JOC*Note*

Regioselective Oxidative Coupling of 4-Hydroxystilbenes: Synthesis of Resveratrol and ϵ-Viniferin (*E*)-Dehydrodimers

Magoichi Sako,* Hiroyuki Hosokawa, Tetsuro Ito, and Munekazu Iinuma

Gifu Pharmaceutical University, 5-6-1, Mitahora-higashi, Gifu 502-8585, Japan

sako@gifu-pu.ac.jp

Received December 7, 2003

Abstract: Treatment of 5-[2-(4-hydroxyphenyl)vinyl]benzene-1,3-diol (resveratrol) with an equimolar amount of silver(I) acetate in dry MeOH at 50 °C for 1 h followed by chromatographic purification with a short silica gel column allowed the isolation of its (*E*)-dehydrodimer, 5-{5-[2-(3,5-dihydroxyphenyl)vinyl]-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol, as a racemic mixture in high yield. The present method was applicable to the oxidative dimerization of 4-hydroxystilbenes such as *trans*-styrylphenol and 5-{6-hydroxy-2-(4-hydroxyphenyl)-4-[2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol (ϵ-viniferin) leading to the corresponding 2-(4-hydroxyphenyl)-2,3-dihydrobenzofurans possessing various types of biological activities.

5-{5-[2-(3,5-Dihydroxyphenyl)vinyl]-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol [resveratrol (*E*)-dehydrodimer] (**2**) is a polyphenolic phytoalexin isolated from grapevines,[1] the lianas of *Gnetum hainanense*,[2] *Vitis vinifera* cell cultures,[3] and the roots of *Rheum maximowiczii*.[4] Recently, this compound has been documented to exhibit interesting biological activities such as antimicrobial,[1] cyclooxygenase (I and II) inhibitory,[3,5] and 5α-reductase inhibitory activities,[6] and cytotoxicity against human lymphoblastoid cells.[5] The dehydrodimer **2** can be obtained as a racemic mixture by the enzymatic oxidations of commercially available 5-[2-(4-hydroxyphenyl)vinyl]benzene-1,3-diol (resveratrol) (**1**) with a horseradish peroxidase−H_2O_2 system[1,6] and a laccase-like stilbene oxidase of *Botrytis cinerea*.[5,7] However, to study the molecular mechanisms that explain its biological effects, a more convenient preparative method for **2** and its analogues was required.

We describe a nonenzymatic and efficient method for the preparation of the dehydrodimer **2** involving the simple treatment of resveratrol (**1**) with silver(I) acetate (AgOAc) under mild conditions followed by chromatographic purification using a short silica gel column. The present method is, in principle, applicable to the oxidative dimerization of 4-hydroxystilbenes and 4-hydroxystyrenes leading to the corresponding 2-(4-hydroxyphenyl)-2,3-dihydrobenzofurans possessing various types of biological activities.[8]

When the mixture of resveratrol (**1**) with an equimolar amount of AgOAc in dry MeOH was heated at 50 °C for 1 h and the resulting mixtures were purified by silica gel column chromatography, the desired dehydrodimer **2** was obtained as an optically inactive product in almost quantitative yield. The structure of the product **2** was confirmed by comparison with the previously reported UV, mass, and ^{1}H NMR spectral data,[1−4,7] e.g., its ^{1}H NMR spectrum showed characteristic signals for the dihydrobenzofuran ring protons at δ 4.45 (d, J = 8.0 Hz) and δ 5.44 (d, J = 8.0 Hz) and for the *trans*-stilbene vinyl protons at δ 6.94 (d) and δ 7.05 (d) with a large coupling constant (J = 16.4 Hz).[1,7] Thus, the present oxidative dimerization proceeded regioselectively to give **2**, though the starting **1** has both the 4-hydroxyphenyl and 3,5-dihydroxyphenyl groups in the molecule, i.e., no formation of the structural isomer, 5-{6-hydroxy-2-(4-hydroxyphenyl)-4-[2-(4-hydroxyphenyl)vinyl]-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol (ϵ-viniferin) (**3**), in this reaction was observed. The efficiency of this reaction significantly depended upon the employed solvent because of the low solubility of AgOAc in an organic solvent, i.e., the use of MeOH as a solvent was the most effective for the smooth formation of the dehydrodimer **2** among the examined solvents that involved acetone, MeCN, and THF. Under the employed conditions, it changed to an ash color because the reaction mixture is colorless during the initial stage and then the formation of a silver mirror on the inside of the used flask was observed, indicating that the redox reaction between the starting **1** [E^{ox}_p = +1.14 V vs SCE in MeCN] and silver(I) cation is involved in this reaction.

On the basis of these facts, the formation of the dehydrodimer **2** in the reaction of resveratrol (**1**) with AgOAc can be reasonably explained by virtue of a single-electron transfer from **1** to the silver(I) cation, a regioselective coupling of the phenoxyl radicals (**A** and **A′**) generated by deprotonation of the 4-hydroxystilbene cation radical, and subsequent intramolecular cyclization leading to **2** as the ultimate product as shown in Scheme 1.

Analogous results were obtained with metallic oxidants such as Ag_2O,[9] Ag_2CO_3,[10] $AgNO_3$, $Mn(OAc)_3$,[11] $Cu(OAc)_n$

(1) Langcake, P.; Pryce, R. J. *Experientia* **1977**, *33*, 151−152. Langcake, P.; Pryce, R. J. *J. Chem. Soc., Chem. Commun.* **1977**, 208−210. Langcake, P.; Pryce, R. J. *Physiol. Plant Pathol.* **1976**, *9*, 77−86.

(2) Huang, K.-S.; Wang, Y.-H.; Li, R.-L.; Lin, M. *J. Nat. Prod.* **2000**, *63*, 86−89.

(3) Waffo-Teguo, P.; Lee, D.; Cuendet, M.; Merillon, J.-M.; Pezzuto, J. M.; Kinghorn, A. D. *J. Nat. Prod.* **2001**, *64*, 136−138.

(4) Shikishima, Y.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O. *Phytochemistry* **2001**, *56*, 377−381.

(5) Cichewicz, R. H.; Kouzi, S. A.; Hamann, M. T. *J. Nat. Prod.* **2000**, *63*, 29−33.

(6) Hirano, Y.; Kondo, R.; Sakai, K. *J. Wood Sci.* **2002**, *48*, 64−68.

(7) Breuil, A.-C.; Adrian, M.; Pirio, N.; Meunier, P.; Bessis, R.; Jeandet, P. *Tetrahedron Lett.* **1998**, *39*, 537−540. Sbaghi, M.; Jeandet, P.; Bessis, R.; Lereux, P. *Plant Pathol.* **1996**, *45*, 139−144.

(8) Roemer, K.; Mahyar-Roemer, M. *Drugs Today* **2002**, *38*, 571−580. Wolter, F.; Stein, J. *Drugs Future* **2002**, *27*, 949−959.

(9) Zhou, L.-X.; Lin, M. *Chinese Chem. Lett.* **2000**, *11*, 515−516. Antus, S.; Gottsegen, A.; Kolonits, P.; Wagner, H. *Liebigs Ann. Chem.* **1989**, 593−594. Antus, S.; Bauer, R.; Gottsegen, A.; Seligmann, O.; Wagner, H. *Liebigs Ann. Chem.* **1987**, 357−360.

(10) Fernandes, E. G. R.; Pinto, M. M. M.; Silva, A. M. S.; Cavaleiro, J. A. S.; Gottlieb, O. R. *Heterocycles* **1999**, *51*, 821−828.

10.1021/jo035791c CCC: $27.50
Published on Web 03/02/2004

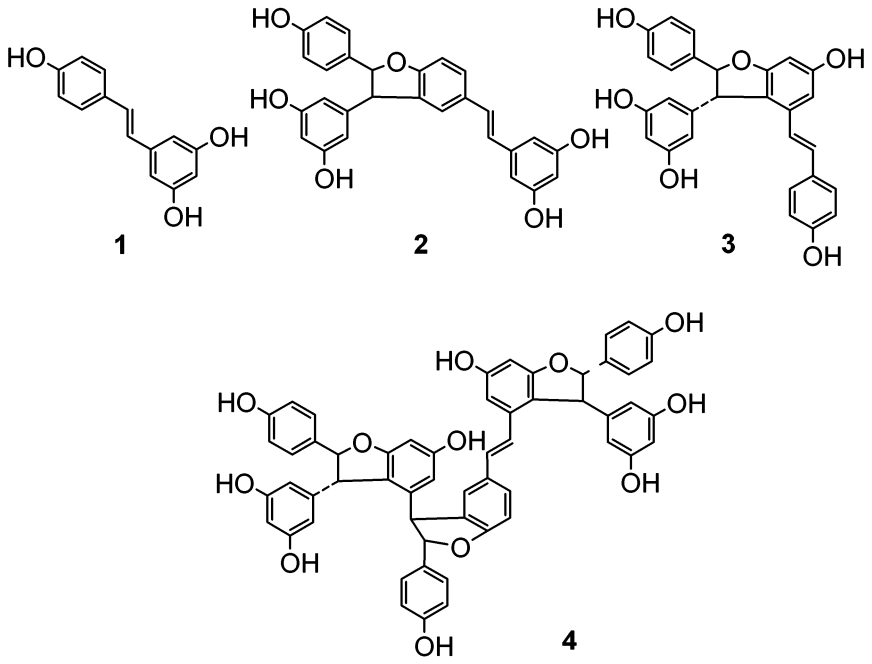
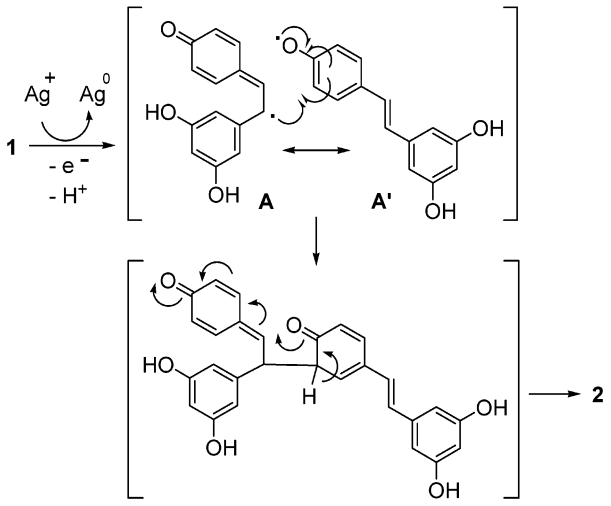


FIGURE 1. Resveratrol (**1**), ϵ-viniferin (**3**), and their dehydrodimers (**2** and **4**).

SCHEME 1. A Most Plausible Mechanism for the Oxidative Dimerization of Resveratrol (1)



(n = 1, 2), and $K_3Fe(CN)_6$ (in pH 5.5 phosphate buffer−MeCN)[12] in place of AgOAc as an oxidant, and also of organic oxidants such as $PhI(OAc)_2$[13] and DDQ in place of the metallic oxidant, though their efficiencies were dependent upon their solubility in the solvents and the oxidation ability of the employed oxidants (see Table 1 and Experimental Section). The dimeric product **2** [E^{ox}_p = +1.12 V vs SCE in MeCN] was very stable under the oxidation conditions; the treatment with AgOAc at 50 °C in MeOH resulted in the recovery of the unchanged **2** even after a prolonged reaction time (*ex* after 3 h). In sharp contrast to this fact, the structural isomer ϵ-viniferin (**3**) [E^{ox}_p = +1.15 V vs SCE in MeCN] was very unstable under the employed oxidation conditions and smoothly dimerized to give 5-{6′-hydroxy-2′-(4-hydroxyphenyl)-5-[2-[3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-4-yl]]vinyl-2′,3-bis(4-hydroxyphenyl)-2,3,-2′,3′-tetrahydro[3,4′]bibenzofuranyl-3′-yl}benzene-1,3-diol (vitisin B, a (*E*)-dehydrodimer of ϵ-viniferin) (**4**),[14] together with another undetermined dimeric product. Thus, the 4-hydroxystyrene moiety is required for the formation of the 2,3-dihydrobenzofuran ring in the present reaction. An analogous oxidative dimerization was observed for the reaction of *trans*-4-styrylphenol with AgOAc in MeOH.[1,15]

TABLE 1. Oxidative Dimerization of Resveratrol (1)

entry	metallic oxidant	reaction conditions[a]	yield (%)[b] unchanged **1**	yield (%)[b] dehydrodimer **2**
1	AgOAc	*a*	~1	97
2	Ag_2O	*a*	8	76
3	Ag_2CO_3	*a*	37	56
4	$AgNO_3$	*a*	95	4
5	$Mn(OAc)_3$	*a*	19	55
6	CuOAc	*a*	57	24
7	$Cu(OAc)_2$	*a*	62	22
8	$K_3Fe(CN)_6$	*b*	32	40

[a] Reaction conditions: (a) MeOH, 50 °C, 1 h; (b) 0.1 M phosphate buffer (pH 5.5)−MeCN (1/1), 50 °C, 1 h. [b] Estimated by TLC densitometry.

Among these results, the selective formation of the resveratrol (*E*)-dehydrodimer **2** during the Fe^{3+}-oxidation of resveratrol (**1**) is interesting in relation to the mechanisms for the enzymatic formation of the polyphenolic phytoalexins, possessing a 2,3-dihydrobenzofuran ring in

(11) Snider, B. B.; Han, L.; Xie, C. *J. Org. Chem*. **1997**, *62*, 6978−6984.
(12) Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519−521.
(13) Juhasz, L.; Kuerti, L.; Antus, S. *J. Nat. Prod*. **2000**, *63*, 866−870.
(14) Ito, J.; Niwa, M. *Tetrahedron* **1996**, *52*, 9991−9998. Oshima, Y.; Kamijou, A.; Ohizumi, Y.; Niwa, M.; Ito, J.; Hisamichi, K.; Takeshita, M. *Tetrahedron* **1995**, *51*, 11979−11986.
(15) Schultz, T. P.; Hubbard, T. F., Jr.; Lin, L.; Fisher, T. H.; Nicholas, D. D. *Phytochemistry* **1990**, *29*, 1501−1507.

the molecule such as the dehydrodimers **2** and ϵ-viniferin (**3**), in grapes and peanuts as a natural fungicide.[1,6,16]

Experimental Section

The melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. ^{1}H NMR spectra were obtained at 400 MHz, using deuterioacetone unless otherwise noted as the solvent. For the thin-layer chromatographic (TLC) analyses, Merck precoated TLC plates (Merck No. 5715; silica gel 60-F_{254}) were used. Column chromatography was performed on silica gel (Cica Merck No. 9385; silica gel 60). ϵ-Viniferin (**3**) was isolated from the stem bark of *Vateria indica*.[17] Unless otherwise noted, the materials obtained from commercial suppliers were used without further purification.

Oxidation of Resveratrol (1): (a) With Ag^+ Oxidants. A mixture of resveratrol (**1**) (SIGMA, 99% purity; 9.2 mg, 0.04 mmol) and AgOAc (Kishida Chemicals, >99.0% purity; 6.8 mg, 0.04 mmol) in dry MeOH (2.0 mL) was heated at 50 °C for 1 h. The reaction mixture turned to an ash color with time and the formation of a silver mirror was observed on the inside of the employed flask. After removal of the solvent under reduced pressure, the resulting residue was subjected to column chromatography by eluting with chloroform-MeOH (10/1) to isolate the optically inactive 5-{5-[2-(3,5-dihydroxyphenyl)vinyl]-2-(4-hydroxyphenyl)-2,3-dihydrobenzofuran-3-yl}benzene-1,3-diol [resveratrol (*E*)−dehydrodimer] (**2**) (7.8 mg, 86%) as a colorless amorphous powder: mp 156−157 °C (from chloroform) (lit.[3] mp 150−152 °C); IR (KBr) 3400, 1602, 1509, 1489 cm^{-1}; UV (MeOH) 320, 310, 220 (sh) nm; mass *m*/*z* (rel intensity) 454 (M^+, 100), 408 (4), 360 (12), 347 (12), 228 (12); ^{1}H NMR δ 4.45 (1H, d, J = 8.0 Hz), 5.44 (1H, d, J = 8.0 Hz), 6.18 (2H, d, J = 2.0 Hz), 6.24 (1H, t, J = 2.0 Hz), 6.27 (1H, t, J = 2.0 Hz), 6.52 (2H, d, J = 2.0 Hz), 6.84 (2H, d, J = 8.8 Hz), 6.87 (1H, d, J = 8.8 Hz), 6.90 (1H, d, J = 16.4 Hz), 7.05 (1H, d, J = 16.4 Hz), 7.25 (2H, d, J = 8.3 Hz), 7.25 (1H, br s), 7.42 (1H, br d, J = 8.3 Hz), 8.17 (2H, s), 8.20 (2H, s), 8.44 (1H, s); anal. calcd for $C_{28}H_{22}O_6$ *m*/*z* 454.1417, found *m*/*z* 454.1423. TLC analyses of the reaction mixtures obtained after the AgOAc oxidation of resveratrol (**1**) showed the complete consumption of **1** and almost quantitative conversion to the dehydrodimer **2**.

The oxidation of **1** (2.3 mg, 0.01 mmol) in dry MeOH (0.5 mL) was carried out with Ag_2O, Ag_2CO_3, or $AgNO_3$ in place of AgOAc as the oxidant. TLC densitometric analyses (detection at 320 nm) of the mixtures obtained after the reactions (at 50 °C for 1 h) showed the formation of the dehydrodimer **2**, with recovery of the starting **1** and with the concurrent formation of a small amount of an undetermined more polar product. The yields of the unchanged **1** and the dehydrodimer **2** are summarized in Table 1. TLC analyses of the reaction mixtures obtained after the oxidation of **1** (2.3 mg, 0.01 mmol) with AgOAc in dry acetone, MeCN, and THF (each 2.0 mL) (at 50 °C, for 1 h) showed the formation of **2** in 90%, 86%, and 19% yields, respectively, with recovery of the starting **1** and with the formation of a trace amount of an undetermined polar product.

(b) With Other Metallic Oxidants. The use of an equivalent amount of $Mn(OAc)_3$, CuOAc, and $Cu(OAc)_2$ in place of AgOAc for the oxidation of **1** (2.3 mg, 0.01 mmol) allowed the formation of **2** in moderate to low yields. The yields of the unchanged **1** and the dehydrodimer **2** estimated by TLC densitometry are summarized in Table 1. The starting compound **1**, however, was unchanged after treatment with an equivalent amount of $Hg(OAc)_2$, $Cd(OAc)_2$, or $Pd(OAc)_2$ in dry MeOH at 50 °C for 1 h.

A mixture of **1** (11.4 mg, 0.05 mmol) and $K_3Fe(CN)_6$ (16.5 mg, 0.05 mmol) in 0.1 M phosphate buffer (pH 5.5)−MeCN (1/1) (2.0 mL) was stirred at 50 °C for 1 h. After being diluted with water (10 mL) and adjusted to pH 3 with 0.1 M HCl, the mixture was extracted with ethyl acetate (20 mL, two times). The obtained residue after evaporation of the extract was subjected to column chromatography by eluting with chloroform−MeOH (10/1) to separate the starting **1** (2.9 mg, 25%) and the dehydrodimer **2** (3.4 mg, 30%), together with undetermined products (0.5 mg).

(c) With Organic Oxidants. To a solution of **1** (4.6 mg, 0.02 mmol) in dry MeCN (0.5 mL) was added $PhI(OAc)_2$ (3.3 mg, 0.01 mmol) or DDQ (2.3 mg, 0.01 mmol) and the mixture was heated at 50 °C for 1 h. TLC densitometric analyses of the resulting mixtures showed the formation of **2** in 25% and 7% yields, respectively, with the recovery of **1** in 17% [$PhI(OAc)_2$] and 49% (DDQ) yields. In these reactions, the formation of highly polar polymeric products was observed at the spotted position and the employment of an equivalent amount of the oxidants caused the significant decrease in the formation of **2**.

AgOAc Oxidation of ϵ-Viniferin (3). A mixture of **3** (22.8 mg, 0.05 mmol) and AgOAc (8.4 mg, 0.05 mmol) in dry MeOH (5.0 mL) was heated at 50 °C for 2 h. The formation of a silver mirror during the reaction was observed. After removal of the solvent under reduced pressure, the resulting residue was subjected to column chromatography by eluting with chloroform−MeOH (10/1) to isolate 5-{6′-hydroxy-2′-(4- hydroxyphenyl)-5-[2-[3-(3,5-dihydroxyphenyl)-6-hydroxy-2-(4-hydroxyphenyl)-4-yl]]-vinyl-2,3′-bis(4-hydroxyphenyl)-2,3,2′,3′-tetrahydro[3,4′]bibenzofuranyl-3′-yl}benzene-1,3-diol (vitisin B, a (*E*)-dehydrodimer of ϵ-viniferin) (**4**);[13] 9.0 mg, 40%) as a colorless amorphous powder [mp 225−227 °C (from chloroform); FABMS *m*/*z* 907 (MH^+), 906 ($MH^+ - 1$), 854, 810; IR (KBr) 3402, 1609, 1514, 1484, 1451 cm^{-1}; UV (MeOH) 321, 298, 287, 223 nm; ^{1}H NMR δ 4.31 (1H, d, J = 4.4 Hz), 4.44 (1H, d, J = 5.4 Hz), 4.52 (1H, d, J = 4.4 Hz), 5.40 (2H, d, J = 4.4 Hz), 5.52 (1H, d, J = 5.4 Hz), 6.10 (2H, d, J = 2.0 Hz), 6.18 (1H, d, J = 2.0 Hz), 6.19−6.24 (5H, m), 6.30 (2H, d, J = 2.0 Hz), 6.55−6.80 (4H, m), 6.59 (2H, d, J = 8.8 Hz), 6.62 (1H, d, J = 16.0 Hz), 6.76 (1H, d, J = 16.0 Hz), 6.82 (2H, d, J = 8.8 Hz), 6.90 (2H, d, J = 8.8 Hz), 7.13 (1H, d, J = 8.3 Hz), 7.19 (2H, d, J = 8.8 Hz), 7.24 (2H, d, J = 8.8 Hz), 8.07 (2H, s), 8.11 (2H, s), 8.13 (1H, s), 8.26 (1H, s), 8.30 (1H, s), 8.34 (1H, s), 8.52 (1H, s); anal. calcd for $C_{56}H_{43}O_{12}$ *m*/*z* 907.2754 [MH^+], found *m*/*z* 907.2751] and an undetermined isomeric dehydrodimer (7.2 mg, 32%) as a less polar product [FAB MS *m*/*z* 907 (MH^+), 906 ($MH^+ - 1$), 853; IR (KBr) 3393, 1611, 1516, 1483, 1451 cm^{-1}; UV (MeOH) 320, 298, 287, 223 nm; ^{1}H NMR δ 3.77 (1H, d, J = 4.9 Hz), 4.32 (1H, d, J = 8.8 Hz), 4.50 (1H, d, J = 4.9 Hz), 5.23 (1H, d, J = 4.9 Hz), 5.28 (1H, d, J = 8.8 Hz), 5.39 (1H, d, J = 4.9 Hz), 5.96 (2H, d, J = 2.0 Hz), 6.10 (1H, d, J = 16 Hz), 6.30 (1H, d, J = 16 Hz), 6.22−6.32 (5H, m), 6.66−6.83 (13H, m), 7.02 (2H, d, J = 8.8 Hz), 7.15 (1H, d, J = 8.8 Hz), 7.20 (2H, d, J = 8.8 Hz), 8.12 (2H, s), 8.20 (2H, s), 8.26 (1H, s), 8.34 (1H, s), 8.37 (2H, br s), 8.39 (1H, s); anal. calcd for $C_{56}H_{43}O_{12}$ *m*/*z* 907.2754 (MH^+), found *m*/*z* 907.2749].

Supporting Information Available: Experimental procedure and characterization data for the (*E*)-dehydrodimer of *trans*-4-styrylphenol and ^{1}H NMR, IR, UV, and MS spectral data for **2**, **4**, and the isomeric compound of **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035791C

(16) For pertinent reviews for the phytoalexins see: Fregoni, C.; Bavaresco, L. *Vignevini* **2002**, *29*, 58−60. Jeandet, P.; Douillet-Breuil, A.-C.; Bessis, R.; Debord, S.; Sbaghi, M.; Adrian, M. *J. Agr. Food Chem.* **2002**, *50*, 2731−2741. Hain, R. *Spec. Publ. R. Soc. Chem. (Pestic. Chem. Biosci.)* **1999**, *233*, 190−203.

(17) Ito, T.; Tanaka, T.; Iinuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Naganawa, H.; Chelladurai, V. *Tetrahedron* **2003**, *59*, 1255−1264.