Regioselective Oxidative Coupling Approach to the Synthesis of (±)-Matairesinol and (±)-Secoisolariciresinol

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Abstract: An efficient method for the synthesis of (±)-matairesinol and (±)-secoisolariciresinol is presented. By using 5-(*tert*-butyl)ferulic acid as a precursor, a regioselective oxidative coupling step was realized, which gave the desired coupling product in much higher yield (91%) than the literature value (ca. 20%).

Key words: (±)-matairesinol, (±)-secoisolariciresinol, synthesis, regioselective, oxidative coupling

Matairesinol (**1**) and secoisolariciresinol (**2**, Figure 1) are naturally occurring dibenzylbutyrolactone and dibenzylbutanediol lignans isolated from plant sources.[1] Both compounds have attracted much interest over the years because of their broad range of biological activities.[2] One classical synthetic route toward lignan structure utilized the direct oxidative coupling reaction of structurally simple precursors.[3] (±)-Matairesinol has been synthesized by Kenji Mori through oxidative coupling of ferulic acid as the key step,[4] but the yield of the oxidative coupling was unsatisfactory (ca. 20%; Scheme 1).[5]

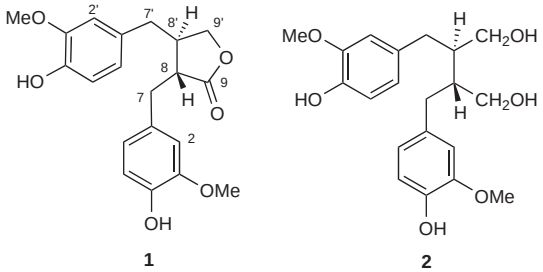
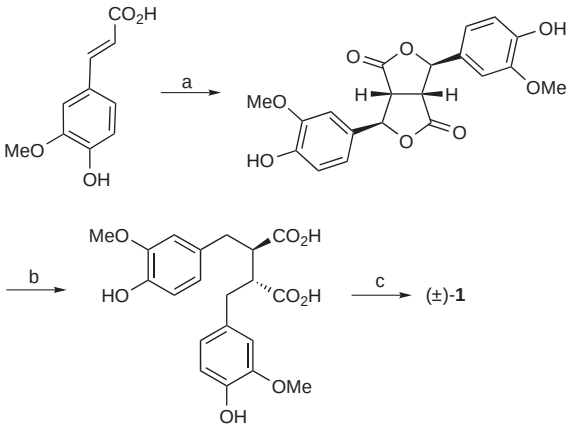


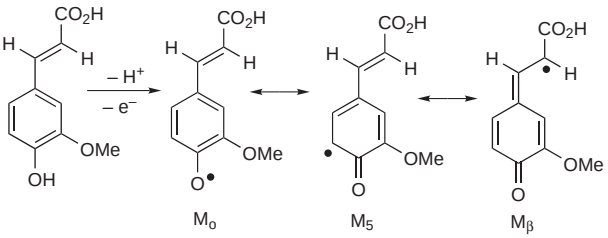
Figure 1

The relative low yield of the desired coupling product in Mori's method could be attributed to the poor regiocontrol in the oxidative coupling step. In fact, there are three important mesomeric forms while ferulic acid is oxidized by ferric chloride–oxygen (Scheme 2).[6] These three mesomers have six different possible coupling modes, β–β, β–5, β–O, 5–5, 5–O, O–O, which lead to a mixture of coupling products.

To effectively increase the yield of the desired β–β-coupling product for the (±)-matairesinol synthesis, a regioselective coupling reaction is essential. For this purpose, 5-



Scheme 1 *Reagents and conditions*: a) $FeCl_3/O_2$, MeOH–H_2O, r.t., ca. 20%; b) 10% Pd/C, H_2, r.t., 92%; c) 1. Ac_2O, THF; 2. LiAlH(O*t*-Bu)$_3$, THF, –5 °C, 78%.



Scheme 2

(*tert*-butyl)ferulic acid was used in this work as a precursor. Substitution of H-5 of ferulic acid **6** by a *tert*-butyl group could block the undesired couplings involving M_5 (i.e., β–5, 5–5 and O–5). Meanwhile, the steric effect of the *tert*-butyl group was also expected to hinder the β–O coupling involving M_o. Therefore, the chance of β–β coupling would be greatly enhanced by incorporating 5-*tert*-butyl group in the ferulic acid precursor. In addition, as a positional protecting group, the *tert*-butyl group could be conveniently introduced and easily removed from the aromatic substrates.[7] Based on this, we conducted the total synthesis of (±)-**1** and (±)-**2** using the following route (Scheme 3).

Our synthetic work began with the preparation of the coupling precursor 5-(*tert*-butyl)ferulic acid (**6**),[8] which was easily obtained in three steps using commercially available creosol (**3**) as starting material. Firstly, **3** was treated with *tert*-butanol and 85% H_3PO_4 at 75 °C to give a colorless oil **4** in 83% yield.[9] Compound **4** was then oxidized

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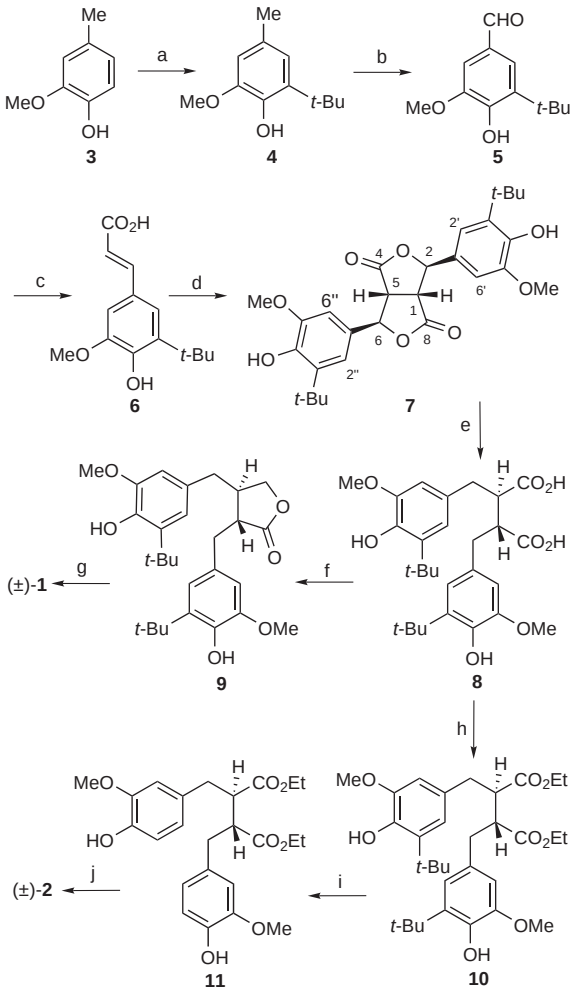

Scheme 3 *Reagents and conditions*: a) *t*-BuOH, 85% H_3PO_4, 75 °C, 83%; b) Br_2, *t*-BuOH, r.t., 85%; c) malonate, pyridine, piperidine, 100 °C, 81%; d) O_2, $FeCl_3$, MeOH–H_2O, r.t., 91%; e) 10% Pd/C, H_2, r.t., 93%; f) DCC, THF, r.t. then $NaBH_4$, THF, r.t., 85%; g) $AlCl_3$, C_6H_6, 50 °C, 83%; h) EtOH, H_2SO_4, reflux, 91%; i) $AlCl_3$, C_6H_6, 50 °C, 82%; j) $LiAlH_4$, THF, –15 °C, 85%.

with Br_2 in *tert*-butanol to provide **5** as a white crystalline solid (85% yield).[10] Treating **5** with malonate in the presence of pyridine and piperidine afforded the coupling precursor **6** in 81% yield. Oxidation of **6** with $FeCl_3/O_2$ gave β–β-coupling product dilactone **7** in high yield (91%),[5,11] which validated our initial thought. Catalytic hydrogenation of **7** over 10% Pd/C in anhydrous ethanol produced diacid **8** in 93% yield.[12] Dehydration of **8** with DCC and subsequent reduction using $NaBH_4$ gave dibenzylbutyrolactone **9**[13] easily in high yield. Thus, (±)-matairesinol (**1**) was obtained after the *tert*-butyl groups of **9** were successfully removed in $AlCl_3$/benzene in 34% overall yield[14] (only 15% in literature[4]). Meanwhile, the esterification of **8** in ethanol formed diester **10**[15] and subsequent removal of the *tert*-butyl protecting groups from **10** gave compound **11** in 82% yield.[16] Finally, the reduction of **11** with $LiAlH_4$ afforded (±)-secoisolariciresinol (**2**) in 33.6% overall yield. All spectral data of (±)-**1**[17] and (±)-**2**[18] were in good agreement with literature values.[1b,c]

The dilactone **7** was assigned as *cis* fusion considering the strain of the lactone rings. The formation of the final racemic *threo*-products also confirmed the *cis* configuration of the dilactone **7**, since the stereochemistry of C-1, C-5 should be retained during the whole transformation process. According to the Karplus equation and Stevenson's analysis of the configuration of analogous dilactone,[19] a small vicinal coupling constant (J_{12} = 0–4 Hz) indicates a H^1–C^1–C^2–H^2 dihedral angle close to 90° and a *trans*-orientation. While in the NMR spectrum of the dilactone **7**, a small coupling constant between H-1 (or H-5) and H-2 (or H-6) ($J_{12} = J_{56}$ = 1.2 Hz) was observed, indicating *trans* orientations of these four protons, respectively. The configuration of these H atoms could be assigned as being axial at C-1 and C-5, and equatorial at C-2 and C-6, which was further confirmed by the NOE difference experiment. Irradiation of the H-1, H-5 afforded a larger NOE at H-6′, H-6″ (+3.62%) and a smaller NOE at H-2, H-6 (+1.53%). Hence, the relative configuration of the four asymmetric centers of **7** was established as shown in Scheme 3.

In conclusion, highly regioselective coupling reaction as the key step of (±)-matairesinol and (±)-secoisolariciresinol total synthesis was achieved by the introduction of *tert*-butyl as protecting group of the coupling precursor. The desired coupling product was obtained in much higher yield than that by the previously reported method.[4] This synthetic strategy may be generally applied as an efficient method for the synthesis of other types of natural lignans and the corresponding research is ongoing in our laboratory.

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(8) 5-(*tert*-Butyl)ferulic acid (**6**): white crystalline solid; mp 185–186 °C. IR (neat): 3506, 2957, 1681 cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ = 1.43 (s, 9 H, CH_3), 3.94 (s, 3 H, OCH_3), 6.38 (d, *J* = 15.9 Hz, 1 H, H-7), 7.15 (d, *J* = 1.8 Hz, 1 H, H-2), 7.27 (br s, 1 H, H-6), 7.62 (d, *J* = 15.9 Hz, 1 H, H-8). ^{13}C NMR (75 MHz, acetone-d_6): δ = 30.0, 35.1, 56.5,

108.3, 115.4, 122.0, 125.9, 136.0, 146.1, 148.0, 148.6, 168.5. MS (EI): *m/z* (%) = 250(8) [M^+], 235 (100) [M – CH_3]$^+$. HRMS (EI): *m/z* calcd for $C_{14}H_{18}O_4$ + H: 251.1278; found: 251.1281.

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(11) Compound **7**: white solid; mp 218–220 °C. IR (neat): 3391, 2950, 1753, 1693, 1652, 1151 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.40 (s, 18 H, CH_3), 3.88 (s, 6 H, OCH_3), 4.11 (d, *J* = 1.2 Hz, 2 H, H-1, -5), 5.79 (br s, 4 H, H-2, H-6), 6.96 (s, 2 H, H-2′, H-2″), 6.97 (s, 2 H, H-6′, H-6″). ^{13}C NMR (75 MHz, acetone-d_6): δ = 29.5 (CH_3), 35.0 (CMe_3), 48.9 (C-1, 5), 56.3 (OCH_3), 83.4 (C-2,6), 107.1 (C-2′, -2″), 117.3 (C-6′, -6″), 129.1 (C-1′, -1″), 135.9 (C-5′, -5″), 145.9 (C-4′, -4″), 148.3 (C-3′, -3″), 175.8 (C=O). MS (EI): *m/z* (%) = 498 (62) [M^+], 483 (40) [M – CH_3]$^+$, 57 (100). HRMS (EI): *m/z* calcd for $C_{28}H_{34}O_8$ + H: 499.2326; found: 499.2328.

(12) Compound **8**: white solid; mp 199–200 °C. IR (neat): 3525, 2955, 1701, 1593, 1297 cm^{-1}. ^{1}H NMR (300 MHz, acetone-d_6): δ = 1.34 (s, 18 H, CH_3), 2.74–2.79 (m, 2 H, CH), 2.86–3.01 (m, 4 H, $ArCH_2$), 3.73 (s, 6 H, OCH_3), 6.68 (br s, 4 H, H-2, H-2′, H-6, H-6′). ^{13}C NMR (75 MHz, acetone-d_6): δ = 29.9, 35.1, 37.7, 50.8, 56.4, 110.8, 120.1, 130.4, 135.3, 143.6, 147.7, 178.3. EIMS: *m/z* (%) = 484 (10) [M – 18]$^+$, 227 (10), 193 (100). HRMS (EI): *m/z* calcd for $C_{28}H_{38}O_8$ + Na: 525.2459; found: 525.2454.

(13) Compound **9**: pale yellow gum. IR (neat): 3524, 2955, 1767, 1595, 1232 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 9 H, CH_3), 1.39 (s, 9 H, CH_3), 2.40–2.70 (m, 4 H, H-7′, H-8, H-8′), 2.91 (dd, *J* = 14.0, 6.3 Hz, 1 H, H-7), 3.03 (dd, *J* = 14.0, 4.8 Hz, 1 H, H-7), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 3.88 (dd, *J* = 9.3, 6.6 Hz, 1 H, H-9′,), 3.96 (dd, *J* = 9.0, 6.6 Hz, 1 H, H-9′), 5.89 (s, 1 H, OH), 5.91 (s, 1 H, OH), 6.33 (d, *J* = 1.2 Hz, 1 H, H-2′), 6.54 (d, *J* = 1.2 Hz, 1 H, H-2), 6.59 (d, *J* = 1.2 Hz, 1 H, H-6′), 6.69 (br s, 1 H, H-6). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.6, 29.7, 34.8, 35.2, 38.9, 41.3, 47.1, 56.3, 71.6, 108.7, 109.5, 119.3, 120.1, 128.1, 128.3, 135.5, 135.8, 143.1, 143.2, 146.8, 147.0, 179.2. MS (EI): *m/z* (%) = 470 (8) [M^+], 193 (100). HRMS (EI): *m/z* calcd for $C_{28}H_{38}O_6$ + NH_4: 488.3007; found: 488.3009.

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(15) Compound **10**: colorless oil. IR(neat): 3526, 2956, 1730, 1595, 1372 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.18 (t, *J* = 6.9 Hz, 6 H, CH_2CH_3), 1.36 (s, 18 H, CH_3), 2.86–2.89 (m, 2 H, CH), 2.90–2.96 (m, 4 H, $ArCH_2$), 3.77 (s, 6 H, OCH_3), 4.08 (q, *J* = 6.9 Hz, 4 H, CH_2CH_3), 5.87 (s, 2 H, OH), 6.43 (s, 2 H, H-2, H-2′), 6.65 (s, 2 H, H-6, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): 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 (EI): *m/z* (%) = 558 (14) [M^+], 279 (10), 193 (88), 149 (100). HRMS (EI): *m/z* calcd for $C_{32}H_{46}O_8$ + H: 559.3265; found: 559.3267.

(16) Compound **11**: colorless oil. IR (neat): 3429, 2934, 1727, 1516 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.2 Hz, 6 H, CH_2CH_3), 2.83–2.86 (m, 2 H CH), 2.91–2.96 (m, 4 H, $ArCH_2$), 3.78 (s, 6 H, OCH_3), 4.10 (q, *J* = 7.2 Hz, 4 H, CH_2CH_3), 5.49 (s, 2 H, OH), 6.48 (s, 2 H, H-2, H-2′), 6.59 (d, *J* = 8.1 Hz, 2 H, H-6, H-6′), 6.79 (d, *J* = 8.1 Hz, 2 H, H-5, H-5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1, 35.3, 47.5, 55.6, 60.6, 112.2, 114.0, 121.9, 130.5, 144.1, 146.3, 179.5. MS (EI): *m/z* (%) = 446 (10) [M^+], 277 (31), 223 (24), 177 (28), 149 (53), 137 (100). HRMS (EI): *m/z* calcd for $C_{24}H_{30}O_8$ + H: 447.2013; found: 447.2021.

(17) (±)-Matairesinol (**1**): pale yellow solid; mp 66–67 °C. IR (neat): 3418, 2935, 1760, 1606, 1239 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40–2.63 (m, 4 H, H-7, H-8, H-8′), 2.87 (dd, *J* = 14.2, 6.8 Hz, 1 H, H-7′), 2.95 (dd, *J* = 14.2, 5.2 Hz, 1 H, H-7′), 3.80 (s, 6 H, OCH_3), 3.89 (dd, *J* = 9.2, 7.2 Hz, 1 H, H-9), 4.15 (dd, *J* = 8.8, 7.2 Hz, 1 H, H-9), 5.64 (br s, 2 H, OH), 6.40 (d, *J* = 1.6 Hz,1 H, H-2), 6.50 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-6), 6.59 (dd, *J* = 8.0, 2.0 Hz, 1 H, H-6′), 6.60 (br s, 1 H, H-2′), 6.79 (d, *J* = 8.4 Hz,1 H, H-5), 6.81 (d, *J* = 8.4Hz, 1 H, H-5′). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 33.7, 36.9, 40.9, 45.7, 55.4, 55.5, 70.8, 112.6, 113.4, 115.4, 120.7, 120.6, 128.9, 129.7, 144.9, 145.1, 147.4, 147.5, 178.6. MS (EI): *m/z* (%) = 358 (4) [M^+], 137 (100). HRMS (EI): *m/z* calcd for $C_{20}H_{22}O_6$ + NH_4: 376.1755; found: 376.1754.

(18) (±)-Secoisolariciresinol (**2**): white solid; mp 116–117 °C. IR (neat): 3351, 2933, 1515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.85 (br s, 2 H, H-8, H-8′), 2.64 (dd, *J* = 13.5, 6.9 Hz, 2 H, H-7, H-7′), 2.74 (dd, *J* = 13.5, 8.1 Hz, 2 H, H-7, H-7′), 3.54 (dd, *J* = 12, 4.2 Hz, 2 H, H-9, H-9′), 3.78–3.85 (m, 2 H, H-9, H-9′), 3.81 (s, 6 H, OCH_3), 6.58 (s, 2 H, H-2, H-2′), 6.62 (d, *J* = 8.4 Hz, 2 H, H-6, H-6′), 6.80 (d, *J* = 8.4 Hz, 2 H, H-5, H-5′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 35.9, 43.8, 55.8, 60.8, 111.4, 114.1, 121.7, 132.4, 143.8, 146.4. MS (EI): *m/z* (%) = 362 (11) [M^+], 277 (6), 189 (6), 137 (100). HRMS (EI): *m/z* calcd for $C_{20}H_{26}O_6$ + NH_4: 380.2068; found: 380.2061.

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