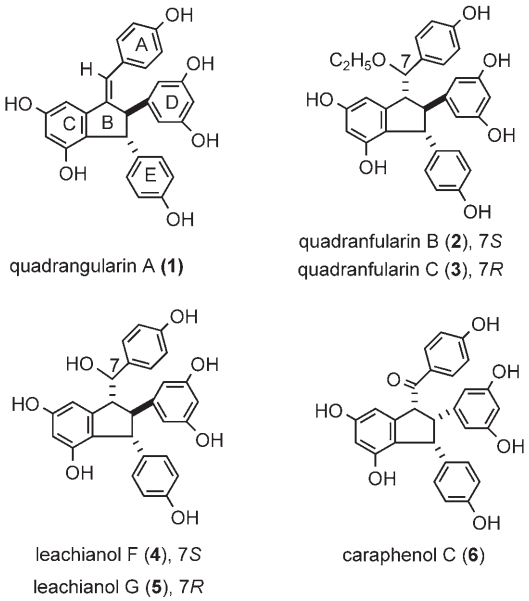
Natural Products Synthesis

DOI: 10.1002/ange.200603097

Total Synthesis of (±)-Quadrangularin A**

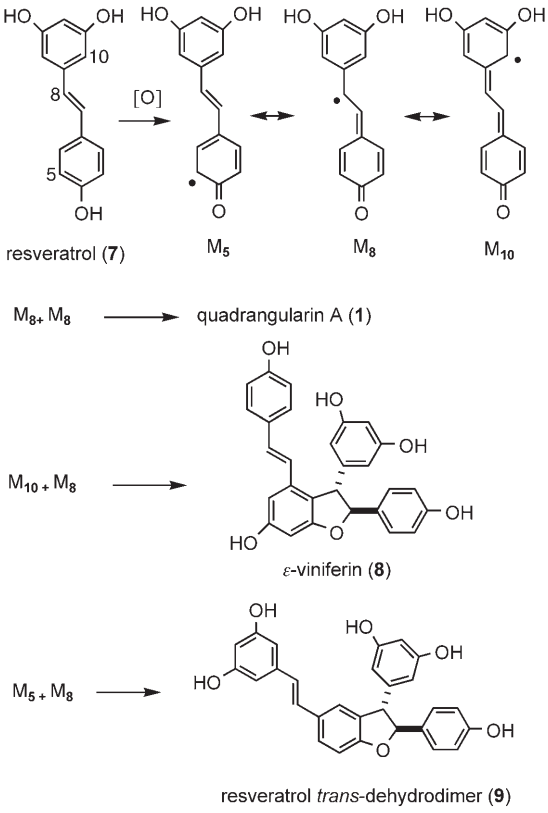
*Wenling Li, Hao Li, Ying Li, and Zijie Hou**

Pais and co-workers isolated (−)-quadrangularin A (**1**) from the stem of *Cissus quadrangularis* in 1999.[1] Several analogues of **1**, compounds **2**–**6**, have been obtained from other plants (Scheme 1).[1,2] These molecules are all dimers or substituted dimers of resveratrol (**7**) with an indane skeleton. To date, no synthetic effort towards this family of compounds has been reported. Although cyclodimerizations of stilbene under acidic conditions to form indanes and/or tetralins have been studied extensively,[3] this strategy is not generally applicable to the synthesis of natural oligostilbenes owning to poor stereoselectivity and the limitation to stilbene substrates. Therefore, it remained a significant challenge for chemists to develop new strategies for the synthesis of these compounds. As part of a program to study the biomimetic synthesis of stilbene oligomers,[4] we report herein an approach to the synthesis of compound **1** based on regioselective oxidative coupling.



Scheme 1. Quadrangularin A (**1**) and analogues **2**–**6**.

To design a synthetic route to **1**, it is essential to understand the possible biosynthetic mechanism for the dimerization of **7** in vivo. At least three important mesomers, M_5, M_8, and M_{10}, have been identified as being derived from **7** under enzymatic catalysis in the organism.[5] Coupling reactions between these radical mesomers could produce various resveratrol dimers, such as the natural products **1**, **8**, and **9** (Scheme 2). The structural complexity of the oligomers results from the diversity of the coupling modes, which also increases the difficulty of their regiocontrolled biomimetic synthesis in vitro.



Scheme 2. Possible biosynthetic pathways of resveratrol dimers.

Resveratrol oligomers have novel structures and a wide range of biological activity but low natural abundance; therefore, many chemists have studied the oxidative coupling of resveratrol under a variety of conditions since ε-viniferin (**8**) was first isolated in 1977 by Langcake and Pryce.[6] However, the major product obtained was mostly the 5–8-coupling product, that is, resveratrol *trans*-dehydrodimer (**9**), regardless of whether enzymes (peroxidase[7] or laccase[8]) or inorganic oxidants ($FeCl_3$, $K_3(FeCN)_6$, or Ag_2O) were used.[9] Thus, we deduced that the 5–8-coupling mode occurs predominantly and that its product **9** is stable under the oxidative conditions employed. We believed that the critical step for the synthesis of the 8–8-coupling product **1** could be

[*] W. Li, H. Li, Prof. Y. Li, Prof. Z. Hou
State Key Laboratory of Applied Organic Chemistry and
Department of Chemistry
Lanzhou University
222 Tianshui Street S., Lanzhou 730000 (P.R. China)
Fax: (+86) 931-891-2582
E-mail: houzj@lzu.edu.cn
W. Li
Department of Chemical and Biological Engineering
Lanzhou Railway University
Lanzhou 730000 (P.R. China)

[**] We are grateful to Prof. H.-L. Zhang and Dr. J.-C. Liao for helpful discussions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

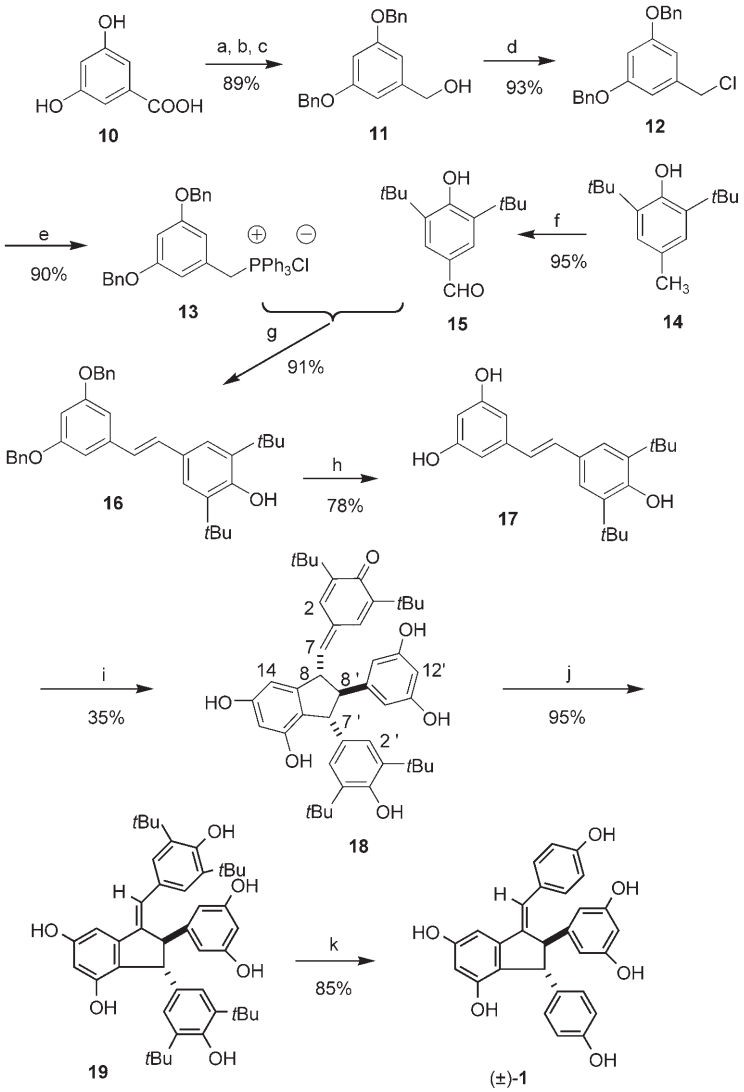
made possible by impeding the formation of the 5–8-coupling product **9**.

Enlightened by the work of Sarkanen and Wallis, who found that the presence of non-hydrogen substituents (OMe or *tert*-butyl) adjacent to the phenolic hydroxy group of some phenylpropanoids hindered the undesired 5–8 and 8–O coupling and greatly enhanced the chance of the 8–8 coupling (Scheme 3),[10] we decided to introduce *tert*-butyl protecting groups at C3 and C5 of resveratrol to favor a regioselective coupling reaction. The advantage of this method is that *tert*-butyl substituents can be conveniently incorporated into and efficiently removed from aromatic substrates.[11] Thus, the synthetic route to **1** was designed and carried as shown in Scheme 4.

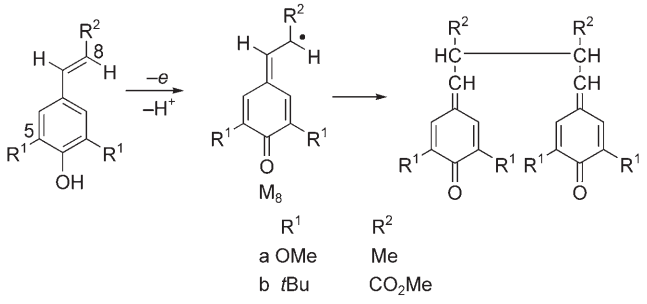
The coupling precursor 3,5-di-(*tert*-butyl)resveratrol (**17**) was prepared in seven steps from 3,5-dihydroxybenzoic acid (**10**). First, the dibenzyl alcohol **11** was made from **10** through a straightforward three-step sequence of esterification, benzyl protection, and reduction.[12] Compound **11** was then converted into the dibenzyl chloride **12**,[13] and **12** was transformed into the phosphonium salt **13**. To form the second substrate for the planned olefination, **14** was oxidized with Br_2 in *tert*-butanol to produce the aldehyde **15**.[14] A Wittig reaction between **13** and **15** in toluene at reflux afforded the *E* stilbene **16** in good yield; it was not necessary to protect the phenolic hydroxy group of **15**. Finally, the benzyl protecting groups were removed[4] from **16** to give the coupling precursor **17** in 53% overall yield.

Next, the treatment of **17** with horseradish peroxidase (HRP) and H_2O_2[15] in aqueous acetone at room temperature under an argon atmosphere for 48 h gave the 8–8-coupling product **18** in 35% yield. This result validated our original hypothesis. It was noted that the prolonged reaction time or the large amount of H_2O_2 used resulted in the formation of minor trimeric products.[16] The structure of **18** was established on the basis of HRMS, ^{1}H NMR, ^{13}C NMR, and 2D correlation NMR spectral data. The presence of a quinone methide moiety in **18** was supported by the existence of three mutually coupled signals corresponding to methine hydrogen atoms (8-H, 8′-H, 7′-H) and a signal corresponding to an olefinic hydrogen atom (7-H) in the ^{1}H NMR spectrum, as well as a signal corresponding to a carbonyl carbon atom (C4) in the ^{13}C NMR spectrum. The HMBC cross peaks of 7-H/C2, 8′-H/C10′,C1′,C7, and 7′-H/C9,C9′,C2′ further confirmed the positions of the aromatic rings on the indane moiety. Furthermore, the relative *trans* configuration of the three methine hydrogen atoms 8-H, 8′-H, and 7′-H was established by an NOE difference experiment, which showed NOE correlations at 8-H/10′-H and 7′-H/10′-H.

Finally, **18** underwent a prototropic rearrangement in the presence of Al_2O_3,[10] and the *tert*-butyl protecting groups were removed from the resulting compound **19**[11] to provide the target racemic product **1**. All spectral data of **1** were in good agreement with the data reported in the literature for the natural product.[1] The relative stereochemistry of **19** was also assigned by an NOE difference experiment. The key NOE correlation between 7-H and 14-H indicated an *E* configuration of the double bond, and NOE interactions



Scheme 4. Total synthesis of (±)-**1**. Reagents and conditions: a) CH_3OH, H_2SO_4, reflux; b) $PhCH_2Br$, K_2CO_3, DMF, RT; c) $LiAlH_4$, Et_2O, RT; d) $SOCl_2$, Et_3N, benzene, 0°C→RT; e) PPh_3, xylene, reflux; f) Br_2, *tert*-butanol, RT; g) *n*BuLi, toluene, RT→reflux; h) $AlCl_3$, $PhNMe_2$, CH_2Cl_2, 0°C; i) HRP/H_2O_2, acetone/water (3:1), RT; j) Al_2O_3, benzene, RT; k) $AlCl_3$, CH_3NO_2, toluene, 60°C. Bn = benzyl, DMF = *N*,*N*-dimethylformamide.



Scheme 3. Proposed coupling mechanism of some phenylpropanoids.

at 8′-H/2′-H and 7′-H/10′-H suggested that rings D and E have a *trans* relationship.

In summary, we have completed the first total synthesis of (±)-quadrangularin A (**1**) in 11 steps and 15% overall yield from 3,5-dihydroxybenzoic acid (**10**). The key coupling reaction could be carried out regioselectively by introducing *tert*-butyl groups to protect alternative reactive positions in the coupling precursor. Most importantly, this strategy may be used as an efficient general method for the synthesis of other naturally occurring oligostilbenes. The application of this synthetic route to analogues of **1** is currently in progress in our laboratory.

Received: July 31, 2006
Published online: October 19, 2006

Keywords: biomimetic synthesis · natural products · oligostilbenes · oxidative coupling · total synthesis

[1] S. A. Adesanya, R. Nia, T. M. Martin, N. Boukamcha, A. Montagnac, M. Pais, *J. Nat. Prod.* **1999**, *62*, 1694.
[2] a) M. Ohyama, T. Tanaka, M. Iiuma, *Phytochemistry* **1995**, *38*, 73; b) H.-F. Luo, L.-P. Zhang, C.-Q. Hu, *Tetrahedron* **2001**, *57*, 4849.
[3] a) M. Hiscock, G. B. Porter, *J. Chem. Soc. Perkin Trans. 2* **1972**, 79; b) J. M. Aguirre, E. N. Alesso, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1353.
[4] W.-L. Li, K.-K. He, Y. Li, Z.-J. Hou, *Acta Chim. Sin.* **2005**, *63*, 1607.
[5] X.-C. Li, D. Ferreira, *Tetrahedron* **2003**, *59*, 1501.
[6] P. Langcake, R. J. Pryce, *Experientia* **1977**, *33*, 151.
[7] a) P. Langcake, R. J. Pryce, *J. Chem. Soc. Chem. Commun.* **1977**, 208; b) Y. Hirano, R. Kondo, K. Sakai, *J. Wood Sci.* **2002**, *48*, 64; c) Y. Takaya, K. Terashima, J. Ito, Y.-H. He, M. Tateoka, N. Yamaguchi, M. Niwa, *Tetrahedron* **2005**, *61*, 10285.
[8] a) A. C. Breuil, M. Adrian, N. Pirio, P. Meunier, R. Bessis, P. Jeandet, *Tetrahedron Lett.* **1998**, *39*, 537; b) R. H. Cichewicz, S. A. Kouzi, M. T. Hamann, *J. Nat. Prod.* **2000**, *63*, 29; c) S. Nicotra, M. R. Cramarossa, A. Mucci, U. M. Pagnoni, S. Riva, L. Forti, *Tetrahedron* **2004**, *60*, 595.
[9] a) K.-S. Huang, M. Lin, Y.-H. Wang, *Chin. Chem. Lett.* **1999**, *10*, 817; b) M. Sako, H. Hosokawa, T. Ito, M. Iinuma, *J. Org. Chem.* **2004**, *69*, 2598; c) Y. Takaya, K. Terashima, J. Ito, Y.-H. He, M. Tateoka, N. Yamaguchi, M. Niwa, *Tetrahedron* **2005**, *61*, 10285.
[10] a) K. V. Sarkanen, A. F. A. Wallis, *J. Chem. Soc. Perkin Trans. 1* **1973**, 1869; b) K. V. Sarkanen, A. F. A. Wallis, *J. Chem. Soc. Perkin Trans. 1* **1973**, 1878.
[11] a) M. Tashiro, T. Itoh, H. Yoshiya, G. Fukata, *Org. Prep. Proced. Int.* **1984**, *16*, 155; b) G. Sartori, F. Bigi, R. Maggi, C. Porta, *Tetrahedron Lett.* **1994**, *35*, 7073; c) S. A. Saleh, H. L. Tashtoush, *Tetrahedron* **1998**, *54*, 14157.
[12] K. Thakkar, R. L. Geahlen, M. Cushman, *J. Med. Chem.* **1993**, *36*, 2950.
[13] M. M. Abelman, L. E. Overman, V. D. Tran, *J. Am. Chem. Soc.* **1990**, *112*, 6959.
[14] T. H. Coffield, A. H. Filbey, G. G. Ecke, A. J. Kolka, *J. Am. Chem. Soc.* **1957**, *79*, 5019.
[15] HRP is a heme-containing enzyme that catalyzes the oxidation of phenolic substrates; H_2O_2 serves as the ultimate electron acceptor; see: a) S. Kobayashi, H. Higashimura, *Prog. Polym. Sci.* **2003**, *28*, 1015, and references therein; b) D. M. X. Donelly, F. G. Murphy, *J. Chem. Soc. Perkin Trans. 1* **1987**, 2719; c) J. C. Pew, W. J. Connors, *J. Org. Chem.* **1969**, *34*, 580.
[16] In the enzyme-catalyzed coupling reaction of **17**, the 8–8-coupling product **18** reacted further with **17** to form two minor trimers **20** and **21** because of the prolonged reaction time or the large amount of H_2O_2 used. The structures of **20** and **21** were determined by 1D and 2D NMR spectroscopy.