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An efficient method for the synthesis of lignans

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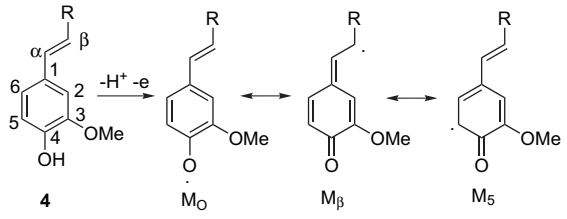
Abstract—An efficient approach for the synthesis of several types of lignans (dibenzylbutanediols, dibenzylbutanes, substituted tetrahydrofurans, aryldihydronaphthalenes, arylnaphthalenes, and aryltetralins) was developed. The regioselective oxidative coupling of ethyl ferulate was used as the key step.

1. Introduction

Lignans, one class of the oldest known natural products, have attracted much interest over the years on account of their broad range of biological activities. The structural diversity of lignans has attracted much attention and many elegant syntheses have been reported.[1–7] One classical route toward lignan structure utilizes the direct oxidative coupling reaction of structurally simple precursors.[6] Though this method is very attractive as it could offer quick access to the skeletons of a wide range of lignans, its application is limited because of the lack of selectivity on the coupling sites. Herein we report an efficient modified strategy hinged on the oxidative coupling reaction for the synthesis of secoisolariciresinol (**1**), dihydroguaiaretic acid (**2**), and divanillyltetrahydrofuran (**3**). Previous attempts to synthesize these compounds using coupling reactions are not successful due to the complexity of coupling pattern and the low yield of the desired product.[8–11] It is expected that other lignan compounds, e.g., arylnaphthalene and aryltetralin derivatives, may also be prepared by this strategy.

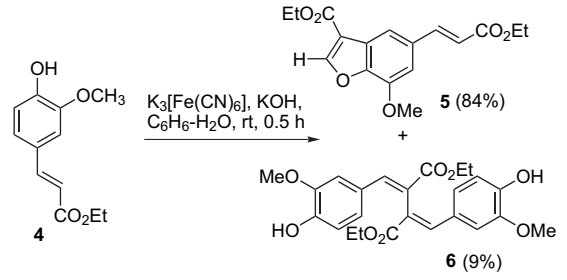
2. Results and discussion

It is known that during the course of oxidative coupling of phenols, phenoxyl radicals are generated as intermediates. In the case of **4** (R=CH_3, CH_2OH), the formed radical has five mesomeric forms, three of which, designated as M_O, M_5, and M_β, are relevant to the coupling reactions (Scheme 1).



Scheme 1.

As a result, six coupling modes for the mesomers are possible (β–β, β–5, β–O, 5–5, 5–O, and O–O), leading to complex products. The major product was reported to be β–5 linked compound.[9] This is verified by our own experiment. Oxidation of ethyl ferulate (**4**: R=CO_2Et) with alkaline potassium ferricyanide in benzene–water two phase system gave rise to β–5 linked **5** as the main product. The desired β–β coupling product **6**[12,13] was only obtained in very low yield (Scheme 2).



Scheme 2.

The chance of β–β coupling could be increased if the β–5 coupling is blocked by another substituent at the 5 position of the phenyl ring.[14] Accordingly, a strategy was developed based on substrate modification. A *tert*-butyl group was introduced to the 5 position of the phenyl ring before oxidation

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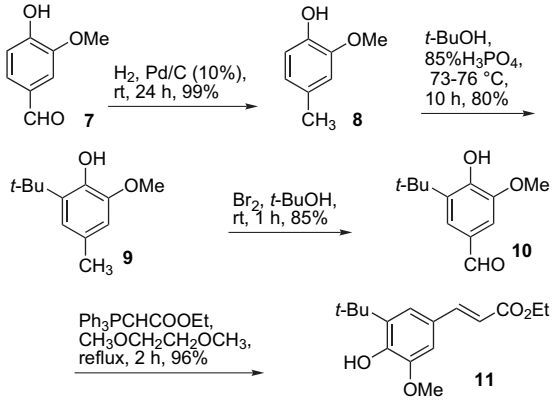
to obstruct the side β–5 coupling. The *tert*-butyl group could be removed afterwards using the method reported by Tashiro et al.[15] It was hoped that this maneuver could improve the yield of desired oxidative coupling product greatly, thus providing a simple concise route for the synthesis of **1**, **2**, and **3**.

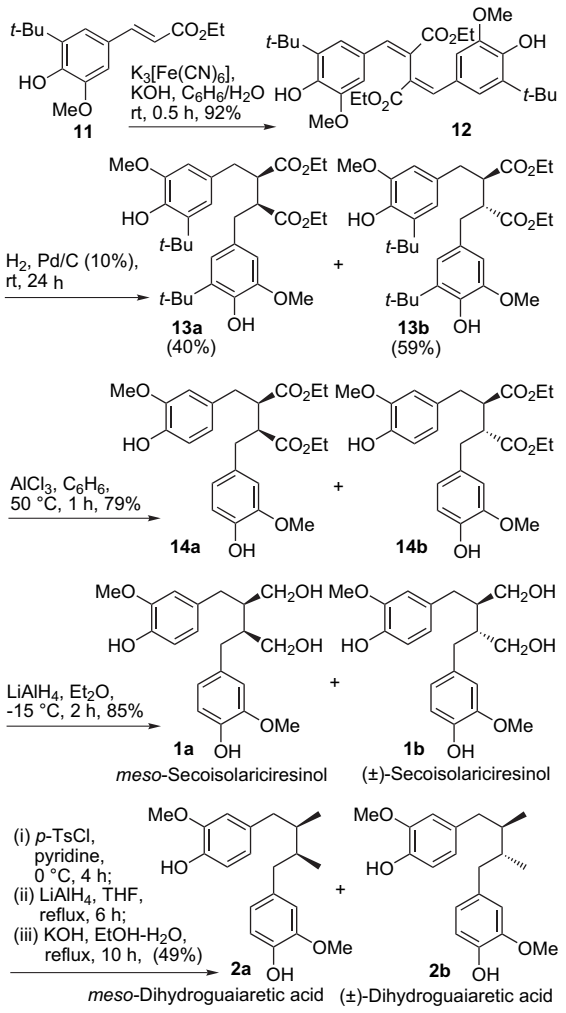
Our syntheses started from the commercially available **7**. Hydrogenation of **7** afforded **8**, which was transformed to **9** by subsequent reaction with *t*-BuOH in H_3PO_4.[16,17] The later step was not complete, but the substrate **8** can be recovered and recycled. Oxidation of **9**, followed by the Wittig reaction, readily gave the desired compound **11**, which served as our key precursor (Scheme 3).[18,19]



Scheme 3.

The stage was now set for the crucial coupling step. As expected, on treatment with alkaline potassium ferricyanide in benzene–water two phase system, **11** was transformed to β–β coupling product **12**[12,13] in excellent yield. Hydrogenation of **12** gave **13** as a mixture of two diastereomers, *erythro*-**13a** and *threo*-**13b**, which could be separated by flash chromatography and each obtained in pure form. The ratio of these two compounds was 2:3 as determined by integration of corresponding signals in the ^{1}H NMR spectra. The relative configurations of **13a** and **13b** were identified by comparing the spectroscopic data of the terminal product **1a** and **1b** with literature data. The *tert*-butyl group was then removed at this stage. Using the method reported by Tashiro et al., the *tert*-butyl groups were transferred from **13a** (**13b**) to solvent benzene via $AlCl_3$ catalyzed Friedel–Crafts reaction.[15] Reduction of **14a** (**14b**) using $LiAlH_4$ afforded **1a** (**1b**). The Compound **2a** (**2b**) was obtained from **1a** (**1b**) by tosylation of the hydroxy groups, reduction with $LiAlH_4$ in THF, and final deprotection of phenol hydroxyl groups with KOH in EtOH–H_2O (Scheme 4).[20,21]

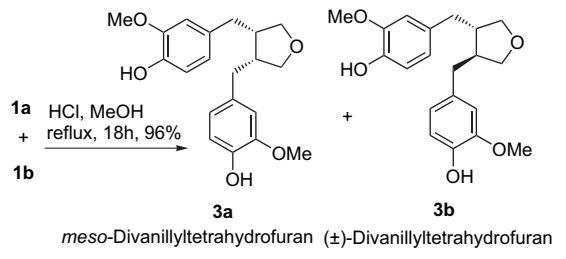
It should be noted that 2,3-dibenzylidenesuccinates, may be in principle readily produced via a double Stobbe condensation, starting from a succinate ester and the appropriate aromatic aldehyde.[12] However, the use of Stobbe condensation reaction for the synthesis of 2,3-dibenzylidenesuccinates containing unprotected phenol hydroxyl group (e.g., compounds **6** and **12**) has not been reported so far to the best of our knowledge. Probably the presence of active phenol hydroxyl group in the starting aromatic aldehyde would hamper the effective condensation. The protection of hydroxyl



Scheme 4.

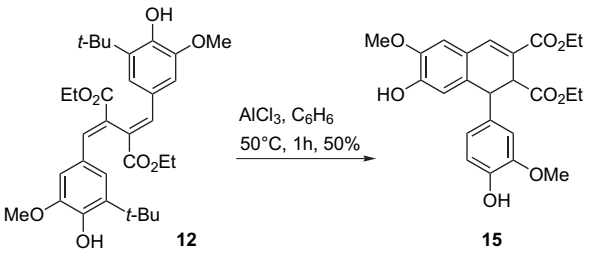
group might overcome this obstacle, but the introduction of a protective group and its removal afterwards would detract from the overall yield and most likely would lead to the generation of byproducts, thus reducing the efficiency of this approach for the preparation of those compounds.

The synthesis of divanillyltetrahydrofuran (**3a** or **3b**) was also achieved by refluxing a methanolic solution of secoisolariciresinol (**1a** or **1b**) under acidic conditions (Scheme 5).



Scheme 5.

Treatment of **12** with $AlCl_3$ in benzene directly afforded aryldihydronaphthalene **15** (Scheme 6). The unreacted starting material **12** can be recovered and recycled.



Scheme 6.

Compound **15** could be converted to a wide variety of arylnaphthalenes and aryltetralins, thus our method reported here might be used for the preparation of these types of natural products.[22,23]

The synthetic secoisolariciresinol (**1**),[24–27] dihydroguaiaretic acid (**2**),[28–31] divanillyltetrahydrofuran (**3**),[32] and aryldihydronaphthalene **15**[33] have identical ^{1}H and ^{13}C NMR spectra to those of the corresponding natural products reported in the literatures.

3. Conclusions

In summary, concise and highly efficient syntheses of dibenzylbutanediol **1**, dibenzylbutane **2**, substituted tetrahydrofuran **3**, and aryldihydronaphthalene **15** have been achieved by employing phenol oxidative coupling reaction as the key step. Modification of the substrate (5–H→5–*t*-butyl) forced the oxidative coupling to undergo an otherwise unfavorable coupling pathway, which dramatically improved the yield of the desired dimer. The *tert*-butyl group can be readily removed via Friedel–Crafts reactions after the coupling. Compared with other methods[34,35] used to synthesize these natural products, secoisolariciresinol (**1**), dihydroguaiaretic acid (**2**), and divanillyltetrahydrofuran (**3**), the strategy described in this paper is convenient and efficient. Furthermore, this route can be applied in the preparation of other lignans, e.g., arylnaphthalenes and aryltetralins via structural modifications. Further investigations will be directed toward stereoselective synthesis of lignan molecules through this methodology.

4. Experimental

4.1. General procedures

All reagents and chemicals were of reagent grade and used as received from commercial suppliers. Melting points were measured on a Kofler apparatus and were uncorrected. IR spectra were obtained in liquid films or KBr disks on an FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with 300 MHz spectrometer. The chemical shifts are referenced in parts per million relative to TMS. Low-resolution mass spectra were recorded in the ES^{+} mode. The high-resolution mass spectra (HRMS) were recorded in the FAB mode. The preparative HPLC separations were performed using a Nova-pak®Silica 6 μm 7.8×300 mm column. The flow rate was 2.5 mL/min utilizing an *n*-hexane/ethyl acetate mobile phase. Flash column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates with petroleum ether/ethyl acetate.

4.1.1. Oxidative coupling of ethyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate (4). The compound **4** (500 mg, 2.25 mmol) in benzene (22.5 mL) was vigorously stirred with an aqueous solution (4.5 mL) containing potassium ferricyanide (1.80 g) and potassium hydroxide (700 mg) for 0.5 h under nitrogen. The organic layer was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (5:1, v/v) to afford **5** (301 mg, 84%) and **6** (45 mg, 9%); **5**, colorless crystals, mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J=7.2 Hz), 1.44 (3H, t, J=7.2 Hz), 4.05 (3H, s), 4.29 (2H, q, J=7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 6.46 (1H, d, J=15.9 Hz), 7.04 (1H, s), 7.79 (1H, d, J=15.9 Hz), 7.82 (1H, s), 8.26 (1H, s). MS *m/z*: 318 (M^{+}), 273, 246, 227. HRMS: $C_{17}H_{18}O_6$+Na calcd 341.0996, found 341.0992; **6**, yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.11 (6H, t, J=6.9 Hz), 3.74 (6H, s), 4.15 (4H, q, J=6.9 Hz), 6.06 (2H, s), 6.84 (2H, d, J=8.1 Hz), 7.06 (2H, dd, J=1.8, 8.1 Hz), 7.13 (2H, d, J=1.8 Hz), 7.86 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.0, 55.6, 61.0, 111.3, 114.5, 124.6, 125.1, 127.3, 142.2, 146.3, 147.3, 167.3. MS *m/z*: 442 (M^{+}), 296, 260, 151, 137.

4.1.2. Synthesis of 2-methoxy-4-methyl-phenol (8). A mixture of compound **7** (200 mg, 1.31 mmol) and 10% Pd/C (5:1, substrate/catalyst) in acetic acid was stirred at 55 °C under hydrogen atmosphere for 24 h, Pd/C was filtered and the solvent was evaporated in vacuo to give **8** (180 mg, 99%) as a colorless oil. ^{1}H NMR data were consistent with literature values.[36] ^{1}H NMR ($CDCl_3$) δ 2.21 (3H, s), 3.74 (3H, s), 5.84 (1H, s), 6.61 (1H, d, J=8.7 Hz), 6.62 (1H, s), 6.80 (1H, d, J=8.7 Hz). MS *m/z*: 138 (M^{+}), 123, 95, 67.

4.1.3. Synthesis of 2-*tert*-butyl-6-methoxy-4-methyl-phenol (9). To a well-stirred emulsion of compound **8** (860 mg, 6.23 mmol) and 85% phosphoric acid (3.20 g, 1.90 mL), *t*-BuOH (1.11 equiv, 0.65 mL) was added at 73–76 °C. The mixture was stirred at the same temperature for 10 h, then the reaction was quenched with water, extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (20:1, v/v) to afford **9** (967 mg, 80%) as a yellowish oil, the unreacted starting material **8** can also be recovered and recycled. ^{1}H and ^{13}C NMR data were consistent with literature values.[37] ^{1}H NMR ($CDCl_3$) δ 1.53 (9H, s), 2.40 (3H, s), 3.94 (3H, s), 5.96 (1H, s), 6.69 (1H, d, J=1.8 Hz), 6.81 (1H, d, J=1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 21.7, 29.7, 34.8, 56.3, 109.6, 119.6, 128.1, 135.4, 142.2, 146.7. MS *m/z*: 194 (M^{+}), 179, 151, 119, 91.

4.1.4. Synthesis of 3-*tert*-butyl-4-hydroxy-5-methoxy-benzaldehyde (10). Bromine (4 equiv, 0.25 mL) was added dropwise with stirring to compound **9** (220 mg, 1.14 mmol) in *t*-BuOH (3.5 mL) at 25 °C. After stirred for 1 h, the mixture was cooled to 20 °C, then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with 10% $NaHSO_3$, distilled water, brine, and dried over $MgSO_4$. The solvent was evaporated

in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (7:1, v/v) to afford **10** (200 mg, 85%) as colorless crystals; mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 3.97 (3H, s), 6.61 (1H, s), 7.32 (1H, d, J=1.8 Hz), 7.45 (1H, d, J=1.8 Hz), 9.82 (1H, s). ^{13}C NMR ($CDCl_3$) δ 29.1, 34.7, 56.3, 106.7, 125.3, 128.3, 135.6, 147.2, 150.3, 191.4. MS *m/z*: 208 (M^+), 193, 165. HRMS: $C_{12}H_{16}O_2$+H calcd 209.1172, found 209.1170.

4.1.5. Synthesis of ethyl (*E*)-3-(3-*tert*-butyl-4-hydroxy-5-methoxyphenyl)-propenoate (11). A solution of $Ph_3PCHCOOEt$ (2 equiv, 719 mg) in ethylene glycol dimethyl ether (20 mL) was added dropwise to the solution of **10** (215 mg, 1.03 mmol) in ethylene glycol dimethyl ether (10 mL), and the mixture was heated under reflux for 2 h. Then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (7:1, v/v) to afford **11** (276 mg, 96%) as white crystals; mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J=6.9 Hz), 1.40 (9H, s), 3.90 (3H, s), 4.26 (2H, q, J=6.9 Hz), 6.29 (1H, d, J=15.6 Hz), 6.30 (1H, s), 6.69 (1H, s), 7.09 (1H, s), 7.63 (1H, d, J=15.6 Hz). MS *m/z*: 278 (M^+), 263, 235, 217, 95. HRMS: $C_{16}H_{22}O_4$+Na calcd 301.1410, found 301.1414.

4.1.6. Synthesis of diethyl (*E*,*E*)-bis(3-*tert*-butyl-4-hydroxy-5-methoxybenzylidene)succinate (12). The compound **11** (200 mg, 0.719 mmol) in benzene (7.2 mL) was vigorously stirred with an aqueous solution (1.45 mL) containing potassium ferricyanide (600 mg) and potassium hydroxide (220 mg) for 0.5 h under nitrogen. The organic layer was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (5:1, v/v) to afford **12** (183 mg, 92%) as a yellow oil; IR (KBr) ν_{max}: 3412, 2957, 1366, 1700, 978 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (6H, t, J=6.9 Hz), 1.34 (18H, s), 3.77 (6H, s), 4.14 (4H, q, J=6.9 Hz), 6.17 (2H, s), 7.03 (2H, s), 7.11 (2H, s), 7.85 (2H, s). MS *m/z*: 554 (M^+), 278, 57. HRMS: $C_{32}H_{42}O_8$+Na calcd 577.2772, found 577.2790.

4.1.7. Synthesis of diethyl bis(3-*tert*-butyl-4-hydroxy-5-methoxybenzyl)succinate (13). A mixture of compound **12** (200 mg, 0.36 mmol) and 10% Pd/C (5:1, substrate/catalyst) in EtOH (15 mL) was stirred at room temperature under hydrogen atmosphere for 24 h, Pd/C was filtrated and the solution was evaporated in vacuo. The residue was purified by column chromatography using benzene to afford **13a** (81 mg, 40%) and **13b** (119 mg, 59%); **13a**, white solid, mp 150–151 °C; IR (KBr) ν_{max}: 3526, 2956, 1726, 1367 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (6H, t, J=6.9 Hz), 1.37 (18H, s), 2.76–2.82 (4H, m), 3.01 (2H, d, J=3.9 Hz), 3.84 (6H, s), 4.01 (4H, q, J=6.9 Hz), 5.87 (2H, s), 6.54 (2H, s), 6.63 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 29.3, 34.3, 36.6, 50.4, 56.1, 60.4, 108.9, 119.3, 128.5, 135.9, 142.7, 146.6, 173.7. MS *m/z*: 558 (M^+), 279, 233, 193, 149, 57. HRMS: $C_{32}H_{46}O_8$+Na calcd 581.3085, found 581.3083. **13b**, yellow oil; IR (KBr) ν_{max}: 3526, 2956, 1730, 1595, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (6H, t, J=6.9 Hz), 1.36 (18H, s), 2.88 (2H, s), 2.92 (4H, s), 3.77 (6H, s), 4.08 (4H, q, J=6.9 Hz), 5.87 (2H, s), 6.43 (2H, s), 6.65 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 29.3, 34.5, 35.7, 48.1, 55.9, 60.5, 108.8, 119.7, 128.2, 134.6, 142.6, 146.4, 173.7. MS *m/z*: 558 (M^+), 279, 193, 149, 57. HRMS: $C_{32}H_{46}O_8$+H calcd 559.3265, found 559.3267.

4.1.8. Synthesis of diethyl bis(4-hydroxy-3-methoxybenzyl)succinate (14). To a solution of compound **13** (**13a** and **13b**, 330 mg, 0.59 mmol) in benzene (20 mL) was added $AlCl_3$ (8 equiv, 631 mg) at 50 °C. The mixture was stirred at the same temperature for 1 h, and then the reaction was quenched with ice, extracted with benzene. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography using benzene and ethyl acetate (8:1, v/v) to afford **14** (208 mg, 79%); **14a**, 83 mg, colorless crystals, mp 180 °C; IR (KBr) ν_{max}: 3422, 2924, 1724, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (6H, t, J=6.9 Hz), 2.72–2.83 (4H, m), 2.98–2.99 (2H, m), 3.85 (6H, s), 4.02 (4H, q, J=6.9 Hz), 5.48 (2H, s), 6.64 (4H, s), 6.80 (2H, d, J=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 36.3, 50.2, 55.9, 60.5, 111.3, 114.1, 121.7, 130.2, 144.2, 146.3, 173.6. MS *m/z*: 446 (M^+), 223, 177, 137, 57. HRMS: $C_{24}H_{30}O_8$+Na calcd 469.1833, found 469.1848. **14b**, 125 mg, colorless oil; IR (KBr) ν_{max}: 3429, 2934, 1727, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, t, J=7.2 Hz), 2.80–2.87 (3H, m), 2.91–2.96 (3H, m), 3.78 (6H, s), 4.10 (4H, q, J=7.2 Hz), 5.49 (2H, s), 6.48 (2H, d, J=1.8 Hz), 6.59 (2H, dd, J=1.8, 8.1 Hz), 6.79 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 35.3, 47.5, 55.6, 60.6, 111.2, 114.0, 121.9, 130.5, 144.1, 146.3, 179.5. MS *m/z*: 446 (M^+), 277, 223, 177, 149, 137, 124, 91. HRMS: $C_{24}H_{30}O_8$+H calcd 447.2013, found 447.2021.

4.1.9. Synthesis of secoisolariciresinol (1). To a suspension of $LiAlH_4$ (1.2 equiv, 6.5 mg) in dry THF (10 mL), compound **14** (**14a** and **14b**, 65 mg, 0.15 mmol) was added at −15 °C, and stirred at same temperature for 2 h. Then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (1:1, v/v) to give the compound **1** (45 mg, 85%); **1** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (1:3, v/v) to afford **1a** (18 mg), colorless oil; **1b** (27 mg), white solid, mp 116–117 °C; **1b**, IR (KBr) ν_{max}: 3351, 2933, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85 (2H, s), 2.64 (2H, dd, J=6.9, 13.5 Hz), 2.74 (2H, dd, J=8.1, 13.5 Hz), 3.54 (2H, dd, J=4.2, 12 Hz), 3.80–3.83 (2H, m), 3.81 (6H, s), 6.58 (2H, s), 6.62 (2H, d, J=8.4 Hz), 6.80 (2H, d, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 35.9, 43.8, 55.8, 60.8, 111.4, 114.1, 121.7, 132.4, 143.8, 146.4. MS *m/z*: 362 (M^+), 277, 189, 137. HRMS: $C_{20}H_{26}O_6$+NH_4 calcd 380.2068, found 380.2061.

4.1.10. Synthesis of dihydroguaiaretic acid (2). A solution of compound **1** (**1a** and **1b**, 420 mg, 1.16 mmol) in pyridine (1.50 mL) was stirred at 0 °C for 20 min, *p*-TsCl (8 equiv, 1.77 g) was added. The mixture was stirred at same temperature for other 4 h, and then the reaction was quenched with 2 N HCl (5 mL). The oil was separated, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated

in vacuo. The residue and $LiAlH_4$ (5 equiv, 182 mg) was added to the solution of dry THF (20 mL), and the mixture was refluxed for 6 h. The reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and a solution (15 mL) of potassium hydroxide (9.0 g) in H_2O (150 mL)–EtOH (150 mL) was added to the residue in three 5 mL portions at 15 min intervals. After reflux for 10 h, the solution was cooled, neutralized with acetic acid, and extracted with ether. The organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (10:1, v/v) to afford **2** (188 mg, 49%); **2** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (9:1, v/v) to afford **2a** (75 mg) and **2b** (113 mg); **2a**, colorless crystals, mp 88–89 °C; IR (KBr) ν_{max}: 3445, 2925, 1513, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (6H, d, J=6.3 Hz), 1.71–1.78 (4H, m), 2.28 (2H, dd, J=9.6, 13.5 Hz), 2.73 (2H, dd, J=5.1, 13.5 Hz), 3.86 (6H, s), 6.61 (2H, d, J=1.8 Hz), 6.65 (2H, d, J=8.4 Hz), 6.82 (2H, d, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 16.2, 30.9, 39.0, 39.2, 55.9, 111.5, 114.0, 121.8, 133.8, 143.7, 146.4. MS *m/z*: 330 (M^+), 208, 193, 165, 149, 137. HRMS: $C_{20}H_{26}O_4-H$ calcd 329.1758, found 329.1766. **2b**, white solid, mp 87–88 °C; IR (KBr) ν_{max}: 3425, 2925, 1513, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (6H, d, J=6.3 Hz), 1.69–1.76 (4H, m), 2.38 (2H, dd, J=6.9, 13.5 Hz), 2.52 (2H, dd, J=6.9, 13.5 Hz), 3.81 (6H, s), 6.52 (2H, s), 6.58 (2H, d, J=8.1 Hz), 6.80 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 13.8, 37.4, 41.0, 55.7, 111.2, 113.8, 121.6, 133.6, 143.5, 146.2. MS *m/z*: 330 (M^+), 137. HRMS: $C_{20}H_{26}O_4-H$ calcd 329.1758, found 329.1759.

4.1.11. Synthesis of divanillyltetrahydrofuran (3). A solution of compound **1** (**1a** and **1b**, 165 mg, 0.46 mmol) in methanol (50 mL) containing 10 N HCl (0.5 mL) was refluxed for 18 h. The solvent was removed and the residue adsorbed on silica gel. Elution with petroleum ether and ethyl acetate (3:1, v/v) afforded **3** (151 mg, 96%); **3** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (3:1, v/v) to afford **3a** (60 mg) and **3b** (91 mg); **3a**, white solid, mp 113–114 °C; IR (KBr) ν_{max}: 3375, 2929, 1603, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47–2.54 (4H, m), 2.80–2.86 (2H, m), 3.64 (2H, dd, J=4.2, 8.1 Hz), 3.79 (2H, dd, J=4.2, 8.1 Hz), 3.87 (6H, s), 5.49 (2H, s), 6.65 (2H, d, J=1.2 Hz), 6.68 (2H, dd, J=1.2, 8.1 Hz), 6.85 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 33.1, 43.8, 55.9, 72.0, 111.2, 114.3, 121.2, 132.5, 143.8, 146.4. MS *m/z*: 344 (M^+), 189, 163, 137. HRMS: $C_{20}H_{24}O_5$ calcd 344.1618, found 344.1622. **3b**, colorless crystals, mp 134–135 °C; IR (KBr) ν_{max}: 3328, 2936, 1606, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13–2.20 (2H, m), 2.48–2.62 (4H, m), 3.53 (2H, dd, J=6.0, 8.7 Hz), 3.82 (6H, s), 3.92 (2H, dd, J=6.0, 8.7 Hz), 5.50 (2H, s), 6.50 (2H, d, J=1.5 Hz), 6.58 (2H, dd, J=1.5, 8.1 Hz), 6.80 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 39.2, 46.4, 55.7, 73.2, 111.0, 114.0, 121.3, 132.3, 143.8, 146.4. MS *m/z*: 344 (M^+), 137, 84. HRMS: $C_{20}H_{24}O_5-H$ calcd 343.1551, found 343.1555.

4.1.12. Synthesis of diethyl 1-(4-hydroxy-3-methoxyphenyl)-1,2-dihydro-6-methoxy-7-hydroxynaphthalene-2,3-dicarboxylate (15). To a solution of compound **12** (200 mg, 0.36 mmol) in benzene (20 mL) was added $AlCl_3$ (12 equiv, 578 mg) at 50 °C. The mixture was stirred at same temperature for 1 h, and then the reaction was quenched with ice, extracted with benzene. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (1:1, v/v) to afford **15** (80 mg, 50%), white solid, mp 153 °C; IR (KBr) ν_{max}: 3402, 2931, 1697, 1512, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J=7.2 Hz), 1.29 (3H, t, J=7.2 Hz), 3.80 (3H, s), 3.91 (3H, s), 3.97 (1H, d, J=4.2 Hz), 4.08 (2H, q, J=7.2 Hz), 4.21 (2H, q, J=7.2 Hz), 4.53 (1H, d, J=4.2 Hz), 5.53 (1H, s), 5.84 (1H, s), 6.45 (1H, dd, J=8.1, 1.8 Hz), 6.63 (1H, d, J=1.8 Hz), 6.68 (1H, s), 6.73 (1H, d, J=8.1 Hz), 6.84 (1H, s), 7.64 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 45.7, 47.4, 55.8, 56.0, 60.7, 61.1, 110.1, 111.1, 114.1, 115.4, 120.5, 123.0, 123.9, 131.2, 134.3, 137.3, 144.3, 145.6, 146.3, 147.5, 166.7, 172.6. MS *m/z*: 442 (M^+), 368, 323, 69, 43. HRMS: $C_{24}H_{26}O_8$+H calcd 443.1700, found 443.1698.

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