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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

† Dedicated to the memory of Dr. John Daly, National Institutes of Health scientist emeritus.

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]

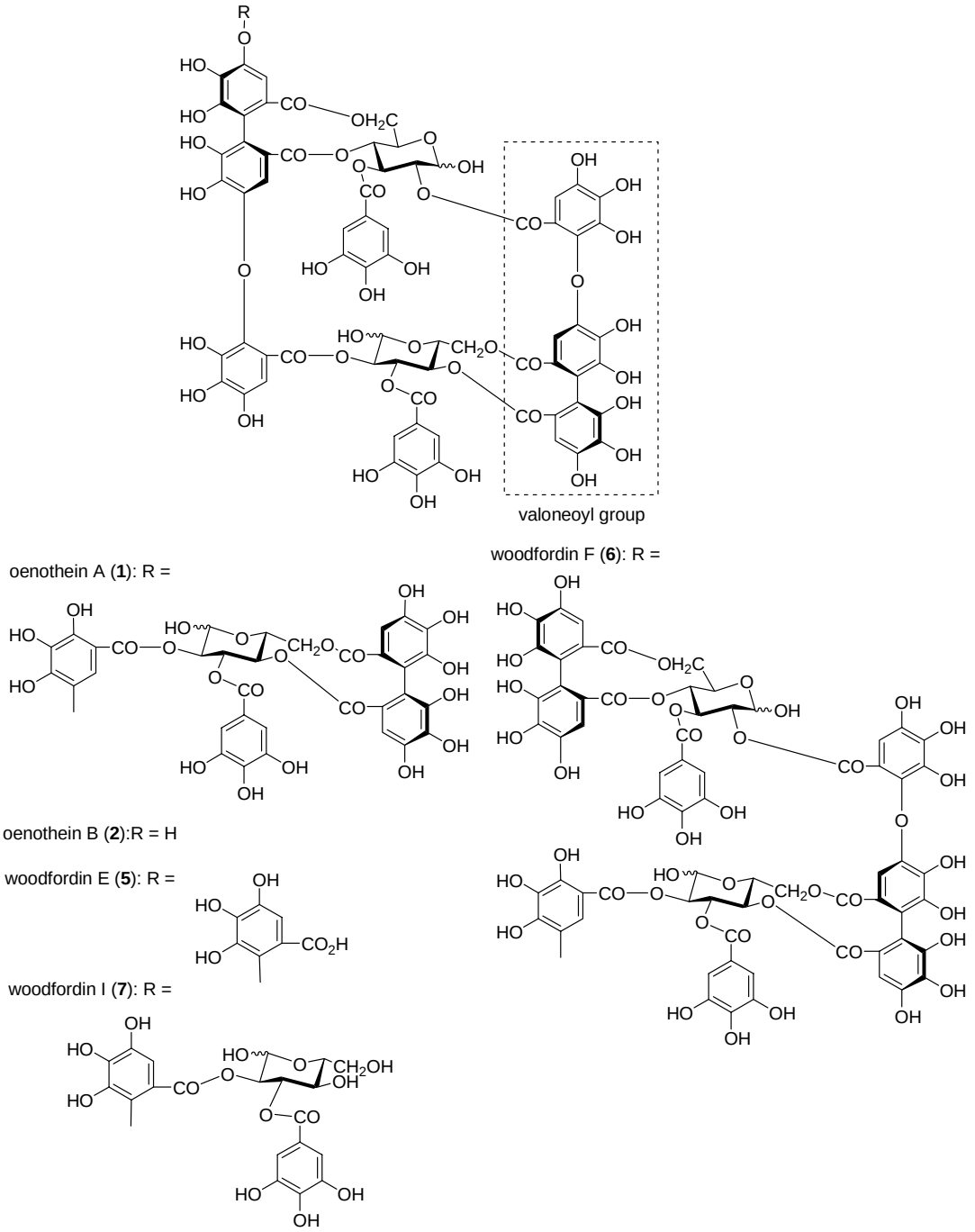

Figure 1. Structures of known oligomeric hydrolyzable tannins isolated from the aerial part of *Oenothera tetraptera*.

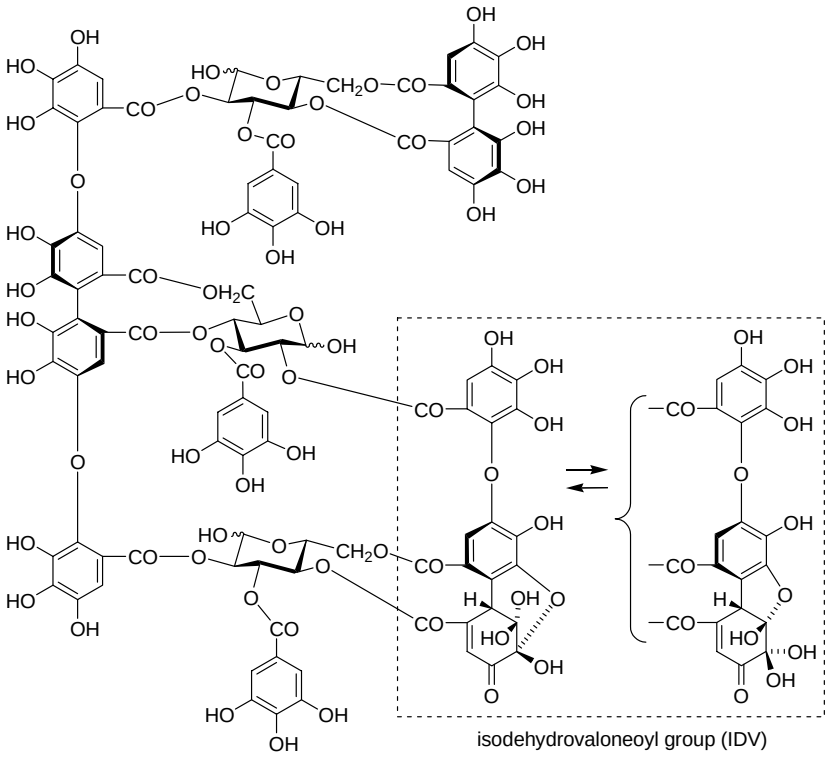

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Figure 2. Structure of oenotherin T_1 (**3**), previously isolated from the aerial part of *Oenothera tetraptera*.

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).

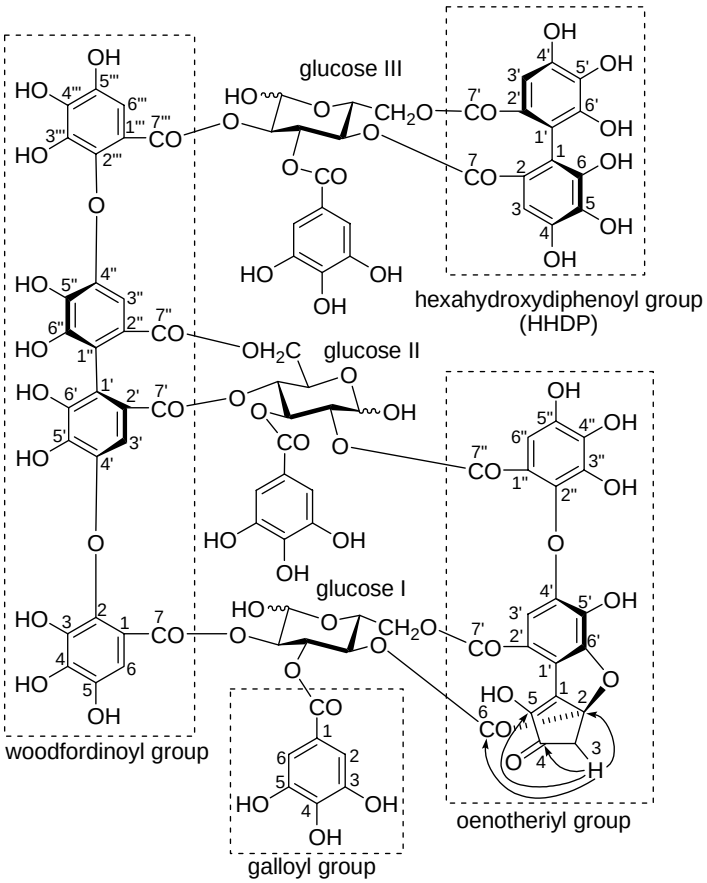

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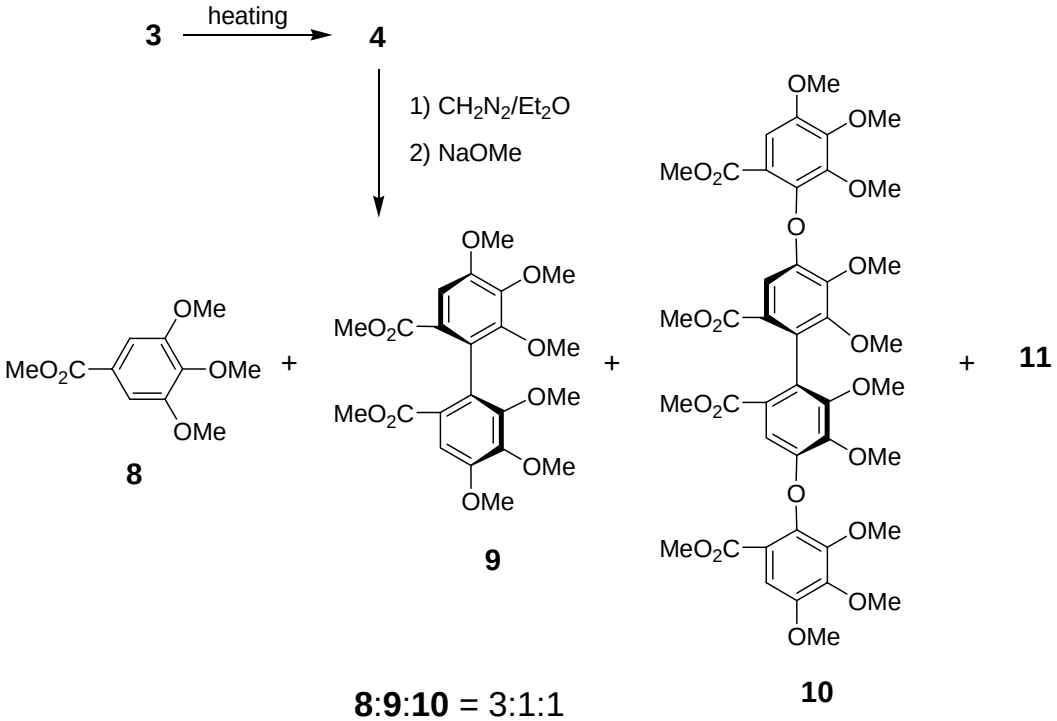
Figure 3. Structure of oenotherin T_2 (**4**) and important HMBC correlations (H→C) observed for **4**.

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, $[\theta]_{264}$ $+4.13 \times 10^4$), 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).

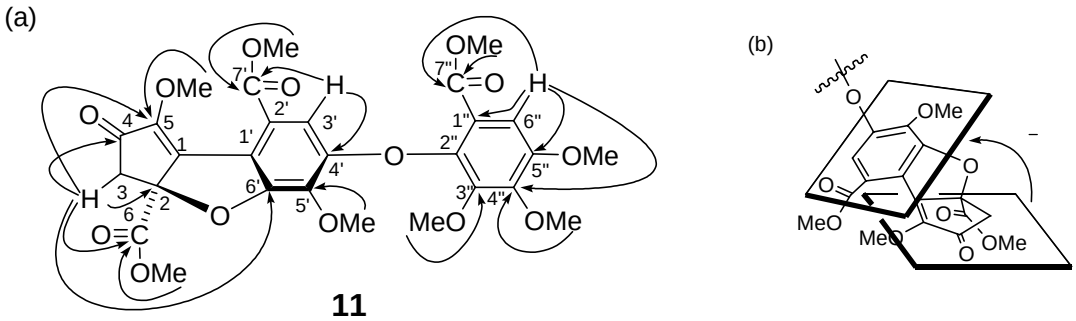
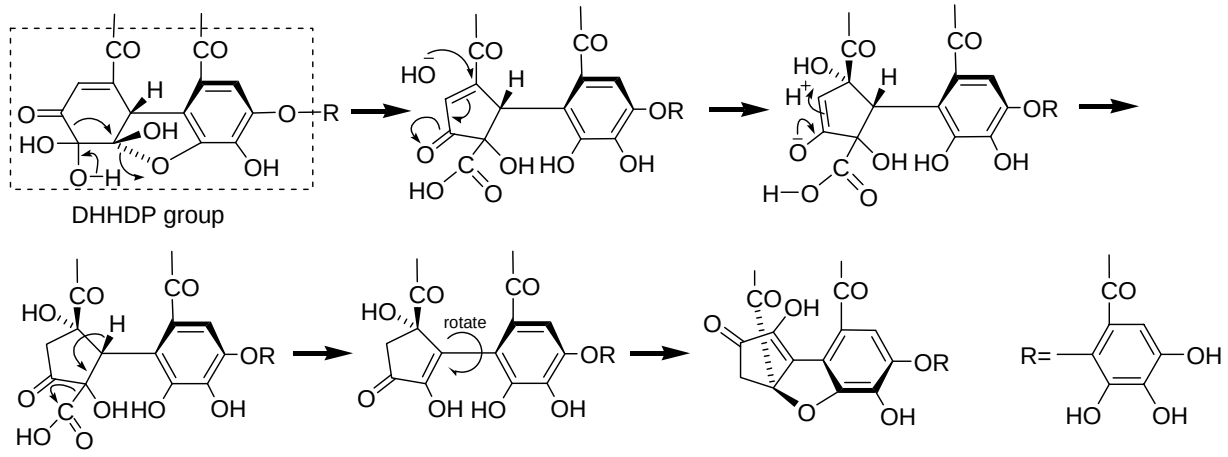


Figure 4. Structure of **11**.

(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 (δ_H 2.04; δ_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 λ_{max} (MeOH) nm (log ε): 220 (5.84), 271 (5.53). CD (MeOH): $[\theta]_{314}$ -7.72×10^4, $[\theta]_{279}$ $+1.26 \times 10^5$, $[\theta]_{258}$ $+2.28 \times 10^3$, $[\theta]_{238}$ $+1.77 \times 10^5$, $[\theta]_{219}$ $+3.18 \times 10^5$. ^{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 λ_{max} (MeOH) nm (log ε): 220 (4.76), 260 (4.59), 280 (infl.). CD (MeOH): $[\theta]_{307}$ -1.09×10^5, $[\theta]_{264}$ $+4.13 \times 10^4$, $[\theta]_{248}$ $+2.40 \times 10^3$, $[\theta]_{229}$ $+1.28 \times 10^5$. 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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