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DETERMINATION OF ABSOLUTE STRUCTURE OF (+)-DAVIDIOL A

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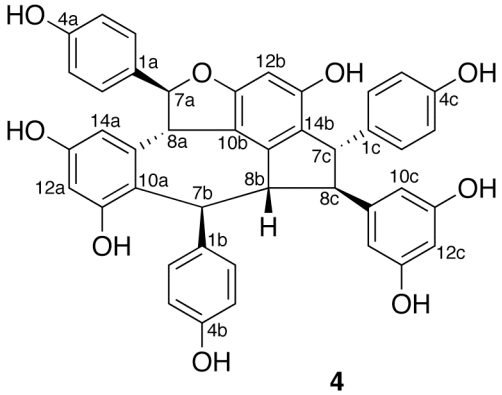
Abstract – The absolute configurations of stilbenetrimers, (+)-davidiol A and (–)-davidiol A were determined on the basis of the enzymatic chemical transformations.

INTRODUCTION

Many oligostilbenes with various types of the molecular skeleton have been isolated mainly from the following families: Vitaceae, Dipterocarpaceae, Leguminosae, Cyperaceae, Gnetaceae, and Umbelliferae.[1] But the oligostilbenes isolated from the Vitaceaeous plants are chemically different from those from other families as shown in case of ε-viniferin (a resveratrol-dimer) and hopeaphenol (a resveratrol-tetramer). (+)-ε-Viniferin (**1**) and (+)-hopeaphenol (**2**) were isolated only from Vitaceaeous plants,[2] while the enantiomers of these compounds were from other families. So Vitaceaeous plants are estimated to have a specific biosynthetic pathway to generate oligostilbenes. As we described previously,[3] ε-viniferin, which would be synthesized enzymatically in plant tissues, seems to be a biogenetically important precursor of many oligostilbenes in plants. But we can propose several patterns of oxidative dimerization of resveratrol (**3**) as shown in our previous report,[4] and a characteristic type of compound is supposed to be obtained in each pathway.



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On the other hand, we previously reported lignan glycosides,[5] oligostilbenes and flavonoids[6] as the constituents of *Vitis thunbergii*, a wild Vitaceaeous plant mainly distributed in Japan, Korea and China. Recently, Chen *et al.* reported on the structures and biological activity of oligostilbenes from the roots of *V. thunbergii*.[7] In the course of our further exploration of the compounds contained in the plant, we isolated a stilbenetrimer, (+)-davidiol A (**4**) from the aerial part of *V. thunbergii*. This is the first report of (+)-davidiol A and the structure including the absolute configuration was deduced from the spectral data and the enzymatic transformation of resveratrol (**3**) and (+)-ε-viniferin (**1**).

RESULTS AND DISCUSSION

Isolation

The methanol extract of the aerial part of *V. thunbergii* collected in Aichi Prefecture was successively partitioned between water and ethyl acetate, and *n*-butanol to give the corresponding solubles. The ethyl acetate soluble was subjected to silica gel column chromatography using a mixture of chloroform – methanol as an eluent to give four fractions. One of the fractions eluted with the mixture of chloroform – methanol (70:30) was fractionated using repeated normal and reversed-phase silica gel, and (+)-davidiol A (**4**) was isolated. From the ethyl acetate soluble, (+)-ε-viniferin (**1**),[8] (+)-*cis*-ε-viniferin,[9] (+)-*trans*-miyabenol C,[10] (+)-*cis*-miyabenol C,[11] (–)-vitisin B,[12] (+)-hopeaphenol (2),[13] (–)-isohopeaphenol,[13] (+)-ampelopsin C,[14] and (+)-ampelopsin E[15] were also isolated. It is interesting that (+)-*trans*-miyabenol C[10] and (+)-*cis*-miyabenol C[11] were also obtained from Umbelliferaeous and Cyperaceaeous plants. This evidence demonstrated that the biogenetic pathways to generate these oligostilbenes are different by the plants.

Structure of (+)-davidiol A

(+)-Davidiol A (**4**), $[\alpha]_D$ +144.0° (*c* 0.19, MeOH) was found to have the molecular formula $C_{42}H_{32}O_9$ determined by high-resolution FABMS spectrum. The ^{1}H NMR spectrum in acetone-d_6 of **4** exhibited signals for three sets of *ortho*-coupled aromatic hydrogens at δ_H 7.20 and 6.77 (each 2H, d, J=8.5 Hz); 7.03 and 6.58 (each 2H, d, J=8.5 Hz); 6.73 and 6.59 (each 2H, d, J=8.5 Hz); one set of *meta*-coupled aromatic hydrogens at δ 6.42 and 6.54 (each 1H, br. s); one set of AX_2 type *meta*-coupled aromatic hydrogens at δ 6.42 (2H, d, J=2.2 Hz) and, 6.17 (1H, t, J=2.2 Hz), one isolated aromatic hydrogen at δ 6.00 (1H, s), one set of aliphatic hydrogens at δ 6.07 (1H, d, *J*=3.3 Hz) and 4.39 (1H, m), and four aliphatic hydrogens at δ 5.26 (1H, brs, H-7b), 4.21 (1H, d, *J*=11.3 Hz, H-8b), 2.95 (1H, dd, *J*=11.3, 9.6 Hz, H-8c), and 4.38 (1H, d, *J*=9.6 Hz, H-8c). These data, along with those of HMBC and NOESY spectra and the sign of the specific rotation, suggested that this compound should be the enantiomer of (–)-davidiol A (**5**).[16]

Absolute configuration of davidiol A

(+)-Davidiol A (**4**) would be generated by either of the pathways shown in Figure 1. In pathway **A**, resveratrol (**3**) oxidatively couples with (+)-ε-viniferin (**1**) followed by cyclization to afford (+)-davidiol A (**4**). On the other hand, pathway **B** demonstrates that two molecules of resveratrol (**3**) dimerize in the first step to give (–)-quadrangularin A (**6**),[17] and then another resveratrol (**3**) couples to (–)-quadrangularin A to form (+)-davidiol A (**4**). We have recently reported the biomimic transformation of resveratrol (**3**)

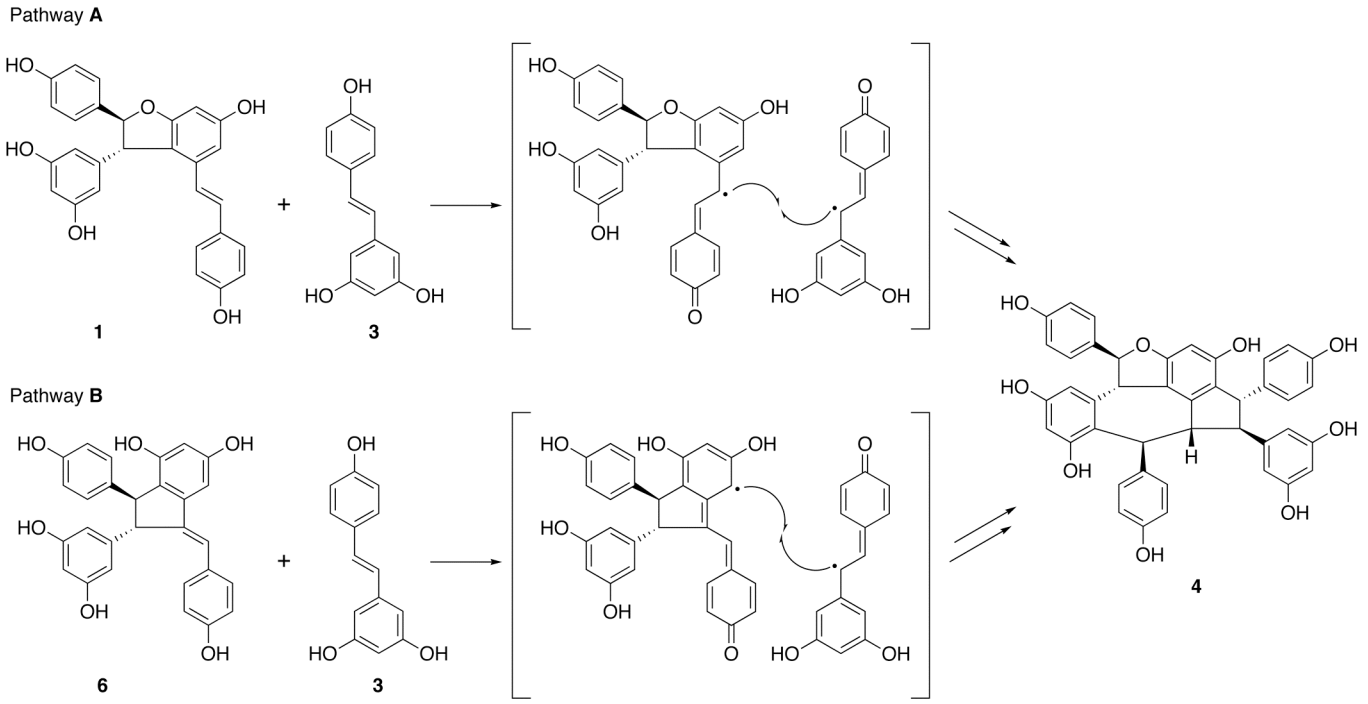

Figure 1 Possible biogenetic pathways of (+)-davidiol A (**4**) from (+)-ε-viniferin (**1**) and resveratrol (**3**).

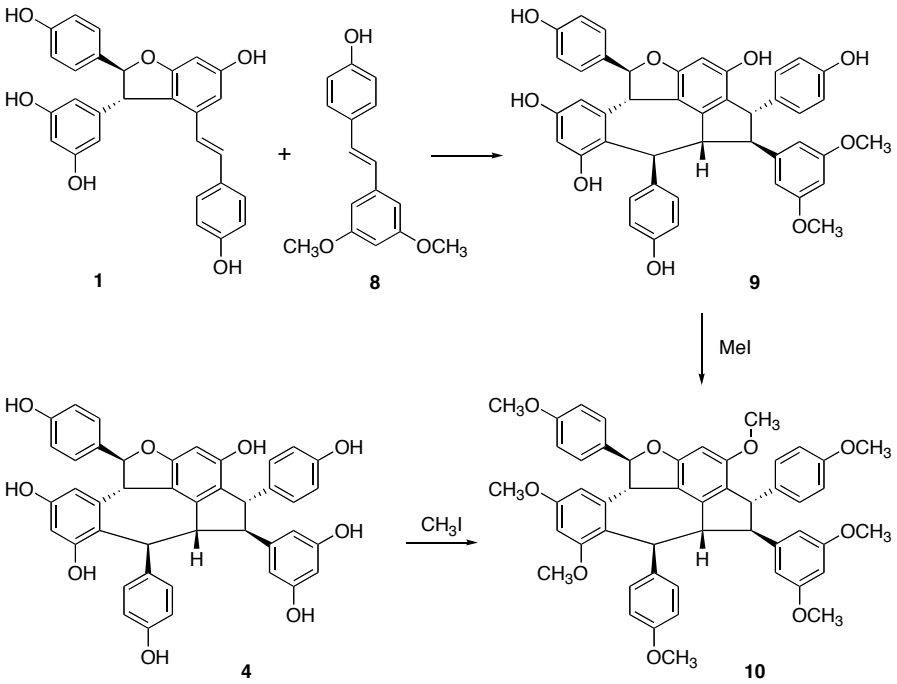

Figure 2 Confirmation of the absolute structure of (+)-davidiol A (**4**).

with several commercially available peroxidases.[4] In this study, we tried again to treat only resveratrol (**3**) with horseradish peroxidase (HRP), but we could get neither ε-viniferin, quadrangularin A, nor davidiol A just like our previous report, even though we analyzed the product precisely by using HPLC. ε-Viniferin was obtained both from Vitaceaeous and other plants, though, to the best of our knowledge, (–)-quadrangularin A (**6**) has never been detected in Vitaceaeous plants. Accordingly, pathway **A** seems to be the promising route to (+)-davidiol A (**4**). Then we treated (+)-ε-viniferin (**1**) and resveratrol (**3**) with HRP to give (+)-davidiol A (**4**) in the yield of 1.1% along with resveratrol-*trans*-dihydrodimer (**7**) (8.5%), resveratrol-*cis*-dehydrodimer (2.0%) and (+)-hopeaphenol (1.5%). The synthetic (+)-davidiol A was identical with natural (+)-davidiol A (**4**) including the optical rotation.

As mentioned above, (+)-davidiol A (**4**) was synthesized from resveratrol (**3**) and (+)-ε-viniferin (**1**), whose absolute configuration is known,[18] and its absolute configuration was estimated to be the antipode of that for (–)-davidiol A (**5**) shown in the paper by Tanaka *et al.*[16] But we further investigated an enzymatic coupling of (+)-ε-viniferin (**1**) and pterostilbene (4´-hydroxy-3,5-dimethoxystilbene) (**8**)[19] so as to confirm that (+)-davidiol A (**4**) is really generated from (+)-ε-viniferin (**1**) and resveratrol (**3**), since we could not deny perfectly that three molecules of resveratrol (**3**) were transformed to (+)-davidiol A (**4**). Prior to the coupling, pterostilbene (**8**) was synthesized by the modified route for the synthesis of resveratrol shown in our previous paper[4] using methyl 3,5-dimethoxybenzoate as the starting material. As shown in Figure 2, (+)-ε-viniferin (**1**) and pterostilbene (**7**) were treated with HRP to give dimethoxy compound (**9**) in the yield of 2.7%. This result demonstrated that pathway **A** in Figure 1 is responsible for the formation of (+)-davidiol (**4**), and the stereochemistry of the product (**9**) was regulated by that of (+)-ε-viniferin (**1**). Compound (**9**) was further methylated with methyl iodide, to give methylated davidiol A (**10**). All spectral data were identical with those of methylated davidiol A (**10**) prepared from the natural (+)-davidiol A (**4**), and thus the absolute configuration of (+)-davidiol A (**4**) was confirmed.

EXPERIMENTAL

General

UV and IR spectra were recorded on JASCO Ubest V-560 (cell length 10 mm) and FT/IR-410 spectrophotometers, respectively. Optical rotations were measured with a JASCO P-1020 polarimeter (cell length 100 mm). ^{1}H and ^{13}C NMR spectra were recorded on JEOL ALPHA-600 (^{1}H: 600 MHz and ^{13}C: 150 MHz) and JEOL ALPHA-400 (^{1}H: 400 MHz and ^{13}C: 100 MHz) spectrometers. Chemical shifts for ^{1}H and ^{13}C NMR are given in parts per million (δ) relative to solvent signal (chloroform-*d*: δ_H 7.26 and δ_C 77.0, acetone-d_6: δ_H 2.04 and δ_C 24.9, and methanol-d_4: δ_H 3.30 and δ_C 49.0) as internal standards, respectively. LR and HR FAB-MS were obtained with JEOL JMS HX-110 using

m-nitrobenzyl alcohol as matrix. Analytical TLC was performed on silica gel 60 F_{254} (Merck). Column chromatography was carried out on silica gel BW-820MH (Fuji Silysia Chemicals, Co. Ltd). ODS (Develosil ODS HG-5, ϕ20 x 250 mm, Nomura Chemical, Seto, Japan), and C-8 (Develosil C8-5, ϕ20 x 250 mm, Nomura Chemical, Seto, Japan) columns were used for preparative HPLC. Peroxidases from horseradish were from Wako Pure Chemicals, Osaka, Japan. Synthetic resveratrol (**3**)[4] and natural (+)-ε-viniferin (**1**) from the roots of *Vitis vinifera* 'Kyoho' were used for the starting material of the enzymatic transformation. All spectral data of these compounds were completely identical with those reported.[20]

Isolation of (+)-davidiol A (4)

A part of the ethyl acetate solubles (1.23 g) prepared from the methanol extract of the aerial part of *V. thunbergii* in our previous paper[5] was fractionated by silica-gel column chromatography using a mixed solvent system of chloroform – methanol (95:5 – 50:50) to give four fractions (F1 – F4). F3 (429 mg, chloroform – methanol (70:30)) was further separated by medium pressure column chromatography (MPCC) using an ODS column (Develosil Lop ODS 30/50 ϕ50 x 320 mm, Nomura Chemical, Seto, Japan) with a mixture of methanol – water (70:30 – 50:50) to give six fractions (F31 – F36). F34 (57 mg, methanol – water (60:40)) was fractionated by silica-gel column chromatography using a mixture of chloroform – methanol (85:15 – 70:30) to give three fractions (F341 – F343). F342 (35 mg, chloroform – methanol (80:20)) was purified by HPLC equipped with C-8 column by using a mixed solvent of methanol – water (4:6), and (+)-davidiol A (**4**) (2.7 mg) was obtained.

(+)-Davidiol A (4). $[\alpha]_D$ +144.0° (*c* 0.19, MeOH);[21] a brown oil; UV λ_{max} (MeOH) [nm (log ε)] 284 (3.75); IR ν_{max} (film) 3321, 1613 cm^{-1}; ^1H NMR (600 MHz, acetone-d_6) δ 7.20 (2H, d, *J*=8.5 Hz; H-2a,6a), 7.03 (2H, d, *J*=8.5 Hz; H-2b,6b), 6.77 (2H, d, *J*=8.5 Hz; H-3a,5a), 6.73 (2H, d, *J*=8.5 Hz; H-2c,6c), 6.59 (2H, d, *J*=8.5 Hz; H-3c,5c), 6.58 (2H, d, *J*=8.5 Hz; H-3b,5b), 6.54 (1H, br s; H-14a), 6.42(1H, br s; H-12a), 6.42 (2H, d, *J*=2.2 Hz; H-10c,14c), 6.17 (1H, t, *J*=2.2 Hz; H-12c), 6.07 (1H, d, *J*=3.3 Hz; H-7a), 6.00 (1H, s; H-12b), 5.26 (1H, br s; H-7b), 4.39 (1H, m; H-8a), 4.38 (1H, d, *J*=9.6 Hz; H-7c), 4.21 (1H, d, *J*=11.3 Hz; H-8b), 2.95 (1H, dd, *J*=11.3, 9.6 Hz; H-8c); ^{13}C NMR (150 MHz, acetone-d_6) δ 159.5 (C-11c,13c), 159.4 (C-11b), 158.4 (C-4b), 158.0 (C-11a), 156.9 (C-4c), 156.8 (C-13a), 155.8 (C-4a), 152.1 (C-13b), 147.1 (C-9a), 143.9 (C-9c), 143.3 (C-9b), 137.5 (C-1b), 134.4 (C-1a), 134.1 (C-1c), 129.9 (C-2c,6c), 129.6 (C-2b,6b), 128.1 (C-2a,6a), 124.2 (C-14b), 119.2 (C-10b), 118.1 (C-10a), 116.0 (C-3a,5a), 115.5 (C-3b,5b), 115.3 (C-3c,5c), 108.3 (C-10c,14c), 103.8 (C-14a), 102.1 (C-12c), 101.5 (C-12a), 95.7 (C-12b), 85.8 (C-7a), 67.5 (C-8c), 56.2 (C-7c), 51.4 (C-8b), 50.4 (C-8a), 36.5 (C-7b); HRFAB-MS: *m/z* 681.2122 $[M+H]^+$ (681.2125 calculated for $C_{42}H_{33}O_9$).

Peroxidase reaction of (+)-ε-viniferin (1) and resveratrol (3)

To a solution of (+)-ε-viniferin (**1**) (50 mg) and resveratrol (**3**) (50 mg) in 50% aqueous acetone (9 mL), a suspension of horseradish peroxidase (HRP) (0.1 mg) in 50% aqueous acetone (1 mL) was added at 25 °C. After 5 min stirring, 30% hydrogen peroxide (25 μL) was added. The reaction solution was kept stirring for 15 min, extracted with ethyl acetate, and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and evaporated. The residue was purified by column chromatography over silica gel using a mixture of chloroform – methanol (90:10 – 50:50) followed by preparative HPLC using C8 column with a mixed solvent of methanol – water (40:60) to afford (+)-davidiol A (**4**) (0.8 mg, 1.1%). $[\alpha]_D$ +135.3° (*c* 0.16, MeOH).

Resveratrol-*trans*-dihydrodimer (**7**) (8.5%), resveratrol-*cis*-dehydrodimer (2.0%), and (+)-hopeaphenol (1.5%) were also obtained, and their spectral data were identical with those reported.[13,17]

Peroxidase reaction of (+)-ε-viniferin (1) and pterostilbene (8)

Pterostilbene (**8**)[19] was synthesized in the modified manner of route for resveratrol (**3**) using methyl 3,5-dimethoxybenzoate as a starting material.[4] Peroxidase reaction of (+)-ε-viniferin (**1**) and pterostilbene (**8**) was carried out in the same manner described above using (+)-ε-viniferin (**1**) (38 mg), pterostilbene (**8**) (41 mg) and 20 μL of 30% hydrogen peroxide. The product was purified by repeated preparative HPLC using ODS column with a mixed solvent of acetonitrile – water (60:40) to give dimethoxy compound (**9**) (1.6 mg, 2.7%).

Pterostilbene (8). ^{1}H NMR (400 MHz, CD_3OD) δ 7.38 (2H, d, *J*=8.8 Hz; H-2,6), 7.05 (1H, d, *J*=16.1 Hz; H-7), 6.89 (1H, d, *J*=16.1 Hz; H-8), 6.76 (2H, d, *J*=8.8 Hz; H-3,5), 6.66 (2H, d, *J*=2.2 Hz; H-10,14), 6.34 (1H, t, *J*=2.2 Hz; H-12), 3.78 (6H, s; $-OCH_3$ x 2); ^{13}C NMR (100 MHz, CD_3OD) δ 162.4 (C-11,13), 158.5 (C-4), 141.3 (C-9), 130.3 (C-1), 130.0 (C-7), 128.9 (C-2,6), 126.8 (C-8), 116.5 (C-3,5), 107.8 (C-10,14), 100.3 (C-12), 55.7 ($-OCH_3$); FAB-MS: *m/z* 257 $[M+H]^+$.

Compound (9). $[\alpha]_D$ +153.3° (*c* 0.054, $CHCl_3$); a brown oil; UV λ_{max} (MeOH) [nm (log ε)] 284 (4.94); IR ν_{max} (film) 3357, 1609 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (2H, d, *J*=8.4 Hz; H-2a,6a), 7.01 (2H, d, *J*=8.4 Hz; H-2b,6b), 6.79 (2H, d, *J*=8.4 Hz; H-2c,6c), 6.77 (2H, d, *J*=8.4 Hz; H-3a,5a), 6.68 (2H, d, *J*=2.2 Hz; H-10c,14c), 6.61 (2H, d, *J*=8.4 Hz; H-3c,5c), 6.58 (2H, d, *J*=8.4 Hz; H-3b,5b), 6.56 (1H, d, *J*=2.4 Hz; H-14a), 6.41 (1H, d, *J*=2.4 Hz; H-12a), 6.27 (1H, t, *J*=2.2 Hz; H-12c), 6.08 (1H, d, *J*=3.0 Hz; H-7a), 6.01 (1H, s; H-12b), 5.26 (1H, br s; H-7b), 4.54 (1H, d, *J*=9.9 Hz; H-7c), 4.37 (1H, d, *J*=3.0 Hz; H-8a), 4.21 (1H, d, *J*=11.7 Hz; H-8b), 3.05 (1H, dd, *J*=11.7, 9.9 Hz; H-8c), 3.70 (6H, s; $-OCH_3$ x 2); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.5 (C-11c,13c), 159.6 (C-11b), 158.1 (C-4a), 158.0 (C-11a), 158.0 (C-13a), 156.9 (C-4c), 155.9 (C-4b), 154.9 (C-13b), 147.2 (C-9a), 144.0 (C-9b), 143.0 (C-9c), 137.3 (C-1b), 134.4

(C-1a), 134.1 (C-1c), 129.9 (C-2c,6c), 129.6 (C-2b,6b), 128.1 (C-2a,6a), 122.2 (C-14b), 119.2 (C-10b), 118.1 (C-10a), 116.0 (C-3a,5a), 115.7 (C-3c,5c), 115.4 (C-3b,5b), 107.8 (C-10c,14c), 104.2 (C-14a), 101.4 (C-12a), 99.3 (C-12c), 96.0 (C-12b), 85.9 (C-7a), 67.5 (C-8c), 55.4 (C-7c), 51.8 (C-8b), 50.4 (C-8a), 36.5 (C-7b), 55.4 (–OCH_3 x 2); HRFAB-MS: *m*/*z* 709.2460 $[M+H]^+$ (709.2438 calculated for $C_{44}H_{37}O_9$).

Methylation of (+)-davidiol A (4) and compound (9)

To a solution of (+)-davidiol A (**4**) (2.0 mg) in acetone (3 mL), methyl iodide (26 μL) and anhydrous potassium carbonate (55 mg) were added. The reaction mixture was refluxed for 21 h, filtered, and evaporated. The resulted residue was purified by silica gel column chromatography using a mixture of benzene – acetone (10:0.2) to give methylated davidiol A (**10**) (1.5 mg). By the same method, compound (**10**) (1.1 mg) was obtained from compound (**9**) (1.6 mg).

Compound (10) (from natural product (4)). $[\alpha]_D$ +130.2° (*c* 0.07, $CHCl_3$); a brown oil; UV λ_{max} (MeOH) [nm (log ε)] 284 (4.03), 241 (4.54); IR ν_{max} (film) 2922, 2835, 1605, 1510 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.29 (2H, d, *J*=8.8 Hz; H-2a,6a), 7.04 (2H, d, *J*=8.8 Hz; H-2b,6b), 6.87 (2H, d, *J*=8.8 Hz; H-3a,5a), 6.75 (1H, d, *J*=2.4 Hz; H-14a), 6.74 (2H, d, *J*=8.8 Hz; H-2c,6c), 6.67 (2H, d, *J*=8.8 Hz; H-3b,5b), 6.64 (2H, d, *J*=8.8 Hz; H-3c,5c), 6.62 (2H, d, *J*=2.2 Hz; 10c,14c), 6.59 (1H, d, *J*=2.4 Hz; H-12a), 6.33 (1H, t, *J*=2.2 Hz; H-12c), 6.29 (1H, d, *J*=2.9 Hz; H-7a), 6.23 (1H, s; H-12b), 5.25 (1H, br s; H-7b), 4.53 (1H, d, *J*=9.7 Hz; H-7c), 4.36 (1H, d, *J*=2.9 Hz; H-8a), 4.30 (1H, d, *J*=11.7 Hz; H-8b), 2.93 (1H, dd, *J*=11.7, 9.9 Hz; H-8c), 3.87 (3H, s; 11a-OCH_3), 3.84 (3H, s; 13a-OCH_3), 3.77 (3H, s; 4a-OCH_3), 3.74 (6H, s; 11c,13c-OCH_3), 3.68 (3H, s; 4c-OCH_3), 3.64 (3H, s; 4b-OCH_3), 3.39 (3H, s; 13b-OCH_3); ^{13}C NMR (150 MHz, $CDCl_3$) δ 161.7 (C-11c,13c), 160.7 (C-11a), 160.4 (C-11b), 160.2 (C-4a), 159.6 (C-13a), 158.8 (C-4c), 158.6 (C-4b), 158.2 (C-13b), 146.8 (C-9a), 143.9 (C-9b), 142.8 (C-9c), 137.8 (C-1b), 136.3 (C-1c), 135.5 (C-1a), 129.5 (C-2b,6b), 129.4 (C-2c,6c), 128.0 (C-2a,6a), 124.4 (C-14b), 120.5 (C-10a), 119.3 (C-10b), 114.6 (C-3a,5a), 114.1 (C-3b,5b), 113.7 (C-3c,5c), 108.0 (C-10c,14c), 103.3 (C-14a), 99.0 (C-12c), 96.7 (C-12a), 93.2 (C-12b), 85.5 (C-7a), 67.5 (C-8c), 56.2 (C-7c), 51.5 (C-8b), 50.8 (C-8a), 36.4 (C-7b), 56.5, 56.2, 55.8, 55.54, 55.4, 55.2 (each –OCH_3), 55.49 (2C, –OCH_3); HRFAB-MS: *m*/*z* 793.3378 $[M+H]^+$ (793.3377 calculated for $C_{50}H_{49}O_9$).

Compound (10) (from compound (9)). $[\alpha]_D$ +123.2° (*c* 0.08, $CHCl_3$); HRFAB-MS: *m*/*z* 793.3400 $[M+H]^+$ (793.3377 calculated for $C_{50}H_{49}O_9$).

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21. The absolute value of the specific optical rotation of **4** was different from that of (–)-davidiol A (**5**) reported ($[\alpha]_D$ –272°) in the reference 16. But the values of natural and synthetic **4** were very similar, and these compounds seemed to be pure judging from the NMR spectra of them. So we report our value in this paper.