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Evaluation of a Synthetic Route to ε-Viniferin Based on a New Method for the Stereoselective Preparation of 2,3-Diaryl-2,3-Dihydrobenzofurans

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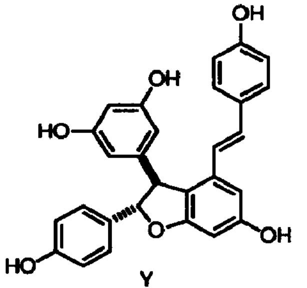
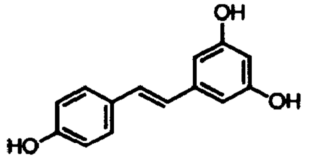
Abstract: Lewis acid-promoted reactions of unsymmetrically substituted (*E*)-stilbenes with 2-methoxy-1,4-benzoquinones regio- and stereoselectively produce trans 2,3-diaryl-2,3-dihydrobenzofurans.

ε-Viniferin (**1**) is one of a number of naturally occurring oxidative oligomers of resveratrol (**2**); other examples include the dimers gnetin G and blanocarpol, the trimers miyabenol C and gnetin H, and the tetramers kobophenol A and hopeaphenol - the first isolated resveratrol oligomer.[1] Interest in the resveratrol oligomers arises from their antifungal and antibacterial properties and their roles as phytoalexins or constitutive defense agents. To our knowledge, no nonenzymatic synthetic route to ε-viniferin has been reported.[2] Indeed, the trans stereochemistry at C-2 and C-3 has only recently been verified chemically.[3] The development of a synthetic route to **1** would allow the preparation of analogs to investigate possible structure/activity relationship profiles and would also be useful in the design of synthetic routes to other oligomers as well.

1





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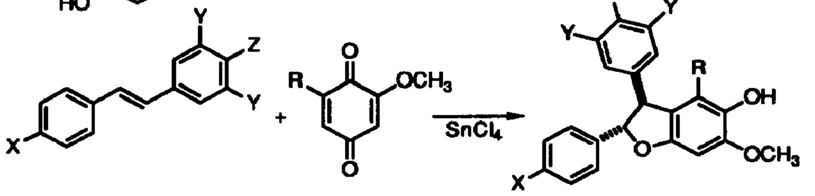


(1)

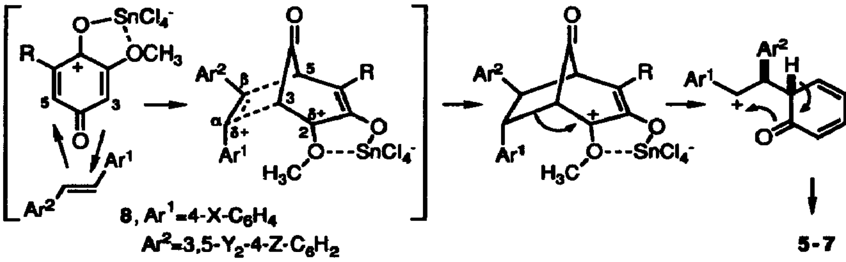
3a, X=Y=Z=H
3b, X=Z=OCH$_3$, Y=H
3c, X=OCH$_3$, Y=Z=H
3d, X=Y=OCH$_3$, Z=H
3e, X=OCH$_3$, Y=Br, Z=H

4a, R=H
4b, R=CH$_3$

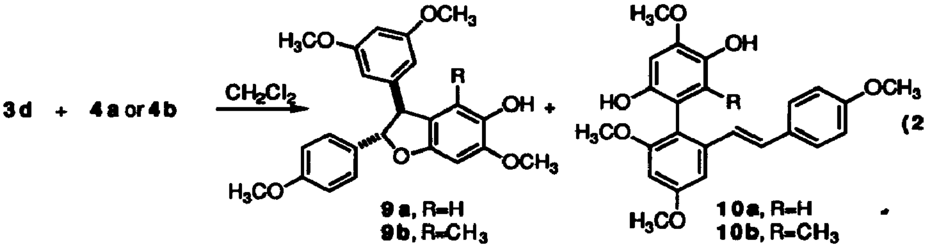
5, X=OCH$_3$, Y=Z=H, R=H; 73%
6, X=OCH$_3$, Y=Z=H, R=CH$_3$; 82%
7, X=OCH$_3$, Y=Br, Z=R=H; 93%

Our synthetic approach was based on the expected Lewis acid-promoted reactions of stilbenes with 1,4-benzoquinones to give 2,3-diaryl-2,3-dihydrobenzofurans (eq 1). Surprisingly, attempted reactions of (*E*)-stilbene (**3a**) and 4,4'-dimethoxy-(*E*)-stilbene (**3b**) with 2-methoxy- (**4a**) or 2-methoxy-6-methyl-1,4-benzoquinone (**4b**) promoted by $TiCl_4$ or $SnCl_4$ failed to provide the desired dihydrobenzofurans. However, reaction of 4-methoxy-(*E*)-stilbene (**3c**) with either **4a** or **4b** promoted by 2 equiv of $SnCl_4$ at -78°C in CH_2Cl_2 gave dihydrobenzofurans **5** and **6** in 73 and 82% yields, respectively.[4] The assignment of regio- and stereochemistry at C-2/C-3 in **5**/**6** was established by ^1H-^1H NOE experiments.[5] The regioselectivity is rationalized based on previous studies on Lewis acid-promoted reactions of styrenes with quinones which have been postulated to proceed via an initial 5+2 cycloaddition of the styrene with the pentadienyl carbocation moiety of the Lewis acid-quinone complex followed by rearrangement (Scheme I).[6] The results of the stilbene experiments suggest an asynchronous cycloaddition transition state (8) in which bond formation between C-5 of the Lewis acid-quinone complex and C-β of the stilbene is more advanced than that between C-3 and C-α resulting in a buildup of positive charge at both C-α and C-2. Thus polarized, nucleophilic stilbenes in which one of the aryl rings can stabilize a positive charge are apparently required.

Scheme I



Reactions of 3,4',5-trimethoxy-(*E*)-stilbene (**3d**) with quinones **4a/b** were examined for the synthesis of ε-viniferin. Unfortunately, promotion of the reactions with $SnCl_4$, $TiCl_4$ or mixtures of $TiCl_4$/$Ti(OiPr)_4$ at -78°C provided the dihydrobenzofurans **9a/b**,[4] respectively, in only low yield (eq 2 and Table); the major products were **10a/b**,[4] which apparently result from an electrophilic aromatic substitution reaction on the electron rich aromatic ring of the stilbene with the Lewis acid-quinone complex as the electrophile. Warming the reactions of stilbene **3d** with quinone **4a** to room temperature resulted in **10a**, and a new product **11**[4] which probably results from protonation of **10a** by HCl, formed from the phenol and $SnCl_4$, followed by cyclization of the resultant benzylic carbocation. Indeed, in a separate experiment treatment of **10a** with $SnCl_4$ at -78°C followed by warming to room temperature gave **11** in 41% yield. The structures of **9-11** were established from chemical and spectral data.[5,7] For example, oxidation of **10a** (DDQ, MeOH) and **11** (DDQ, PhH) gave the corresponding quinones **12** (37%) and **13** (100%).



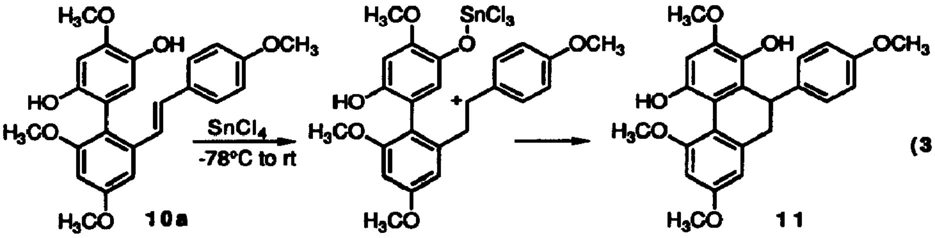
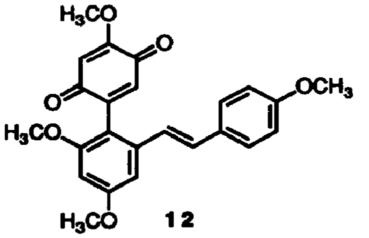


Table. Lewis Acid-Promoted Reactions of Stilbene **3d** with Quinones **4a/b**.

Entry	Quinone	Conditions	Yields (%) 9a or b	Yields (%) 10a or b	Yields (%) 11
1	**4a**	2 equiv $SnCl_4$, -78°C	5	52	-
2	**4a**	1 equiv $TiCl_4$, -78°C	-	52	-
3	**4a**	4 equiv 2:1 $TiCl_4$:$Ti(OiPr)_4$, -78°C	5	59	-
4	**4a**	15 equiv $SnCl_4$, -78°C	13	52[a]	-
5	**4b**	2 equiv $SnCl_4$, -78°C	3	78	-
6	**4b**	15 equiv $SnCl_4$, -78°C	9	58	-
7	**4a**	1 equiv $SnCl_4$, -78°C to rt	-	38	27
8	**4a**	2 equiv $SnCl_4$, -78°C to rt	1	41	36

a) See reference 8.



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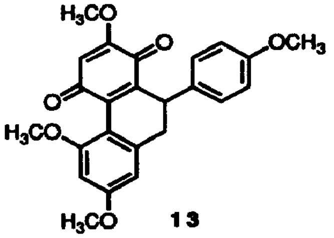

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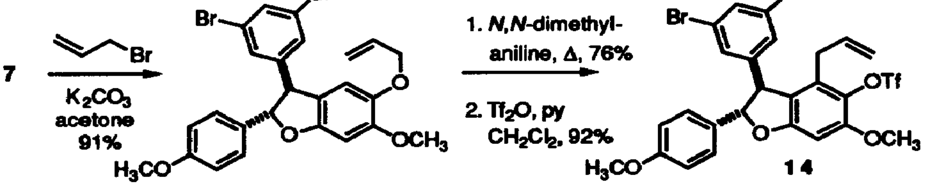
The low yields of **9a/b** from reactions of **3d** precluded the use of this stilbene in the planned synthesis of **1**. For the strategy to be successful, a stilbene was required that was not prone to electrophilic aromatic substitution and yet possessed substituents on the aryl rings that were the synthetic equivalents of the three methoxy groups on **3d**. Thus, stilbene **3e** was prepared[9] and its reaction with quinone **4a** examined. In the presence of one equiv of $SnCl_4$ at -100°C in 15% pentane/CH_2Cl_2, dihydrobenzofuran **7**[4] was produced in an excellent 93% yield. To explore the potential of **7** as an intermediate to **1**, it has been converted to dihydrobenzofuran **14** in good overall yield through a straightforward series of reactions (Scheme II).[4]

Scheme II



In conclusion, we disclose that Lewis acid-promoted reactions of several unsymmetrically substituted (*E*)-stilbenes represent a new and efficient method for the regio- and stereoselective synthesis of highly substituted trans 2,3-diaryl-2,3-dihydrobenzofurans - substructures found in a number of biologically active natural products. We are currently exploring the scope and generality of this new method as well as the completion of the synthesis of ε-viniferin.

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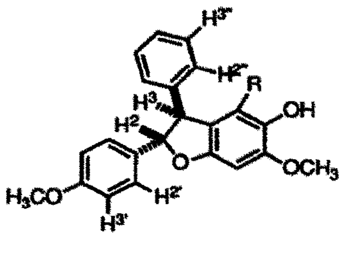
References and Notes

1. a) For a recent review, see Sotheeswaran, S.: Pasupathy, V. *Phytochemistry* **1993**, *32*, 1083-1092. For additional examples, see b) Kitanaka, S.; Ikezawa, T.; Yasukawa, K.; Yamanouchi, S.; Takido, M.; Sung, H. K.; Kim, I. H. *Chem. Pharm. Bull.* **1990**, *38*, 432-435. c) Lins, A. P.; Felicio, J. D.; Braggio, M. M.; Roque, L. C. *Phytochemistry* **1991**, *30*, 3144-3146. d) Sultanbawa, M. U. S.; Surendrakumar, S.; Bladon, P. *ibid.* **1987**, *26*, 799-801.

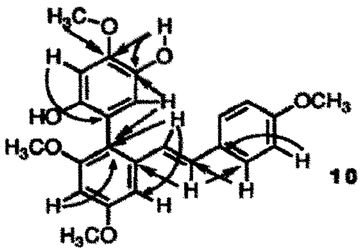
2. a) Schultz, T. P.; Hubbard, T. F., Jr.; Jin, L.; Fisher, T. H.; Nicholas, D. D. *ibid.* **1990**, *29*, 1501-1507. b) Langcake, P.; Pryce, R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 208-210. See also, c) Donnelly, D. M. X.; Murphy, F. G.; Polonski, J.; Prangé, T. *J. Chem. Soc. Perkin I* **1987**, 2719-2722.
3. Kurihara, H.; Kawabata, J.; Ichikawa, S.; Mizutani, J. *Agric. Biol. Chem.* **1990**, *54*, 1097-1099.
4. All new compounds were characterized by ^{1}H (300 or 500 MHz) and ^{13}C (75 or 125 MHz) NMR, IR, elemental analysis and/or exact mass.
5. Summary of ^{1}H-^{1}H NOE data on **5** and **6**. Similar results were found with **9a/b**.



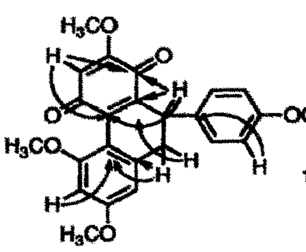
5. R=H		6. R=Me	
Signal Irradiated (ppm)	Observed NOE's	Signal Irradiated (ppm)	Observed NOE's
$H^{2'}$ (7.25)	H^{2} 9%; H^{3} 4%; $H^{3'}$ (6.88) 10.5%.	$H^{2'}$ (7.25)	H^{2} 9%; H^{3} 4%; $H^{3'}$ (6.87) 10.5%.
$H^{2''}$(7.15)	H^{2} 5%; H^{3} 9%; $H^{3''}$ (7.3) 8%.	$H^{2''}$(7.13)	H^{2} 5%; H^{3} 9%; $H^{3''}$ (7.3) 7%.
H^{2} (5.42)	H^{3} 1.6%; $H^{2'}$ 4%; $H^{2''}$ 3%.	H^{2} (5.41)	H^{3} 3%; $H^{2'}$ 5%; $H^{2''}$ 2%.
H^{3} (4.50)	H^{2} 1.6%; $H^{2'}$ 2%; $H^{2''}$ 5%.	H^{3} (4.44)	H^{2} 2%; $H^{2'}$ 2%; $H^{2''}$ 5%; Me 1.1%.
		Me (1.81)	H^{3} 5%; $H^{2''}$ 1.6%.

It should be noted that weak NOE's are observed between H^{2} and H^{3} in spite of their trans orientation; for other reports of this phenomenon, see a) Tih, R. G.; Sondengam, B. L.; Martin, M. T.; Bodo, B. *Tetrahedron Lett.* **1989**, *30*, 1807-1810. b) Kawabata, J.; Ichikawa S.; Kurihara, H.; Mizutani, J. *ibid.* **1989**, *30*, 3785-3788. For this reason, NOE's between H^{2} and $H^{2''}$ and between H^{3} and $H^{2'}$ are more reliable in assigning stereochemistry, see also c) Oshima, Y.; Kamijou, A.; Moritani, H.; Namoa, K.; Ohizumi, Y. *J. Org. Chem.* **1993**, *58*, 850-853. d) Shirataki, Y.; Noguchi, M.; Yokoe, I.; Tomimori, T.; Komatsu, M. *Chem. Pharm. Bull.* **1991**, *39*, 1568-1572. It has also been noted that coupling constants between H^{2} and H^{3} are not reliable for assigning stereochemistry, see e) Nakajima, K.; Taguchi, H.; Endo, T.; Yosioka, I. *ibid.* **1978**, *26*, 3050-3057.

6. a) Engler, T. A.; Combrink, K. D.; Ray, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 7931-7933. b) Engler, T. A.; Letavic, M. A.; Combrink, K. D.; Takusagawa, F. *J. Org. Chem.* **1990**, *55*, 5810-5812.
7. Summary of selected data from HMBC experiments on **10a** and **13**; all other correlations are consistent with these structures. All ^{1}H and ^{13}C signals were assignable based on data from decoupling, HETCOR and HMBC experiments.



10a



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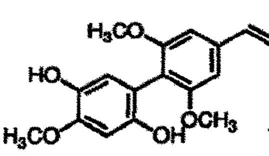
8. In this experiment, small amounts (8%) of a second isomer, **15**, were also found. This compound was very insoluble and was characterized as its quinone derivative **16** (SiO_2, O_2).



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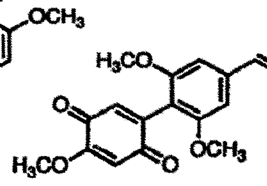

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9. Stilbene **3e** was prepared by a Wittig reaction of *p*-anisaldehyde with the triphenylphosphonium salt from α,3,5-tribromotoluene to give an (*E*)/(*Z*) mixture of olefins which when treated with I_2 in benzene provided the pure (*E*)-isomer **3e**.

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