Biosynthesis of Resveratrol Dimers by Regioselective Oxidative Coupling Reaction

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Abstract: A wide array of natural resveratrol dimers was prepared by the regioselective oxidative coupling reaction of 3,5-di-(*tert*-butyl)resveratrol using several types of metal oxidants (Ag_2O, Ag_2CO_3, MnO_2, and $FeCl_3·6H_2O$) in different solvent systems (benzene–acetone and dichloromethane). Subsequent debutylation of these coupling products resulted in racemic pallidol and ampelosin F.

Key words: resveratrol dimmer, pallidol, ampelosin F, oxidative coupling, biosynthesis

Resveratrol (**1**) and its oligomers are a class of plant polyphenols that have attracted intense interest over the past thirty years on account of their intricate structures and diverse biological activities.[1] Currently, the synthesis of resveratrol dimers, such as **2**–**6** (Figure 1) and their analogues has been a popular research topic. However, only a few syntheses have so far been reported because of the complex molecular architectures of dimeric resveratrol. Thus, their total synthesis remains a great challenge for chemists.

Resveratrol dimers are formed in nature by oxidative dimerization of resveratrol. At least three important mesomers, M_5, M_8, and M_{10}, have been identified as being derived from **1** through enzymatic catalysis (Scheme 1).[2] The diversity of coupling modes leads to the structural complexity of the oligomers, which increases the difficulty of their regiocontrolled synthesis. Within the limited studies on the biosynthesis of oligostilbenes, Snyder's group developed an elegant and versatile route for the synthesis of several dimeric resveratrols such as quadragularin A (**4**), pallidol (**5**), and ampelosin F (**6**) by constructing the ring system from brominated stilbenes.[3] Sarpong and co-workers reported on the synthesis of potential precursors that may be used to assemble the carbon framework of several resveratrol-derived dimeric products by palladium-catalyzed cascade reaction.[4] Nearly all in vitro biosynthetic efforts have been devoted to the direct oxidative coupling reaction of resveratrol (**1**) and its analogues, owing to its advantage of quick access to the skeleton of a wide range of oligomers from structurally simple precursors. However, with natural resveratrol as the coupling precursor, the 8–5 coupling product δ-viniferin (**3**) has always been predominant in the dimeric mixture and ε-viniferin (**2**) has been rarely isolated by either enzymatic oxidation (horseradish, laccases, soybean, and

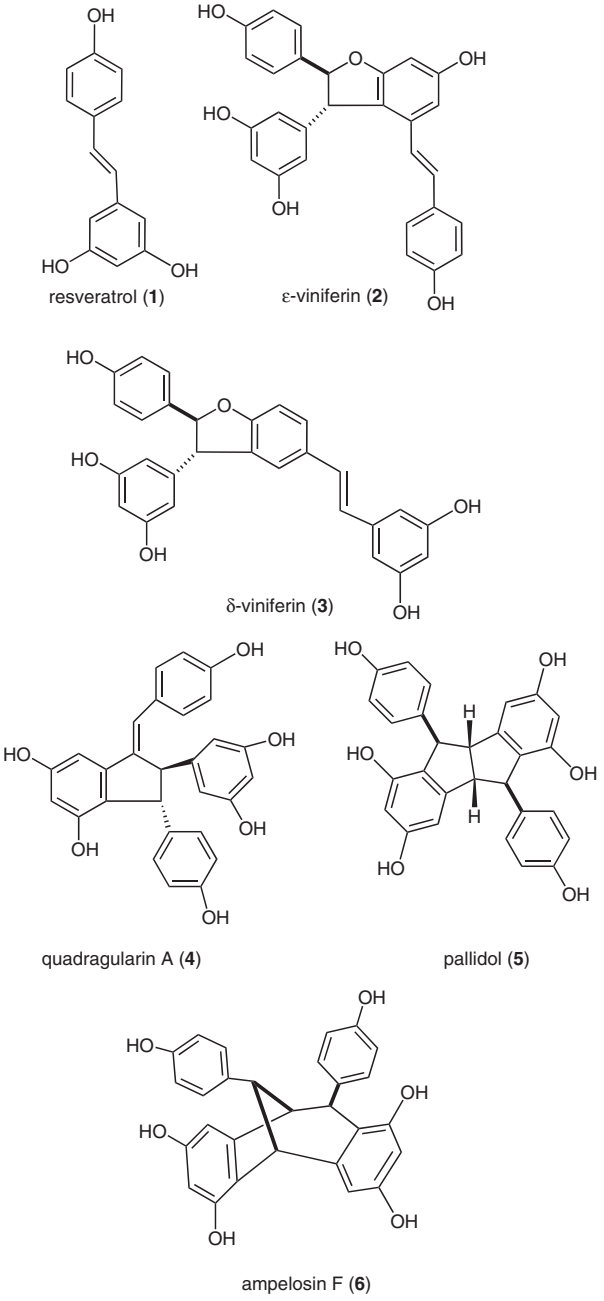

Figure 1 Resveratrol (**1**) and selected natural resveratrol dimers

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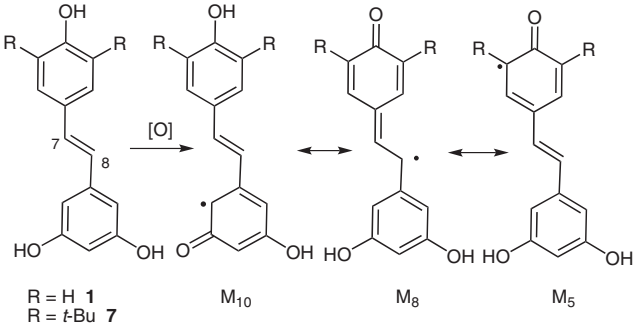
fungi peroxidase)[5,6] or the use of a variety of conventional inorganic oxidants [$K_3Fe(CN)_6$, Ag(I), Cu(I)), Cu(II), Mn(II), and $FeCl_3$).[7] The application of the oxidative coupling reaction for the synthesis of diverse oligostilbenes is thus largely restricted by the lack of selectivity on the coupling sites. Based on the aforementioned facts, our previous work reported the successful synthesis of racemic **4** by introducing bulky butyl groups in **1** to impede the undesired 8–5 coupling mode in the oxidative coupling reaction promoted by horseradish peroxidase.[8] In order to intensively investigate this strategy, a study was conducted on the dimerization of 3,5-di-(*tert*-butyl) resveratrol (**7**, Scheme 1) by means of $FeCl_3$ and other one-electron oxidants in different solvents to obtain structurally diverse resveratrol dimers.



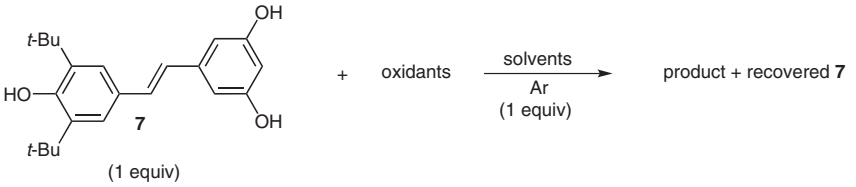
Scheme 1 Three important mesomers of **1** and **7**

Compound **7** was subjected to oxidative dimerization by means of several metallic oxidants under different conditions. The major isolated products are described in Table 1 and Scheme 2. When **7** was treated with an equimolar amount of Ag_2O in a mixture of benzene and acetone at a ratio of 2:1 (v/v) under argon atmosphere at room temperature for 6 hours, the dimeric intermediate **8**[9] was isolated as a major product with a 22% yield, and 12% unchanged **7** was recovered. When CH_2Cl_2 was used as the solvent instead of benzene and acetone, the same product **8** was obtained, with a largely improved yield of 48%, and 28.5% of unreacted **7** was recovered. Similar reaction results and solvent effects were observed when **7** was treated with Ag_2CO_3 and MnO_2 in benzene–acetone and CH_2Cl_2. However, the solvent effects of CH_2Cl_2 on Ag_2CO_3 and MnO_2 were more obvious than on Ag_2O because most of the starting material was recovered unchanged in the former reactions. Nevertheless, the predominant formation of the 8–8 coupling product **8** further confirmed the hindrance effect of bulky *tert*-butyl groups at the C-3 and C-5 positions of resveratrol (**1**), which was consistent with our previous report.[8]

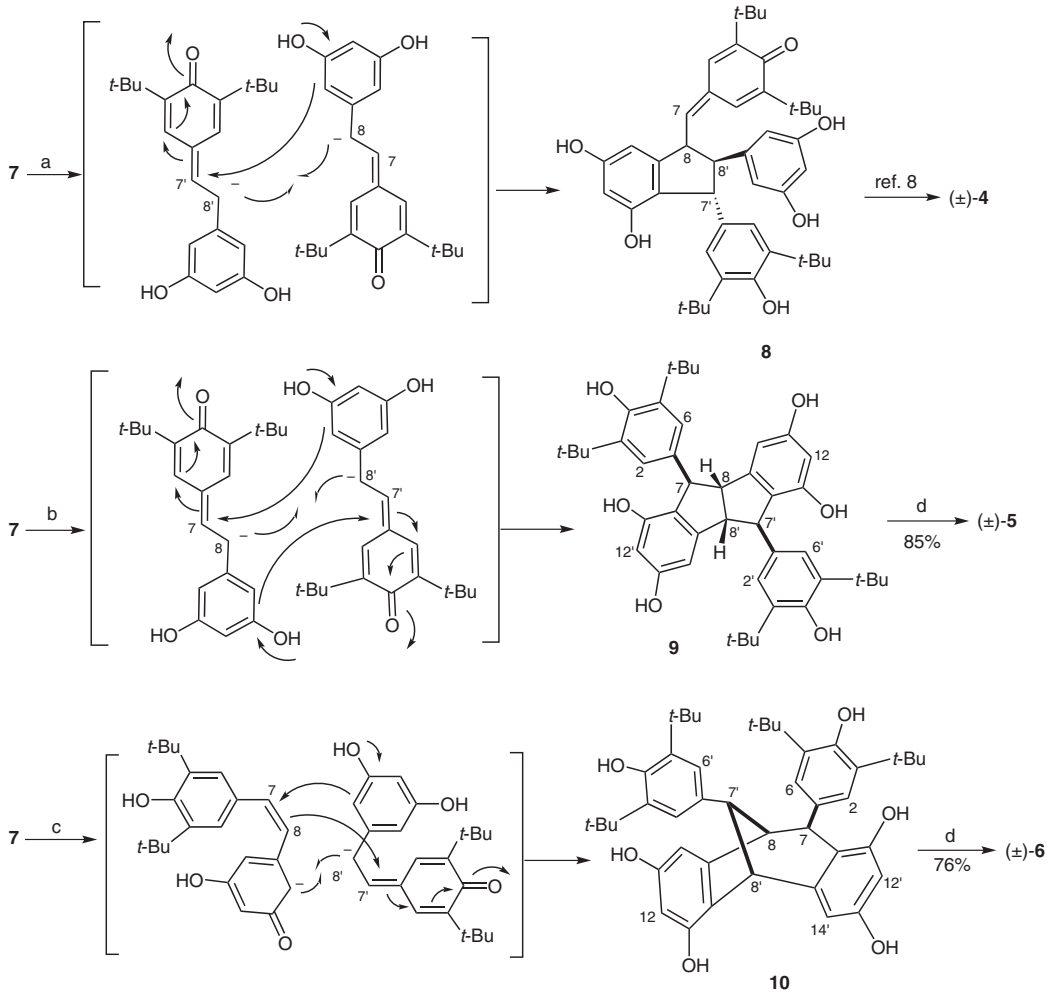
When compound **7** was treated with an equimolar amount of $FeCl_3 \cdot 6H_2O$ at room temperature, the reaction outcome differed for the various solvent systems. When the reaction was carried out in benzene–acetone, a pallidol-like intermediate **9**[10] was obtained as the 8–8 coupling product in a 55% yield. The use of CH_2Cl_2 resulted in an ampelosin F derived compound **10**[11] as the 8–10 coupling product with a 45% yield. Product **9** was not found under these reaction conditions (Scheme 2). This result was slightly different from the work of Velu's group,[12] which reported the oxidative dimerization of stilbene derivatives catalyzed by $FeCl_3 \cdot 6H_2O$ in CH_2Cl_2, giving rise to a mixture of pallidol (**5**) and ampelosin F (**6**) analogues in low yields. Thus, the variance of the coupling products under the same oxidative conditions may be largely attributed to the substituent effects on the stilbene rings.

With three dimeric intermediates **8**, **9**, and **10**, the synthesis of the related natural resveratrol dimers by their debutylation reaction could be conducted. First, as we reported previously,[8] dimer **8** could easily be converted to (±)-**4** via a prototropic rearrangement followed by a debutylation

Table 1 Coupling Dimerization of **7** with Oxidizing Reagents



Entry	Oxidants	Solvents	Temp (°C)	Time (h)	Product	Conversion (%)	Recovered **7** (%)
1	Ag_2O	benzene–acetone (2:1)	25	6	**8**	22	12
2	Ag_2O	CH_2Cl_2	25	24	**8**	48	28.5
3	Ag_2CO_3	benzene–acetone (2:1)	25	6	**8**	19	12.5
4	Ag_2CO_3	CH_2Cl_2	25	24	**8**	59	64.4
5	MnO_2	benzene–acetone (2:1)	25	6	**8**	16	24
6	MnO_2	CH_2Cl_2	25	24	**8**	54	76
7	$FeCl_3 \cdot 6H_2O$	benzene–acetone (2:1)	25	24	**9**	55	45
8	$FeCl_3 \cdot 6H_2O$	CH_2Cl_2	25	3	**10**	45	25



Scheme 2 *Reagents and conditions*: a) Ag_2O, Ag_2CO_3, or MnO_2, benzene–acetone (2:1) or CH_2Cl_2, r.t., Ar; b) $FeCl_3{\cdot}6H_2O$, benzene–acetone (2:1), r.t., Ar; c) $FeCl_3{\cdot}6H_2O$, CH_2Cl_2; r.t., Ar; d) $AlCl_3$, $MeNO_2$, toluene, 60 °C.

reaction with $AlCl_3/MeNO_2$ in toluene. Next, dimeric product **9** was subjected to a direct debutylation reaction promoted by $AlCl_3/MeNO_2$,[13] smoothly producing racemic **5** in good yield.[14] Finally, compound **10** was subjected to the same debutylation reaction to produce the desired natural product (±)-**6** (Scheme 2).[15] All the spectra data of (±)-**5** and (±)-**6** are in good agreement with literature values,[16] which confirms the configuration of **9** and **10**, since the stereochemistry of H-7, H-8, H-7′, H-8′ in **9** and **10** should be retained during the transformation processes.

In summary, highly regioselective oxidative coupling reactions catalyzed by several metallic oxidants using 3,5-di-(*tert*-butyl) resveratrol (**7**) as a potentially useful precursor were studied. The reaction produced the corresponding coupling products **8**, **9**, and **10** in higher yields as compared to previously reported biosynthetic routes.[7c,8,12] Three resveratrol dimers, (±)-**4**, (±)-**5**, and (±)-**6**, could be synthesized by the subsequent debutylation of the coupling dimers with good yields. Further detailed investigation of the stereoselective synthesis of a wide array of resveratrol oligomers through this methodology is currently ongoing in our laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) The spectra data of compound **8** were completely consistent with literature data.[8]

(10) **Analytical Data for Compound 9**
Pale yellow amorphous powder. IR (neat): 3641, 3348, 2957, 1688, 1605, 1510, 1432, 1238, 1018 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 1.40 (s, 36 H, *t*-Bu), 3.91 (br s, 2 H, H-8, H-8′), 4.58 (br s, 2 H, H-7, H-7′), 5.84 (br s, 2H, OH), 6.18 (d, *J* = 2.0 Hz, 2 H, H-14, H-14′), 6.62 (d, *J* = 1.2 Hz, 2 H, H-12, H-12′), 7.06 (br s, 4 H, H-3, H-5, H-3′, H-5′), 7.88 (br s, 2 H, OH), 8.09 (br s, 2 H, OH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 30.8, 35.0, 54.5, 60.5, 102.3, 103.3, 123.4, 124.4, 137.6, 137.8, 150.2, 152.7, 155.3, 159.1. ESI-HRMS: *m/z* calcd for $C_{44}H_{54}O_6$ + H: 679.3993; found: 679.3999.

(11) **Analytical Data for Compound 10**
Pale yellow amorphous powder. IR (neat): 3420, 2852, 1628, 1530, 1472, 1308, 1054 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 1.25 (s, 18 H, *t*-Bu), 1.40 (s, 18 H, *t*-Bu), 3.28 (br s, 1 H, H-8), 3.67 (br s, 1 H, H-7′), 4.14 (br s, 1 H, H-8′), 4.22 (br s, 1 H, H-7), 5.73 (br s, 1 H, OH), 5.83 (br s, 1 H, OH), 6.08 (d, *J* = 1.6 Hz, 1 H, H-14), 6.15 (d, *J* = 2.0 Hz, 1 H, H-14′), 6.44 (d, *J* = 2.0 Hz, 1 H, H-12′), 6.50 (d, *J* = 1.6 Hz, 1 H, H-12), 6.71 (br s, 2 H, H-2′, H-6′), 7.12 (br s, 2 H, H-2, H-6), 7.35 (br s, 1 H, OH), 7.92 (br s, 1 H, OH), 7.93 (br s, 1 H, OH), 8.01 (br s, 1 H, OH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 30.6, 30.8, 35.0, 35.1, 48.0, 49.3, 51.9, 59.6, 101.6, 104.3, 105.7, 114.2, 124.8, 125.3, 128.2, 135.8, 137.4, 137.6, 138.2, 147.4, 147.8, 152.7, 153.0, 157.1, 157.9, 158.5. ESI-HRMS: *m/z* calcd for $C_{44}H_{54}O_6$ + H: 679.3993; found: 679.3988.

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(14) **Representative Procedure**
A solution of $AlCl_3$ (0.1 g, 0.72 mmol) in $MeNO_2$ (1 mL) was added to a solution of compound **9** (46 mg, 0.06 mmol) in dry toluene (10 mL) at 60 °C. The reaction mixture was stirred for 30 min. Then quenched with ice-water (5 mL), and extracted with EtOAc. The combined organic layer was washed with sat. brine and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue puried on a silica gel (CH_2Cl_2–MeOH, 15:1) to afford (±)-pallidol (**5**, 24 mg, 85%) as a pale yellow amorphous powder. IR (neat): 3402, 2956, 2826, 1638, 1508, 1462, 1246, 1080 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 3.80 (br s, 2 H, H-8, H-8′), 4.56 (br s, 2 H, H-7, H-7′), 6.18 (d, *J* = 2.0 Hz, 2 H, H-14, H-14′), 6.61 (d, *J* = 2.0 Hz, 2 H, H-12, H-12′), 6.70 (d, *J* = 8.4 Hz, 4 H, H-3, H-3′, H-5, H-5′), 6.97 (d, *J* = 8.4 Hz, 4 H, H-2, H-2′, H-6, H-6′), 7.84 (br s, 2 H, OH), 8.06 (br s, 2 H, OH), 8.08 (br s, 2 H, OH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 54.0, 60.5, 102.5, 103.4, 115.8, 123.2, 129.0, 137.7, 150.3, 155.3, 156.3, 159.4. ESI-HRMS: *m/z* calcd for $C_{28}H_{22}O_6$ + H: 455.1489; found: 455.1490.

(15) **Analytical Data for (±)-Ampelosin F (6)**
Pale yellow amorphous powder. IR (neat): 3380, 2854, 1628, 1495, 1354, 1205, 1055 cm^{-1}. ^1H NMR (400 MHz, acetone-d_6): δ = 3.35 (br s, 1 H, H-8), 3.64 (br s, 1 H, H-7′), 4.12 (br s, 1 H, H-8′), 4.19 (br s, 1 H, H-7), 6.06 (d, *J* = 2.0 Hz, 1 H, H-14), 6.15 (d, *J* = 2.0 Hz, 1 H, H-14′), 6.44 (d, *J* = 2.0 Hz, 1 H, H-12′), 6.52 (d, *J* = 2.0 Hz, 1 H, H-12), 6.56 (d, *J* = 8.0 Hz, 2 H, H-3′, H-5′), 6.75 (d, *J* = 8.0 Hz, 2 H, H-3, H-5), 6.78 (d, *J* = 8.0 Hz, 2 H, H-2′, H-6′), 7.08 (d, *J* = 8.0 Hz, 2 H, H-2, H-6), 7.48 (br s, 1 H, OH), 7.88 (br s, 1 H, OH), 7.97 (br s, 1 H, OH), 8.03 (br s, 1 H, OH), 8.04 (br s, 1 H, OH), 8.10 (br s, 1 H, OH). ^{13}C NMR (100 MHz, acetone-d_6): δ = 46.9, 49.4, 50.2, 58.0, 101.6, 101.9, 104.0, 105.4, 113.0, 113.1, 115.3, 127.5, 129.0, 129.6, 135.2, 138.1, 147.0, 147.3, 152.9, 156.0, 156.9, 157.5, 158.0, 158.4. ESI-HRMS: *m/z* calcd for $C_{28}H_{22}O_6$ + H: 455.1489; found: 455.1496.

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