation (HMBC) spectrum of **4** revealed the correlations of oenotheriyl H-3 with C-2, C-4, C-5, and C-6 (Figure 3). These correlations, in combination with MS data, suggested that the oenotheriyl group possesses a structure with a five-membered ring, as shown in formula **4**.

Methylation of oenotherin $T_2$ (**4**) with diazomethane and subsequent methanolysis gave methyl tri-*O*-methylgallate (**8**), dimethyl hexamethoxydiphenate (**9**), tetramethyl deca-*O*-methylwoodfordinate (**10**), and a product derived from the new acyl group (**11**). The production of **8**, **9**, and **10** from **4** was compared to that of an analogous treatment of oenothein A (**1**),[3] indicating a molar ratio of 3:1:1 for **8**:**9**:**10** (Scheme 1). The strong positive Cotton effects at $[\theta]_{238}$ +1.77 × $10^5$ and $[\theta]_{219}$ +3.18 × $10^5$ in the CD spectrum of **4** suggested the *S*-configuration of the HHDP and woodfordinoyl groups.[20]




**Scheme 1.** Conversion from **3** to **4** and methylation of **4** followed by methanolysis to give **8**, **9**, **10**, and **11**.

The structure of **11** was further investigated. The high resolution ESI-MS of **11** indicated its molecular formula, $C_{28}H_{28}O_{14}$, based on the $[M + H]^+$ ion peak. The $^1$H-NMR spectrum of **11** (in acetone-$d_6$) showed two aromatic singlets [δ 7.39 (H-6”), 7.54 (H-3’)], eight 3H singlets arising from methoxyl groups [δ 3.55 (OC$\underline{H}_3$ at C-7’), 3.56 (OC$\underline{H}_3$ at C-7”), 3.57, 3.67 (OC$\underline{H}_3$ at C5’, C-3”), 3.77 (OC$\underline{H}_3$ at C-6), 3.88 (OC$\underline{H}_3$ at C-4”), (3.95 OC$\underline{H}_3$ at C-5”), 4.14 (OC$\underline{H}_3$ at C-5)], and a pair of geminal protons [δ 2.93, 3.17 (each 1H, d, $J$ = 17.5 Hz, H-3)]. The $^{13}$C-NMR spectrum showed a conjugated carbonyl carbon (δ 191.9, C-4), three ester carbonyl carbons [δ 166.3 (C-7’), 167.3 (C-7”), 169.3 (C-6)], eight oxygenated aromatic carbons [δ 137.9 (C-5), 140.2 (C-2”), 141.1 (C-4’), 146.4 (C-4”), 147.8, 152.2 (C-5’, C-3”), 150.3 (C-6’), 153.5 (C-5”)], four quaternary aromatic carbons [δ 125.2, 126.1, 126.4 (C-1, C-1’, C-2’),

130.6 (C-1")], and an oxygen-bearing quaternary carbon [δ 76.1 (C-2)], in addition to two aromatic methine carbons [δ 109.9 (C-6"), 114.1 (C-3')], eight methoxy carbons [δ 51.9 (O<u>C</u>H$_3$ at C-7'), 52.0 (O<u>C</u>H$_3$ at C-7"), 54.1 (O<u>C</u>H$_3$ at C-6), 56.3 (O<u>C</u>H$_3$ at C-5"), 59.1 (O<u>C</u>H$_3$ at C-5), 60.68, 60.74 (O<u>C</u>H$_3$ at C-5', C-3"), 60.9 (O<u>C</u>H$_3$ at C-4")], and a methylene carbon [δ 44.3 (C-3)]. The methoxy protons were correlated with three ester carbonyl carbons and five oxygenated aromatic carbons on the HMBC spectrum, as shown in Figure 4(a). HMBC correlations were also observed for H-3 with C-2, C-4, C-5, and C-6'. The correlation H3/C-6' via four bonds indicated the presence of an ether linkage between C-2 and C-6'. This linkage was consistent with the molecular formula provided by the ESI-MS. Structure **11** for the new methylated acyl group was therefore assigned.

The CD spectrum of **11** showed a negative couplet at around 280 nm ($[\theta]_{307}$ −1.09 × 10$^5$, $[\theta]_{264}$ +4.13 × 10$^4$), corresponding to the *S*-configuration at C-2. This couplet is attributable to the helicity between the conjugated carbonyl system on the five-membered ring and the phenyl group, as shown in Figure 4(b).

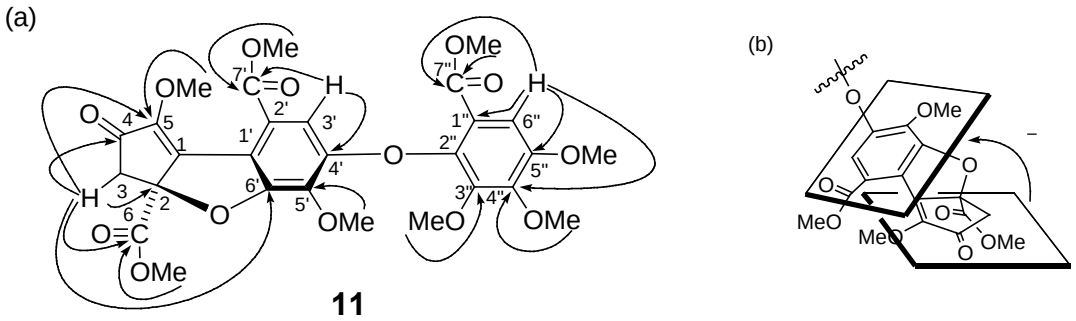
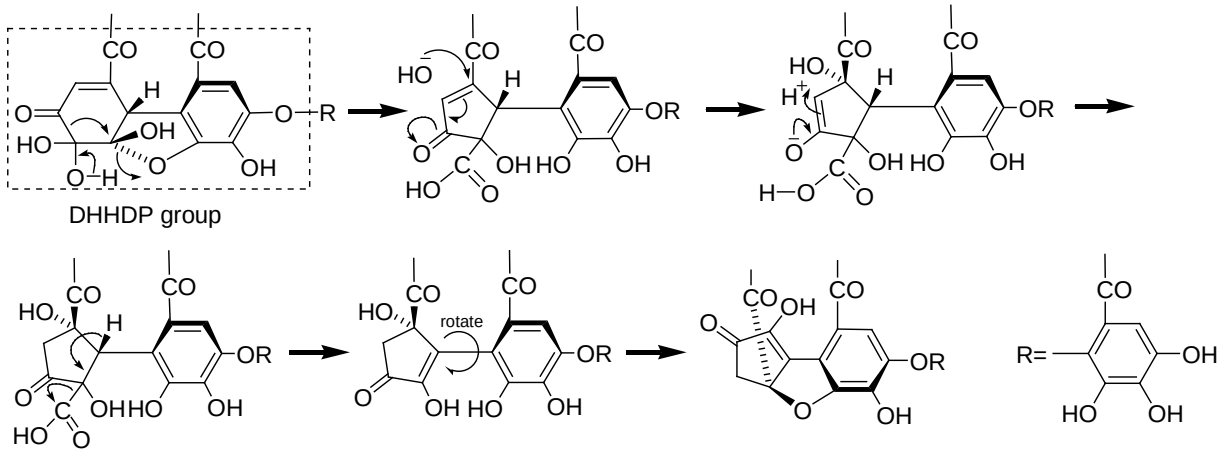



**Figure 4.** Structure of **11**.

(a) The HMBC (H→C) correlations observed for **11**.
(b) The spatial relationship of the conjugated carbonyl system on the five-membered ring and the phenyl group.




**Scheme 2.** A possible pathway of oenotheriyl group formation from IDV.

Oenotherin $T_1$ (**3**) is a trimeric hydrolyzable tannin having the isodehyrovaloneoyl group (IDV), in which a galloyl group and a dehydro-HHDP (DHHDP) group are linked via an ether oxygen (Figure 2). Heating a solution of oenotherin $T_1$ (**3**) gave oenotherin $T_2$ (**4**) (Scheme 1). The conversion of oenotherin $T_1$ (**3**) to oenotherin $T_2$ (**4**) may be explained by oxidative cleavage of the cyclohexene ring followed by a rearrangement, as shown in Scheme 2. Since **3** is abundant in the aerial parts of *O. tetraptera*, **4** might be formed from **3** in plant tissues.

Hydrolyzable tannins with an acyl group having analogous five-membered ring structures, such as repandinins A and B were previously reported,[21,22] and these structures were assumed to be formed via an oxidative change of the DHHDP group.[23]

## EXPERIMENTAL

**General procedures.** $^1$H- and $^{13}$C-NMR spectra were measured in acetone-$d_6$ on a Varian INOVA AS600 spectrometer. Chemical shifts are given in δ (ppm) values relative to that of the solvent signals of acetone-$d_6$ ($\delta_H$ 2.04; $\delta_C$ 29.8) on a tetramethylsilane scale. ESI-MS were recorded using a Micromass AutoSpec OA-Tof mass spectrometer with a solvent of 50% MeOH, 0.1% $AcONH_4$. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter, CD spectra were recorded on a JASCO J-720 spectrophotometer, and elemental analysis was performed on a Yanaco CHN recorder MT-5.

**Extraction and isolation.** The *O. tetraptera* plants used in this experiment were cultivated in the medicinal botanical garden of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences. Dried leaves and stems (245 g) of *O. tetraptera* were extracted with 70% acetone, and the extract was subjected to column chromatography using Diaion HP-20 (Mitsubishi Chemical).[3] A portion (1.8 g) of the 40% MeOH eluate (14.9 g) from the column was chromatographed on a column of Toyopearl HW-40 (Tosoh) with 70% EtOH and then with EtOH–$H_2O$–acetone (9:2:1), to give (+)-catechin (2.6 mg), 1,2,6-tri-*O*-galloyl-β-D-glucose (4.0 mg), gemin D (10.1 mg), tellimagrandin I (25.2 mg), tellimagrandin II (38.0 mg), oenothein B (**2**) (105.6 mg), oenotherin $T_1$ (**3**) (101.5 mg), and oenothein A (**1**) (297.1 mg), along with a flavonoid fraction and a tannin fraction. The tannin fraction was purified on a Sep-Pak C18 cartridge (Waters) to give geraniin (4.0 mg). The flavonoid fraction was further purified on a Sep-Pak C18 cartridge and by preparative HPLC to give quercetin 3-*O*-β-D-glucuronide (3.0 mg) and myricetin 3-*O*-β-D-glucuronide (0.9 mg). In a separate experiment, the 40% MeOH eluate (5.0 g) from the Diaion HP-20 column was purified by column chromatography on Toyopearl HW-40, MCI-gel CHP-20P (Mitsubishi Chemical), and YMC-gel ODS AQ 120-S-50 (YMC) and by preparative HPLC to give 1,2,6-tri-*O*-galloyl-β-D-glucose (20.5 mg), tellimagrandin I (37.3 mg),

oenothein A (**1**) (1.07 g), oenotherin $T_2$ (**4**) (93.4 mg), woodfordin E (**5**) (23.1 mg), woodfordin I (**7**) (3.1 mg), woodfordin F (**6**) (199.9 mg), and heterophylliin A (0.8 mg).

**Oenotherin $T_2$ (4).** A pale yellow powder, $[\alpha]_D^{16}$ +68.4 (c 0.5, MeOH). ESI–MS *m/z*: 2340 $[M+NH_4]^+$. *Anal*. Calcd. for $C_{101}H_{70}O_{65}$•$16H_2O$: C, 46.5; H, 3.9%, Found: C, 46.4; H, 3.9%. UV $\lambda_{max}$ (MeOH) nm (log ε): 220 (5.84), 271 (5.53). CD (MeOH): $[\theta]_{314}$ $-7.72 \times 10^4$, $[\theta]_{279}$ $+1.26 \times 10^5$, $[\theta]_{258}$ $+2.28 \times 10^3$, $[\theta]_{238}$ $+1.77 \times 10^5$, $[\theta]_{219}$ $+3.18 \times 10^5$. $^{13}$C-NMR (150 MHz, acetone-$d_6$+$D_2O$) δ: 45.9–46.0 (oenotheriyl C-3), 63.5, 64.2–64.3, 64.9, 65.5 (glucose C-6), 66.7–66.8, 69.0, 70.9–73.0, 73.7–75.6 (glucose C-2, C-3, C-4, C-5), 76.4–76.9 (oenotheriyl C-2), 90.6–91.2 [glucose C-1(α)], 94.8–96.0 [glucose C-1(β)], 102.8, 103.7, 106.1–108.1, 109.6–110.9 (galloyl C-2, C-6, HHDP C-3, C-3', oenotheriyl C-3', C-6", woodfordinoyl C-6, C-3', C-3", C-6"'), 113.4–114.8, 115.5–116.8, 119.4–121.4 (galloyl C-1, HHDP C-1, C-1', oenotheriyl, C-1, C-1', C-1", woodfordinoyl C-1, C-1', C-1", C-1"'), 125.2–126.3 (HHDP C-2, C-2', woodfordinoyl C-2', C-2"), 128.3, 128.5 (oenotheriyl C-2'), 133.3–133.4, 135.8–137.4, 138.5–141.0, 142.8–143.4, 144.2–145.7 (galloyl C-3, C-4, C-5, HHDP C-4, C-5, C-6, C-4', C-5', C-6', oenotheriyl C-5', C-6', C-2", C-3", C-4", C-5", woodfordinoyl C-2, C-3, C-4, C-5, C-5', C-6', C-5", C-6", C-2"', C-3"', C-4"', C-5"'), 146.4–147.0 (oenotheriyl C-4', woodfordinoyl C-4', C-4"), 147.8 (oenotheriyl C-5), 164.4–165.0, 167.1–169.6 (galloyl C-7, HHDP C-7, C-7', oenotheriyl C-7', C-7", woodfordinoyl C-7, C-7', C-7", C-7"'), 171.5–171.7 (oenotheriyl C-6), 194.1, 194.3, 194.4 (oenotheriyl C-4).

**Methylation of 4 followed by methanolysis.** Compound **4** (10 mg) in EtOH (0.5 mL) was treated with $CH_2N_2$–$Et_2O$ for 1 h. After removal of the solvent, the residue was treated with 0.2% NaOMe in MeOH (0.1 mL) at rt for 6 h. The residue was partitioned between EtOAc and $H_2O$, and the solvent of the EtOAc layer was removed *in vacuo*. The residue was further treated with $CH_2N_2$–$Et_2O$. The product mixture obtained from 90 mg of **4** was combined and subjected to preparative TLC over Kieselgel $PF_{254}$ (Merck) with *n*-hexane–$CHCl_3$–acetone (6:3:1), to give **8** (18.8 mg), **9** (7.1 mg), **10** (10.3 mg) and a product mixture (1.3 mg). The mixture was purified by preparative HPLC (column, YMC-pack ODS A-303, 4.6 × 250 mm; detection, 280 nm; solvent, 58% MeOH) to give **11** (0.5 mg) as a white powder, $[\alpha]_D^{27}$ –180.1 (*c* 0.2, MeOH). ESI-MS *m/z*: 589 $[M+H]^+$, 606 $[M+NH_4]^+$, 611 $[M+Na]^+$. HRE-ESI-MS *m/z*: 589.1578 $[M+H]^+$ ($C_{28}H_{28}O_{14}$ + H, 589.1557). UV $\lambda_{max}$ (MeOH) nm (log ε): 220 (4.76), 260 (4.59), 280 (infl.). CD (MeOH): $[\theta]_{307}$ $-1.09 \times 10^5$, $[\theta]_{264}$ $+4.13 \times 10^4$, $[\theta]_{248}$ $+2.40 \times 10^3$, $[\theta]_{229}$ $+1.28 \times 10^5$. The identification of compounds **9** and **10** was based on comparisons of the $^1$H-NMR spectral data with those of authentic specimens.[3]

**Quantitative analysis of the constituent polyphenolic acids of 4.** An ethereal $CH_2N_2$ (1 mL) was added to an EtOH solution (0.1 mL) of **4** (1 mg) and the mixture was left to stand for 2 h. After removal of the solvent under a $N_2$ stream, the residue was treated with 0.2% NaOMe in MeOH (1 mL) overnight at rt. The reaction mixture was then acidified with 10% HCl and the solvent was removed by evaporation *in vacuo*. The reaction mixture was analyzed by HPLC [column, YMC-pack SIL A-003, 4.6 × 250 mm; solvent, *n*-hexane–EtOAc (2:1)] to show the presence of **8** ($R_t$ 3.7 min), **9** ($R_t$ 7.3 min), and **10** ($R_t$ 29.1 min) in the mixture. The amounts of the products were estimated based on the comparison of the peak areas of **8**, **9** and **10** obtained by an analogous treatment of oenothein A (**1**).

**Conversion of 3 to 4.** An aqueous solution (2 mL) of **3** (20 mg) was heated in a boiling water bath for 2.5 h. The solution was then passed through a Sep-Pak C18 cartridge. The adsorbed materials were eluted successively with $H_2O$, followed by 10%, 20%, 30%, and 40% MeOH. The eluates of 20% and 30% MeOH were combined and purified by preparative HPLC [column, YMC-pack ODS A-324, 10 × 300 mm; solvent, 0.01 M $H_3PO_4$–0.01 M $KH_2PO_4$–EtOH–EtOAc (43:43:9:5)] to give **4** (1.7 mg), which was identified based on co-HPLC, $[\alpha]_D$ (+64.5, MeOH) and the $^1$H-NMR spectral comparison.

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