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Efficient Synthesis of Several Natural Oligostilbenes from the Biomimetic Oxidation of Brominated Isorhapontigenin

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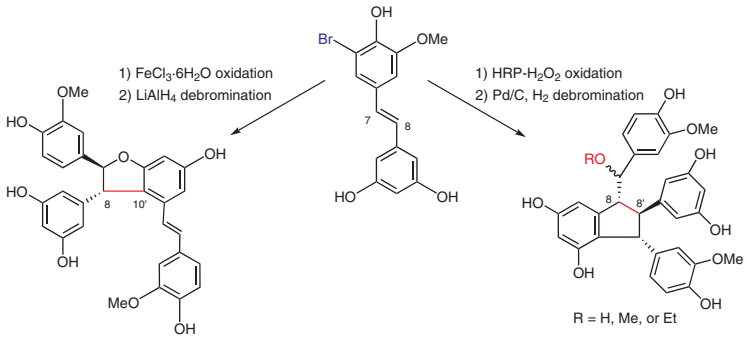

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Abstract This study extensively investigated the regioselective oxidative coupling reactions of 5-bromoisorhapontigenin catalyzed by $FeCl_3·6H_2O$ or HRP/H_2O_2 in different solvent systems and the distinct reductive debromination of the isolated dimeric coupling intermediates. Natural (±)-bisisorhapontigenin A and (±)-lehmbachol A and B were efficiently prepared. (±)-Gnetuhainin I, (±)-gnemontanin E, (±)-7-*O*-ethylgnetuhainin I, and (±)-gnemontanin F were synthesized for the first time.

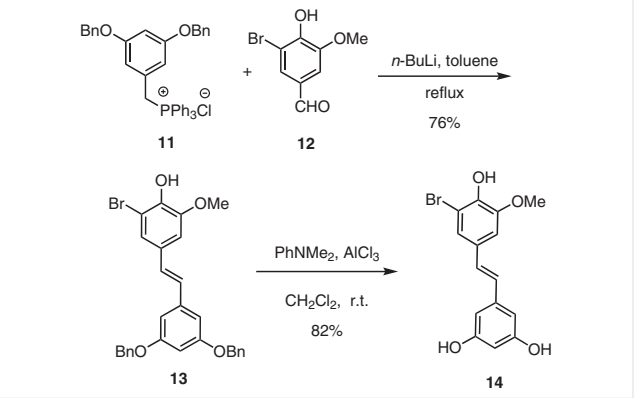
Key words isorhapontigenin, oligostilbenes, regioselectivity, biomimetic synthesis, oxidative coupling, debromination

Isorhapontigenin (**2**), an important natural stilbene in addition to resveratrol (**1**), is used to form a number of complex oligostilbenes, such as natural dimers **3**–**8**, through enzyme-induced single-electron oxidation in plants (Figure 1).[1] Traditional biomimetic oxidation methods and well-designed chemical routes toward the synthesis of resveratrol oligomers have been extensively studied in the past four decades.[2] However, few studies have reported on the preparation of oligomeric isorhapontigenins,[3] thereby limiting further investigation on their structure-bioactivity relationship.

Previous studies on the construction of diverse skeletons of isorhapontigenin dimers mainly focused on the direct oxidative coupling reactions of **2** catalyzed by inorganic metallic oxidants and enzyme systems. The 8–5-coupled dimer **3** was predominant in the complex coupling product mixture when Ag_2O, AgOAc, $FeCl_3·6H_2O$, or horseradish peroxidase (HRP)/H_2O_2 were used as catalyst.[4] To impede the formation of 8–5-coupled product **3** and improve the possibility of other coupling modes, our group systematically investigated the regioselective coupling reactions of 5-*tert*-butyl-isorhapontigenin (**9**) under various oxidative conditions. We successfully produced several dimeric intermediates with different skeletons.[5] Nevertheless, the expected natural products such as **4** and **6** were difficult to obtain because of their structural instability under strongly acidic conditions required for the removal of *tert*-butyl groups from the obtained coupling intermediates. Relatively stable architectures **5**, **7**, and **8** were finally synthesized in moderate yields. Thus, the efficient synthesis of natural products **4** and **6** remains an important part of our future research work.

Inspired by our recent success in concise synthesis of some natural oligostilbenes by using the regioselective oxidative coupling reactions of 3,5-dibromoresveratrol (**10**) under different catalytic conditions,[6] we intended to apply this synthetic strategy to prepare several isorhapontigenin dimers, including natural **4** and **6**.

Prior to synthesis, coupling precursor, namely, 5-bromoisorhapontigenin (**14**), was prepared (Scheme 1). The key Wittig reaction of phosphonium salt **11** with 5-bromo-



Scheme 1 Preparation of *trans*-stilbene **14**

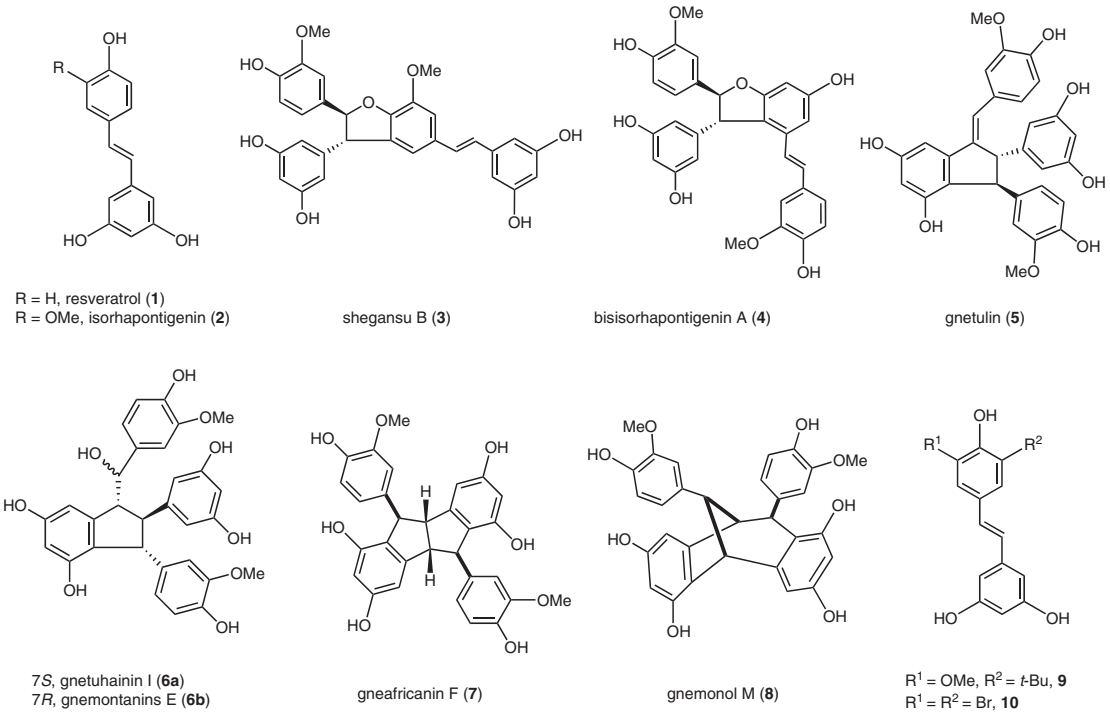


Figure 1 Several stilbenes and representative isorhapontigenin dimers

vanillin (**12**) generated *trans*-stilbene **13** in 76% yield. The product was then subjected to the debenzylation reaction to obtain target precursor **14** in 82% yield.

We first explored the $FeCl_3·6H_2O$-promoted oxidation of stilbene **14** on the basis of our recent research on the coupling dimerizations of **10**.[5a] As illustrated in Scheme 2 and Table 1, the 8–10-coupled dimeric intermediate **15** as the predominant coupling product was found when the precursor **14** was treated with 3.0 equimolar amounts of $FeCl_3·6H_2O$ in various solvent systems for 8 hours (Table 1, entries 1–4). The solvent effects on the coupling reactions of **14** were largely reflected by differences in the isolated yields of dimer **15**. The 42% yield of **15** in acetone solvent was relatively higher than that in acetone–benzene (37%) or acetone–H_2O (33%) and in dichloromethane–methanol system (27%). The dihydrobenzofuran **15** was then subjected to 20 equivalents of $LiAlH_4$ in THF at room temperature for 18 hours to obtain racemic bisisorhapontigenin A (**4**) in 85% yield.

We next investigated the enzyme-mediated oxidative dimerizations of stilbene **14** in three different solvent systems according to our previous work (Scheme 3 and Table 2).[5b] As predicted, the coupling of two M_8 semi-quinone radicals was predominant under the HRP–H_2O_2 catalytic condition. The initially formed bisquinone methide was nucleophilically attacked by the H_2O, MeOH, or EtOH molecule from the solvent systems and subjected to intramolecular Friedel–Crafts alkylation to obtain dimeric mixtures **16a**/**16b**, **17a**/**17b**, or **18a**/**18b** with varied molar ratio. No other oligomers, such as the predicted pallidol-type structure like dimer **7**, were found in the coupling product. Finally, the reductive debromination reaction of the isomeric in-

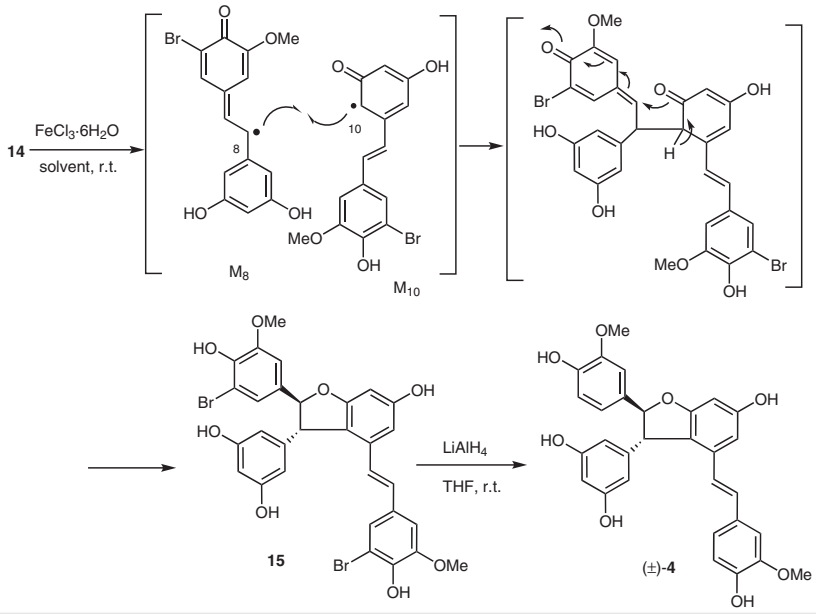
Table 1 Coupling Products of **14** in Different Catalytic Systems

Entry	$FeCl_3·6H_2O$ (equiv)	Solvents (volume ratio)	Time (h)	Product **15** (yield %)
1	3.0	acetone	8	42
2	3.0	acetone–benzene (3:1)	8	37
3	3.0	acetone–H_2O (3:1)	8	33
4	3.0	CH_2Cl_2–MeOH (4:1)	8	27

Table 2 Coupling Products from the Enzyme-Oxidation of **14** in Different Solvent Systems

Entry	Catalyst[a]	Solvents (volume ratio)	Time (h)	Coupling products (molar ratio,[b] yield)
1	HRP-H_2O_2	acetone–H_2O (3:1)	14	**16a**:**16b** (1.4:1, 50%)
2	HRP-H_2O_2	MeOH–H_2O (3:1)	24	**17a**:**17b** (1:1, 53%)
3	HRP-H_2O_2	EtOH–H_2O (3:1)	12	**18a**:**18b** (1.5:1, 49%)

[a] HRP [RZ (Reinheitszahl): >3; activity: ≥300 U/mg].
[b] Determined by ^1H NMR spectrum of the crude product.



Scheme 2 Synthesis of (±)-**4** from the oxidation of **14** and the debromination of **15**

dane mixtures **16a** and **16b** under the Pd-C/Et_3N-catalyzed hydrogenation condition easily formed natural (±)-gnetuhainin I (**6a**) and (±)-gnemontanins E (**6b**) in 73% yield. The dimeric mixtures **17a**/**17b** or **18a**/**18b** were treated with the same Pd-C/Et_3N-mediated debromination to obtain natural products (±)-lehmbachol A (**19a**) and (±)-lehmbachol B (**19b**) or (±)-7-*O*-ethylgnetuhainin I (**20a**) and (±)-gnemontanin F (**20b**) in 87% or 77% yield, respectively. The spectral data of natural products **6**, **19**, and **20** that we synthesized were consistent with those in the literature.[1d,e]

In conclusion, the biomimetic oxidative coupling reactions of brominated isorhapontigenin **14** under different catalytic conditions were extensively investigated. The introduction of bromine atom as positional protection for the stilbene precursor efficiently hampered the undesired 8–5-coupling mode, which was predominant in the typical oxidative coupling reaction of isorhapontigenin. The $FeCl_3·6H_2O$-promoted coupling reaction of **14** in various solvent systems invariably formed 8–10-coupled dihydrobenzofuran structure **15**. By contrast, the HRP-H_2O_2-mediated oxidations of **14** in aqueous acetone, methanol, or ethanol generated the corresponding 8–8-coupled dimeric isomers, namely, **16a**/**16b**, **17a**/**17b**, and **18a**/**18b**, which contain indane skeletons. The dimeric coupling intermediates **15** and **16**–**18** were subjected to the distinct debromination reactions to finally accomplish the efficient preparation of isorhapontigenin dimers (±)-**4** and (±)-**19a**/**19b**, and the first synthesis of natural (±)-**6a**/**6b**, (±)-**20a**/**20b**.

Structural determinations of the isolated compounds were based on ^1H, ^{13}C NMR, NOESY, ^1H-^1H COSY, HMBC spectra, and HRMS analysis. All NMR spectra were recorded on a Varian Mercury 400 or 600 MHz instrument in a solvent as indicated. HRMS spectra were measured on an Autostec-3090 mass spectrometer. All solvents were freshly purified and dried by standard techniques prior to use. Purification of products was performed by column chromatography on silica gel (200–300 mush), purchased from Qingdao Marine Chemical Co. (Qingdao, China).

Stilbene 13

A stirred solution of phosphonium salt **11** (3.14 g, 5.0 mmol) in anhyd toluene (80 mL) under argon atmosphere was added to a solution of *n*-BuLi (2.5 mL, 13.6 mmol) in *n*-hexane. After stirring for 30 min, aldehyde **12** (1.0 g, 4.0 mmol) was added and then stirred for an additional 5 h under reflux at 110 °C, after which MeOH (6 mL) was added. The reaction mixture was concentrated and extracted with EtOAc (3 × 80 mL). The combined organic extracts were washed with H_2O and brine, and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (PE–EtOAc 8:1) to give stilbene **13** as a pale white solid; yield: 1.76 g (79%); mp 132–134 °C; R_f = 0.42 (PE–EtOAc 4:1).

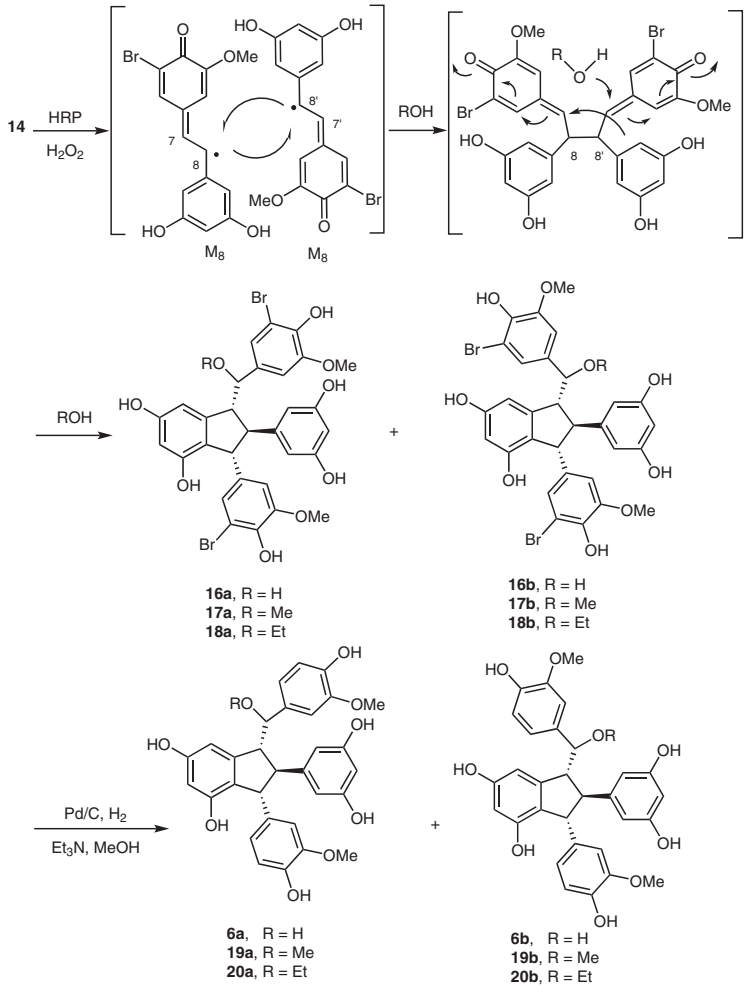
^1H NMR (400 MHz, CD_3Cl): δ = 3.96 (s, 3 H), 5.07 (s, 4 H), 5.96 (br s, 1 H), 6.56 (t, *J* = 2.0 Hz, 1 H), 6.74 (d, *J* = 2.0 Hz, 2 H), 6.87 (d, *J* = 16 Hz, 1 H), 6.93 (d, *J* = 16 Hz, 1 H), 6.95 (br s, 1 H), 7.23–7.46 (m, 10 H).

^{13}C NMR (100 MHz, CD_3Cl): δ = 56.5, 70.3 (2 C), 101.8, 105.8 (2 C), 107.8, 108.7, 123.6, 127.7 (4 C), 127.9, 128.0, 128.2 (2 C), 128.8 (5 C), 130.6, 137.0, 139.3, 143.0, 147.4, 160.3 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{29}H_{25}BrO_4$ + H: 517.10090; found: 517.10034.

Coupling Precursor 14

N,*N*-Dimethylaniline (32 mL, 0.41 mol) was added to a well-stirred solution of stilbene **13** (2.77 g, 8.0 mmol) in anhyd CH_2Cl_2 (60 mL) at 0 °C. After 5 min, anhyd $AlCl_3$ (6.4 g, 48.0 mmol) was added to the reaction mixture. After stirring for an additional 3 h at r.t., the mixture was quenched with H_2O at 0 °C and poured into aq 2.0 M HCl (30 mL). The resulting mixture was extracted with EtOAc (3 × 50 mL), and the



Scheme 3 Synthesis of **6** and **19–20** from the oxidation of **14** and the debromination of **16–18**

combined organic extracts were washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (PE–EtOAc 3:1) to give the coupling precursor **14** as a pale yellow solid; yield: 1.55 g (86%); mp 118–120 °C; R_f = 0.20 (PE–EtOAc 2:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.92 (s, 3 H), 6.29 (t, *J* = 2.0 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 2 H), 6.97 (d, *J* = 16.2 Hz, 1 H), 7.00 (d, *J* = 16.2 Hz, 1 H), 7.22 (d, *J* = 2.4 Hz, 1 H), 7.28 (d, *J* = 2.4 Hz, 1 H), 8.36 (br s, 2 H), 8.44 (br s, 1H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 56.7, 103.1, 105.8 (2 C), 109.1, 109.6, 124.1, 127.9, 128.6, 131.2, 140.4, 144.7, 149.2, 159.6 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}BrO_4$ + H: 337.00709; found: 337.00708.

$FeCl_3$·6H_2O-Catalyzed Coupling Reaction of 14 in Different Solvents

$FeCl_3$·6H_2O (121 mg, 0.45 mmol) was slowly added to a solution of stilbene **14** (50 mg, 0.15 mmol) in varied solvent system (6.0 mL) (Table 1). The reaction mixture was kept out of sun and stirred at r.t. under argon atmosphere for 8 h. After the removal of the solvent under reduced pressure, the resulting residue was extracted with EtOAc (3 ×). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and evaporated in vacuo. The crude products was subjected to silica gel column chromatography (CH_2Cl_2–MeOH 30:1) to give the unreacted **14**, and the dimer **15** as a yellow amorphous powder; R_f = 0.25 (CH_2Cl_2–MeOH 20:1). For yields, see Table 1.

^{1}H NMR (400 MHz, acetone-d_6): δ = 3.83 (s, 3 H), 3.86 (s, 3 H), 4.55 (d, *J* = 6.4 Hz, 1 H), 5.44 (d, *J* = 6.4 Hz, 1 H), 6.27 (t, *J* = 2.0 Hz, 1 H), 6.29 (d, *J* = 2.0 Hz, 2 H), 6.37 (d, *J* = 2.0 Hz, 1 H), 6.72 (d, *J* = 16.2 Hz, 1 H), 6.75 (d, *J* = 2.0 Hz, 1 H), 6.81 (d, *J* = 2.0 Hz, 1 H), 6.88 (d, *J* = 16.2 Hz, 1 H), 7.00 (d, *J* = 2.0 Hz, 1 H), 7.04 (d, *J* = 2.0 Hz, 1 H), 7.09 (d, *J* = 2.0 Hz, 1 H), 8.26 (br s, 2 H), 8.34 (br s, 1 H), 8.36 (br s, 1 H), 8.48 (br s, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.6, 56.7, 57.3, 93.3, 97.2, 102.2, 104.4, 107.2 (2 C), 107.7, 109.3 (2 C), 120.1, 122.6 (2 C), 124.8 (2 C), 125.1, 128.7 (2 C), 131.1, 134.7, 135.8, 146.9 (2 C), 159.7, 159.9 (2 C), 162.2 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{24}Br_2O_8$ + H: 670.99107; found: 670.99116.

Debromination of 15 for the Synthesis of (±)-4

Excess $LiAlH_4$ (0.055 g, 1.44 mmol) was added to a stirred solution of dimer **15** (48.6 mg, 0.072 mmol) in anhyd THF (10 mL) at ice-bath temperature under argon atmosphere and the stirring of the mixture was continued at room tempreature for 18 h. Ice-water was added slowly to quench the reaction and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (anhyd $MgSO_4$), and evaporated in vacuo. The crude product was subjected to silica gel column chromatography (CH_2Cl_2–MeOH 15:1) to give (±)-bisisorhapontigenin A (**4**) as a yellowish oil; yield: 52.3 mg (85%); R_f = 0.22 (CH_2Cl_2–MeOH 10:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.80 (s, 3 H), 3.82 (s, 3 H), 4.51 (d, *J* = 7.2 Hz, 1 H), 5.42 (d, *J* = 7.2 Hz, 1 H), 6.26 (t, *J* = 2.4 Hz, 1 H), 6.28 (d, *J* = 2.4 Hz, 2 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.68 (d, *J* = 16.2 Hz, 1 H), 6.71 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.73 (d, *J* = 1.8 Hz, 1 H), 6.77 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.81 (d, *J* = 2.0 Hz, 2 H), 6.90 (d, *J* = 16.2 Hz, 1 H), 7.00 (d, *J* = 1.8 Hz, 1 H), 7.66 (br s, 2 H), 8.22 (br s, 2 H), 8.37 (br s, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.1, 56.3, 57.4, 94.3, 96.9, 102.2, 104.0, 107.3, 108.8, 110.4 (2 C), 115.7, 119.6 (2 C), 120.2, 121.8 (2 C), 123.4, 130.0, 130.4, 133.9 (2 C), 136.2 (2 C), 147.2 (2 C), 159.9 (2 C), 161.5 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{27}O_8$ + H: 515.17004; found: 515.17004.

Enzyme-Mediated Coupling Reactions of 14 in Aqueous Acetone

A solution of compound **14** (0.10 g, 0.296 mmol) and horseradish peroxidase (10 mg, RZ >3, activity ≥300 U/mg) in acetone (12 mL) and H_2O (4.0 mL) was treated with H_2O_2 (3%, 1 mL) at r.t. under argon atmosphere and continuously stirred for 12 h. Acetone was removed and the aqueous reaction mixture was extracted with EtOAc (20 mL), the organic layer washed with brine, and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was puried by silica gel column chromatography (CH_2Cl_2–MeOH 25:1) to give the unreacted **14** (20 mg) and a mixture of the dimer **16a** and **16b** in a 1.4:1 molar ratio as yellowish amorphous powder; yield: 40 mg (50%).

16a

R_f = 0.28 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 2.97 (t, *J* = 4.2 Hz, 1 H), 3.45 (d, *J* = 6.0 Hz, 1 H), 4.21 (d, *J* = 3.6 Hz, 1 H), 4.38 (d, *J* = 4.8 Hz, 1 H), 4.54 (dd, *J* = 7.2, 4.8 Hz, 1 H), 5.95 (d, *J* = 2.4 Hz, 2 H), 6.14 (t, *J* = 2.4 Hz, 1 H), 6.20 (d, *J* = 2.4 Hz, 1 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.61 (d, *J* = 2.0 Hz, 1 H), 6.65 (d, *J* = 2.4 Hz, 1 H), 6.73 (d, *J* = 2.4 Hz, 1 H), 6.75 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.0, 56.4, 56.5, 101.4, 102.6, 106.0, 106.2 (2 C), 108.4, 108.7, 108.9, 110.2, 110.9, 111.3, 121.8, 123.8, 123,9, 134.9, 137.4, 138.8, 139.0, 143.1, 143.8, 148.6, 148.7, 150.0, 155.2, 158.8, 159.2 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}Br_2O_9$ + Na: 710.98358; found: 710.98425.

16b

R_f = 0.28 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.43 (t, *J* = 4.2 Hz, 1 H), 3.85 (dd, *J* = 4.8, 8.4 Hz, 1 H), 4.22 (d, *J* = 3.0 Hz, 1 H), 4.42 (d, *J* = 4.8 Hz, 1 H), 4.61 (dd, *J* = 8.4, 4.8 Hz, 1 H), 5.98 (d, *J* = 2.4 Hz, 1 H), 6.10 (d, *J* = 2.4 Hz, 2 H), 6.16 (d, *J* = 2.4 Hz, 1 H), 6.26 (d, *J* = 2.4 Hz, 1 H), 6.69 (d, *J* = 2.4 Hz, 1 H), 6.74 (d, *J* = 2.4 Hz, 1 H), 6.84 (d, *J* = 2.4 Hz, 1 H), 6.98 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.6, 56.7, 56.9, 101.3, 102.6, 105.3, 106.3 (2 C), 108.5, 108.7, 110.9, 122.6, 123.9, 124.2, 124.3, 136.9, 139.7, 142.9, 143.9, 147.2 (2 C), 148.5, 148.8 (2 C), 150.7, 155.1, 159.1, 159.4 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{26}Br_2O_9$ + Na: 710.98358; found: 710.98425.

Enzyme-Mediated Coupling Reaction of 14 in Aqueous Methanol

A solution of compound **14** (0.25 g, 0.74 mmol) and horseradish peroxidase (25 mg, RZ >3, activity ≥300 U/mg) in MeOH (9 mL) and H_2O (3 mL) was treated with H_2O_2 (3%, 2.5 mL) at r.t. under argon atmosphere and continuously stirred for 24 h. MeOH was removed and the aqueous reaction mixture was extracted with EtOAc (50 mL). The EtOAc layer washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was puried by silica gel column chromatography (CH_2Cl_2–MeOH 25:1) to give the unreacted **14** (71 mg), and a mixture of the dimer **17a** and **17b** in a 1:1 molar ratio as yellowish amorphous powder; yield: 98 mg (53%).

17a

R_f = 0.30 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 2.81 (t, *J* = 3.6 Hz, 1 H), 3.06 (s, 3 H), 3.35 (dd, *J* = 3.6, 8.4 Hz, 1 H), 3.76 (s, 3 H), 3.68 (s, 3 H), 3.98 (d, *J* = 8.4 Hz, 1 H), 4.20 (d, *J* = 3.6 Hz, 1 H), 5.83 (d, *J* = 2.4 Hz, 2 H), 6.01 (d, *J* = 2.4 Hz, 1 H), 6.11 (t, *J* = 2.4 Hz, 1 H), 6.36 (d, *J* = 1.8 Hz, 1 H), 6.59 (d, *J* = 1.8 Hz, 1 H), 6.66 (d, *J* = 1.8 Hz, 1 H), 6.70 (d, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 2.4 Hz, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 55.9, 56.6, 56.7, 56.9, 59.3, 60.7, 88.0, 101.3, 105.5, 106.3, 108.7, 110.6, 111.3, 115.2, 122.7, 123.9 (2 C), 125.0 (2 C), 132.0, 133.1, 139.0, 143.1, 144.5, 148.7, 148.8, 150.1, 155.2, 159.1, 159.4 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{29}Br_2O_9$ + H: 703.01728; found: 703.01624.

17b

R_f = 0.30 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (600 MHz, acetone-d_6): δ = 3.10 (s, 3 H), 3.32 (t, *J* = 4.2 Hz, 1 H), 3.47 (dd, *J* = 4.8, 7.2 Hz, 1 H), 3. 75 (s, 3 H), 3.77 (s, 3 H), 4.03 (d, *J* = 7.2 Hz, 1 H), 4.21 (d, *J* = 4.2 Hz, 1 H), 6.13 (d, *J* = 2.4 Hz, 2 H), 6.18 (d, *J* = 2.4 Hz, 1 H), 6.26 (d, *J* = 1.8 Hz, 1 H), 6.50 (d, *J* = 1.8 Hz, 1 H), 6.59 (d, *J* = 1.8 Hz, 1 H), 6.62 (d, *J* = 1.8 Hz, 1 H), 6.69 (d, *J* = 1.8 Hz, 1 H), 6.82 (d, *J* = 1.8 Hz, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 56.2, 56.6, 56.7, 56.9, 59.0, 60.3, 87.0, 101.4, 102.7, 105.9, 111.0, 111.2, 124.2 (2 C), 125.3 (2 C), 129.6, 133.4, 139.5, 143.2, 144.5, 146.7 (2 C), 148.7, 148.8, 149.1, 150.1, 155.2, 159.2, 159.5 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{29}Br_2O_9$ + H: 703.01728; found: 703.01624.

Enzyme-Mediated Coupling Reaction of 14 in Aqueous Ethanol

A solution of compound **14** (201 mg, 0.57 mmol) and horseradish peroxidase (20 mg, RZ >3, activity ≥300 U/mg) in EtOH (6.0 mL) and H_2O (2.0 mL) was treated with H_2O_2 (3%, 2.0 mL) at r.t. under argon atmosphere and continuously stirred for 12 h. EtOH was removed and the aqueous reaction mixture was extracted with EtOAc (50 mL). The EtOAc layer washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 25:1) to give the

unreacted **14** (68 mg), and a mixture of the dimer **18a** and **18b** in a 1.5:1 molar ratio as yellowish amorphous powder; yield: 65.2 mg (49%).

18a

R_f = 0.32 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.10 (t, *J* = 7.2 Hz, 3 H), 2.82 (t, *J* = 3.6 Hz, 1 H), 3.18 (dd, *J* = 6.8, 9.2 Hz, 1 H), 3.40 (q, *J* = 7.2 Hz, 2 H), 4.07 (d, *J* = 8.8 Hz, 1 H), 4.21 (d, *J* = 3.2 Hz, 1 H), 5.84 (d, *J* = 2.0 Hz, 2 H), 6.11 (t, *J* = 2.0 Hz, 1 H), 6.36 (d, *J* = 2.0 Hz, 1 H), 6.51 (d, *J* = 2.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 1 H), 6.91 (d, *J* = 2.0 Hz, 1 H), 7.83 (s, 1 H), 7.98 (s, 1 H), 8.04 (s, 1 H), 8.10 (s, 2 H), 8.19 (s, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 15.5, 55.8, 56.6, 56.7, 59.2, 60.4, 64.7, 85.8, 101.3, 105.9 (2 C), 106.1, 108.6, 108.9, 110.5, 111.2, 121.5, 123.9, 124.8, 134.2, 139.0, 143.1, 144.3, 148.7 (2 C), 148.9, 149.2, 150.2, 155.1, 159.3 (2 C), 159.4.

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{30}Br_2O_9$ + Na: 739.01488; found: 739.01471.

18b

R_f = 0.32 (CH_2Cl_2–MeOH 15:1).

^{1}H NMR (400 MHz, acetone-d_6): δ = 1.02 (t, *J* = 7.2 Hz, 3 H), 3.08 (dd, *J* = 6.8, 9.6 Hz, 1 H), 3.30 (q, *J* = 7.2 Hz, 2 H), 3.81 (t, *J* = 5.6 Hz, 1 H), 4.11 (d, *J* = 7.6 Hz, 1 H), 4.24 (d, *J* = 3.6 Hz, 1 H), 5.95 (d, *J* = 2.0 Hz, 1 H), 6.15 (d, *J* = 2.0 Hz, 2 H), 6.18 (d, *J* = 2.0 Hz, 1 H), 6.27 (d, *J* = 2.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.71 (d, *J* = 2.0 Hz, 2 H), 6.83 (d, *J* = 2.0 Hz, 1 H), 7.76 (s, 1 H), 8.01 (s, 1 H), 8.09 (s, 2 H), 8.10 (s, 1 H), 8.17 (s, 1 H).

^{13}C NMR (150 MHz, acetone-d_6): δ = 15.5, 55.9, 56.6, 56.7, 59.1, 60.9, 64.6, 84.8, 101.4, 105.7, 106.3 (2 C), 108.6, 108.8, 111.1, 111.3, 122.6, 124.2, 125.2, 133.8, 139.5, 143.0, 144.4, 146.7, 148.8 (2 C), 150.3, 155.2, 159.0, 159.4 (3 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{29}Br_2O_9$ + Na: 739.01488; found: 739.01471.

Debromination of 16a/16b for the Preparation of 6a/6b

After two vacuum/H_2 cycles to remove air from a round-bottomed flask, a suspension of the mixture of **16a** and **16b** (56 mg, 0.081 mmol), 10% Pd/C (26 mg), and Et_3N (0.3 mL) in anhyd MeOH (3 mL) was vigorously stirred using a stir bar under H_2 atmosphere at r.t. After stirring for 15 h, the reaction mixture was filtered. The filtrate was washed with dil HCl and then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 15:1) to obtain a mixture of (±)-gnetuhainin I (**6a**) and (±)-gnemontanins E (**6b**) in a 1.3:1 molar ratio as a yellowish oil; yield: 32 mg (73%).

(±)-**6a**

R_f = 0.26 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (500 MHz, acetone-d_6): δ = 2.96 (dd, *J* = 3.5, 3.5 Hz, 1 H), 3.37 (dd, *J* = 3.5, 8.0 Hz, 1 H), 3.65 (s, 3 H), 3.72 (s, 3 H), 4.22 (d, *J* = 3.5 Hz, 1 H), 4.50 (d, *J* = 8.0 Hz, 1 H), 5.91 (d, *J* = 2.0 Hz, 2 H), 6.12 (t, *J* = 2.0 Hz, 1 H), 6.31 (d, *J* = 2.0 Hz, 1 H), 6.46 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.51 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.56 (d, *J* = 2.0 Hz, 1 H), 6.62 (d, *J* = 2.0 Hz, 1 H), 6.64 (d, *J* = 2.0 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 6.71 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 56.0 (2 C), 56.3, 59.4, 61.9, 77.4, 101.2, 102.4, 106.1 (2 C), 106.4, 111.3, 112.3, 115.1, 115.3, 120.4, 120.8, 122.4, 136.6, 138.1, 145.7, 146.4, 147.7, 148.1, 149.0, 150.7, 155.1, 158.7, 159.1 (2 C).

^{1}H NMR (500 MHz, CD_3OD): δ = 2.80 (dd, *J* = 3.5, 3.5 Hz, 1 H), 3.35(dd, *J* = 3.5, 8.0 Hz, 1 H), 3.64 (s, 3 H), 3.73 (s, 3 H), 4.19 (d, *J* = 3.5 Hz, 1 H), 4.41 (d, *J* = 8.0 Hz, 1 H), 5.81 (d, *J* = 2.0 Hz, 2 H), 6.02 (t, *J* = 2.0 Hz, 1 H), 6.25 (d, *J* = 2.0 Hz, 1 H), 6.41 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.43 (d, *J* = 2.0 Hz, 1 H), 6.45 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.55 (d, *J* = 2.0 Hz, 1 H), 6.63 (d, *J* = 8.0 Hz, 1 H), 6.64 (d, *J* = 2.0 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 56.1, 56.3, 56.4, 60.2, 62.1, 78.7, 101.2, 102.6, 106.3 (3 C), 111.9, 112.4, 115.7 (2 C), 120.9 (2 C), 123.0, 136.5, 138.8, 145.6. 146.7, 148.5, 148,7, 149.5, 151.3, 155.5, 159.2, 159.3 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{28}O_9$ + H: 533.18061; found: 533.18036.

(±)-**6b**

R_f = 0.26 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (500 MHz, acetone-d_6): δ = 3.43 (dd, *J* = 4.5, 4.0 Hz, 1 H), 3.46 (dd, *J* = 4.5, 8.0 Hz, 1 H), 3.71 (s, 3 H), 3.73 (s, 3 H), 4.22 (d, *J* = 4.0 Hz, 1 H), 4.56 (d, *J* = 8.0 Hz, 1 H), 5.95 (d, *J* = 2.0 Hz, 1 H), 6.13 (d, *J* = 2.0 Hz, 2 H), 6.16 (d, *J* = 2.0 Hz, 1 H), 6.22 (d, *J* = 2.0 Hz, 1 H), 6.46 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.61 (d, *J* = 2.0 Hz, 1 H), 6.64 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.67 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 8.0 Hz, 1 H), 6.92 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, acetone-d_6): δ = 56.1, 56.2, 56.6, 59.0, 62.3, 77.3, 101.0, 102.2, 105.7, 106.3 (2 C), 111.9 (2 C), 114.8, 115.3, 120.9, 121.4, 130.6, 136.2, 138.6, 145.7, 146.6, 147.4, 147.8, 148.1, 151.1, 154.9, 158.7, 159.3 (2 C).

^{1}H NMR (500 MHz, CD_3OD): δ = 3.23 (dd, *J* = 5.0, 5.0 Hz, 1 H), 3.55 (dd, *J* = 5.0, 8.0 Hz, 1 H), 3.67 (s, 3 H), 3.71 (s, 3 H), 4.14 (d, *J* = 5.0 Hz, 1 H), 4.54 (d, *J* = 8.0 Hz, 1 H), 6.08 (t, *J* = 2.0 Hz, 1 H), 6.09 (d, *J* = 2.0 Hz, 2 H), 6.13 (d, *J* = 2.0 Hz, 1 H), 6.14 (d, *J* = 2.0 Hz, 1 H), 6.35 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.43 (d, *J* = 2.0 Hz, 1 H), 6.61 (d, *J* = 8.0 Hz, 1 H), 6.62 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 6.88 (d, *J* = 2.0 Hz, 1 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 56.2, 56.3, 57.4, 60.0, 61.8, 78.0, 101.3, 102.6, 106.0, 106.9 (2 C), 112.0, 112.4, 115.3, 115.6, 121.1, 122.0, 123.9, 135.5, 139.0, 145.5, 146.9, 147.4, 148.5, 148,7, 150.7, 155.4, 158.8, 159.4 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{30}H_{28}O_9$ + H: 533.18061; found: 533.18036.

Debromination of 17a/17b for the Synthesis of 19a/19b

After two vacuum/H_2 cycles to remove air from a round-bottomed flask, a suspension of the mixture of **17a** and **17b** (60 mg, 0.085 mmol), 10% Pd/C (60 mg), and Et_3N (0.6 mL) in MeOH (5.0 mL) was vigorously stirred using a stir bar under H_2 atmosphere at r.t. After stirring for 23 h, the reaction mixture was filtered. The filtrate was washed with dil HCl and then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was separated by silica gel column chromatography (CH_2Cl_2–MeOH 15:1) to obtain a mixture of (±)-lehmbachol A (**19a**) and (±)-lehmbachol B (**19b**) in a 1:1 molar ratio as a yellowish oil; yield: 40.7 mg (87%).

(±)-19a

R_f = 0.30 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (600 MHz, CD_3OD): δ = 3.12 (s, 3 H), 2.75 (br s, 1 H), 3.38 (dd, *J* =3.0, 7.2 Hz, 1 H), 3.74 (s, 3 H), 3.76 (s, 3 H), 3.97 (d, *J* = 3.0 Hz, 1 H), 4.21 (br s, 1 H), 5.77 (br s, 2 H), 6.04 (br s, 1 H), 6.18 (br s, 1 H), 6.29 (br s, 1 H), 6.38 (d, *J* = 7.8 Hz, 1 H), 6.42 (br s, 1 H), 6.63 (d, *J* = 7.8 Hz, 1 H), 6.69 (d, *J* = 8.4 Hz, 1 H), 6.71 (br s, 1 H), 6.73 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 56.2, 56.3, 56.5, 57.1, 60.0, 60.6, 89.4, 101.2, 102.6, 106.0, 106.2 (2 C), 112.4, 112.5, 115.4, 115.6, 120.9, 121.2, 122.8, 123.9, 132.2, 138.9, 145.6, 147.3, 148.7, 149.0, 150.7, 155.4, 158.7, 159.2 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{30}O_9$ + H: 547.19626; found: 547.19568.

(±)-19b

R_f = 0.30 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (600 MHz, CD_3OD): δ = 3.13 (s, 3 H), 3.21 (dd, *J* = 4.8, 5.4 Hz, 1 H), 3.58 (dd, *J* = 3.0, 6.0 Hz, 1 H), 3.65 (s, 3 H), 3.70 (s, 3 H), 4.03 (d, *J* = 6.6 Hz, 1 H), 4.17 (d, *J* = 4.8 Hz, 1 H), 6.13 (br s, 2 H), 6.14 (br s, 1 H), 6.15 (br s, 1 H), 6.29 (br s, 1 H), 6.42 (d, *J* = 7.8 Hz, 1 H), 6.56 (br s, 1 H), 6.64 (dd, *J* = 1.8, 7.8 Hz, 1 H), 6.65 (d, *J* = 7.8 Hz, 1 H), 6.72 (d, *J* = 7.8 Hz, 1 H), 6.85 (br s, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 56.2, 56.3, 56.7, 56.8, 59.9, 60.8, 87.9, 101.4, 102.7, 106.1, 106.9 (2 C), 112.5, 112.7, 115.6, 115.8, 120.9, 121.2, 121.9, 123.1, 132.8, 138.8, 145.5, 147.3, 148.7, 149.8, 151.2, 155.4, 159.2, 159.4 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{31}H_{30}O_9$ + H: 547.19626; found: 547.19568.

Debromination of 18a/18b for the Synthesis of 20a/20b

After two vacuum/H_2 cycles to remove air from a round-bottomed flask, a suspension of the mixture of **18a** and **18b** (62 mg, 0.087 mmol), 10% Pd/C (62 mg), and Et_3N (1.5 mL) in MeOH (10 mL) was vigorously stirred using a stir bar under H_2 atmosphere at r.t. After stirring for 9 h, the reaction mixture was filtered. The filtrate was washed with dil HCl and then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine and dried (anhyd $MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH 15:1) to obtain a mixture of (±)-7-*O*-ethylgnetuhainin I (**20a**) and (±)-gnemontanin F (**20b**) in a 1.3:1 molar ratio as a yellowish oil; yield: 37.1 mg (77%).

(±)-20a

R_f = 0.32 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (600 MHz, CD_3OD): δ = 1.13 (t, *J* = 7.2 Hz, 3 H), 2.74 (3.19 (dd, *J* =3.0, 3.6 Hz, 1 H), 3.19 (q, *J* = 7.2 Hz, 2 H), 3.26 (dd, *J* = 4.2, 4.8 Hz, 1 H), 3.63 (s, 3 H), 3.75 (s, 3 H), 4.03 (d, *J* = 9.0 Hz, 1 H), 4.20 (d, *J* = 3.0 Hz, 1 H), 5.75 (d, *J* = 2.4 Hz, 2 H), 6.02 (d, *J* = 2.4 Hz, 1 H), 6.05 (d, *J* = 2.4 Hz, 1 H), 6.39 (br s, 1 H), 6.42 (d, *J* = 8.4 Hz, 1 H), 6.44 (br s, 1 H), 6.56 (d, *J* = 2.4 Hz, 1 H), 6.66 (d, *J* = 7.8 Hz, 1 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.72 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 15.4, 56.2, 56.3 (2 C), 59.8, 60.8, 65.0, 87.4, 101.1, 102.6, 106.2 (2 C), 106.3, 112.4, 112.5, 115.6, 115.8, 120.9, 121.2, 123.8, 133.6, 138.8, 145.6, 146.9, 147.1, 148.6, 148.7, 150.0, 155.3, 159.1, 159.4 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{32}O_9$ + H: 561.21191; found: 561.21222.

(±)-20b

R_f = 0.30 (CH_2Cl_2–MeOH 8:1).

^{1}H NMR (600 MHz, CD_3OD): δ = 1.07 (t, *J* = 7.2 Hz, 3 H), 3.12 (q, *J* = 7.2 Hz, 2 H), 3.50 (dd, *J* = 5.4, 6.6 Hz, 1 H), 3.58 (dd, *J* = 3.0, 6.0 Hz, 1 H), 3.69 (s, 3 H), 3.73 (s, 3 H), 4.10 (d, *J* =7.8 Hz, 1 H), 4.17 (d, *J* = 4.8 Hz, 1 H), 6.12 (d, *J* = 2.4 Hz, 2 H), 6.16 (d, *J* = 2.4 Hz, 1 H), 6.28 (d, *J* = 2.4 Hz, 1 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.38 (d, *J* = 7.8 Hz, 1 H), 6.44 (br s, 1 H), 6.60 (d, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 6.83 (br s, 1 H).

^{13}C NMR (150 MHz, CD_3OD): δ = 15.5, 56.3 (2 C), 56.8, 60.1, 59.5, 60.9, 64.9, 85.8, 101.4, 102.6, 106.2, 106.8 (2 C), 112.0, 112.7, 115.3, 115.6, 121.2, 121.7, 122.9, 133.0, 139.0, 145.5, 147.2, 148.7, 150.6, 151.3, 155.4, 158.7, 159.2 (2 C).

HRMS (ESI): *m*/*z* calcd for $C_{32}H_{32}O_9$ + H: 561.21191; found: 561.21222.

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Supporting Information

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