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# Manganese triacetate oxidative lactonisation of electron-rich stilbenes possessing catechol and resorcinol substitution (resveratrol analogues)

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**Abstract**—Treatment of 3,5-dimethoxy-12-benzyloxystilbene **10a** or 3,4-dimethoxy-12-benzyloxystilbene **10b** with $Mn(OAc)_3$ in acetic anhydride containing 13% acetic acid produced the lactones 4-(4′-benzyloxyphenyl)-5-(3′,5′-dimethoxyphenyl)-furan-2-one **11a** and 4-(4-benzyloxyphenyl)-5-(3′,4′-dimethoxyphenyl)-furan-2-one **13** in yields of 35% as a 3:1 diastereomeric mixture (but as one regioisomer) and 13% as a mixture of regioisomers (1:1), respectively. 

## 1. Introduction

Resveratrol is a stilbene with significant anti-platelet[1] as well as anti-oxidant properties.[2] Interest in compounds related to resveratrol is justified by the following observation. Firstly, resveratrol is the biosynthetic precursor of most oligostilbenoids, natural polyphenols of restricted distribution, but present in economically important plants such as grape vine or South-east Asian timber trees, especially the dipterocarps.[3,4] Secondly, we consider it retrosynthetically reasonable to exploit resveratrol as a starting material for the synthesis of the simplest oligostilbenoid polymer, i.e. the dimer ε-viniferin **1**[4] (Scheme 1). For all these reasons, we embarked on a programme to synthesise resveratrol and its catechol analogues and to study oxidative lactonisation using one-electron oxidants. To the best of our knowledge this reaction has not been reported on electron rich stilbenes. Fristad et al.[5,6] reported that the treatment of an unfunctionalised (lacking any oxysubstituents) stilbene with $Mn(OAc)_3$ produced the γ-butyrolactone in only 4% yield. They also reported that the $Mn(OAc)_3$ treatment of electron rich alkenes tended to yield diacetates rather than lactones. With this background, and the above-mentioned retrosynthetic analysis, we attempted to find conditions which would allow the elaboration of γ-butyrolactones from the electron rich stilbenes **10a** and **10b**.

## 2. Results and discussion

Examination of the retrosynthetic scheme (Scheme 1) indicates that the γ-butyro-lactone **4** is a key intermediate, which we believe should be accessible by oxidative lactonisation of protected resveratrol **5** by means of manganese triacetate. The $Mn(OAc)_3$ lactonisation of olefins has been the subject of a number of papers and reviews, for example, by Heiba,[7–10] Snider,[11] Melikyan,[12] etc. By heating a mixture of 4-iodobenzylether **8** and styrene **9a** or **9b** in the presence of palladium dichloride, triphenylphosphine, potassium acetate and silver nitrate in DMF[13,14] for 1 week, we obtained the stilbenes **10a** and **10b** in 64 and 63% yields, respectively. Oxidative lactonisation of stilbenes **10** using manganese triacetate in refluxing acetic anhydride (with 13% acetic acid) produced the lactones **11a** and **13** in yields of 35% (as a 3:1 diastereoisomeric mixture) and 13% (a 1:1 mixture of regioisomers), respectively (Scheme 2). These lactones were subjected to extensive 1- and 2D NMR experiments. More specifically, the regiochemical assignments were based on the $^2J_{C-H}$ and $^3J_{C-H}$ correlations recorded in HMBC spectra. The numbering system for the lactones is as shown in Scheme 2. The HMBC spectrum of **11a**

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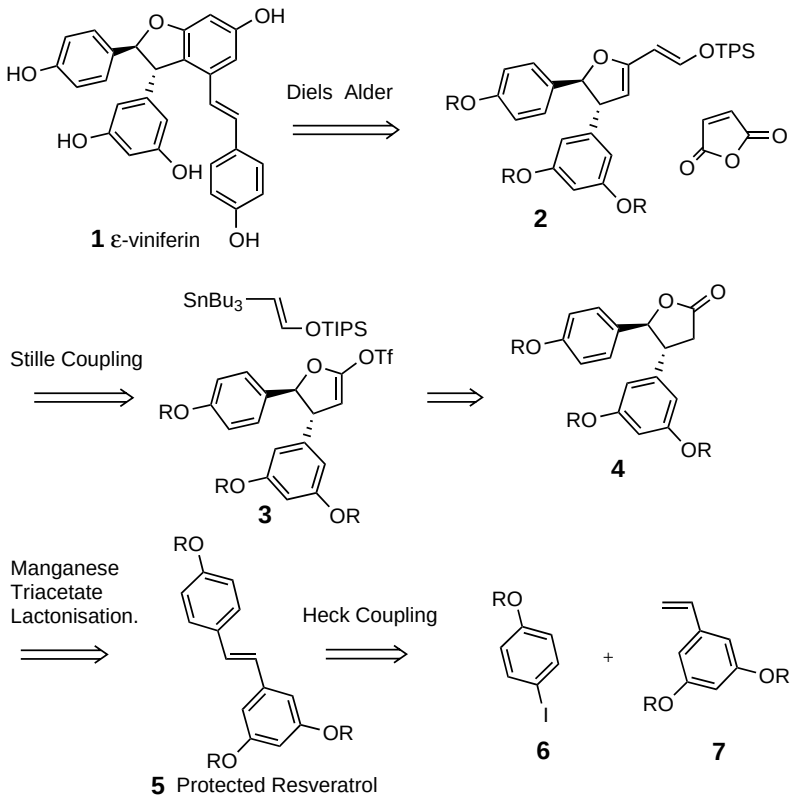



**Scheme 1.** Retrosynthesis of ε-viniferin **1**.

displayed notably the two cross-peaks H-2′,6′/C-5 and H-2″,6″/C-4, which allowed us to establish unambiguously the structure as shown. The determination of the relative stereochemistry of each isomer is in progress and will be reported later. A reasonable mechanistic proposal for the formation of **11a** is as follows: radical **17** attacks C-7 of **10a**′ along reversible pathway B as shown in Scheme 3. This allows formation of the presumably more stable radical **18a** (compared to **18b**) (via **18b**→**10a**′→**18a**). Oxidation of **18a** gives rise to the benzylic cation **19a** which is more stable (superior charge delocalisation) than the alternative **19b**. Alternatively, pathway A is favoured by virtue of the faster rate of addition of **17** to C-8 of **10a**″. This may be a reflection of the greater stability of benzylic radical **18a** over **18b** in a manner that parallels carbocation stability, although this need not necessarily be the case.[15] Thus on mechanistic grounds, the favoured lactone is **11a** (pathway A) and this is in good agreement with our experimental findings.

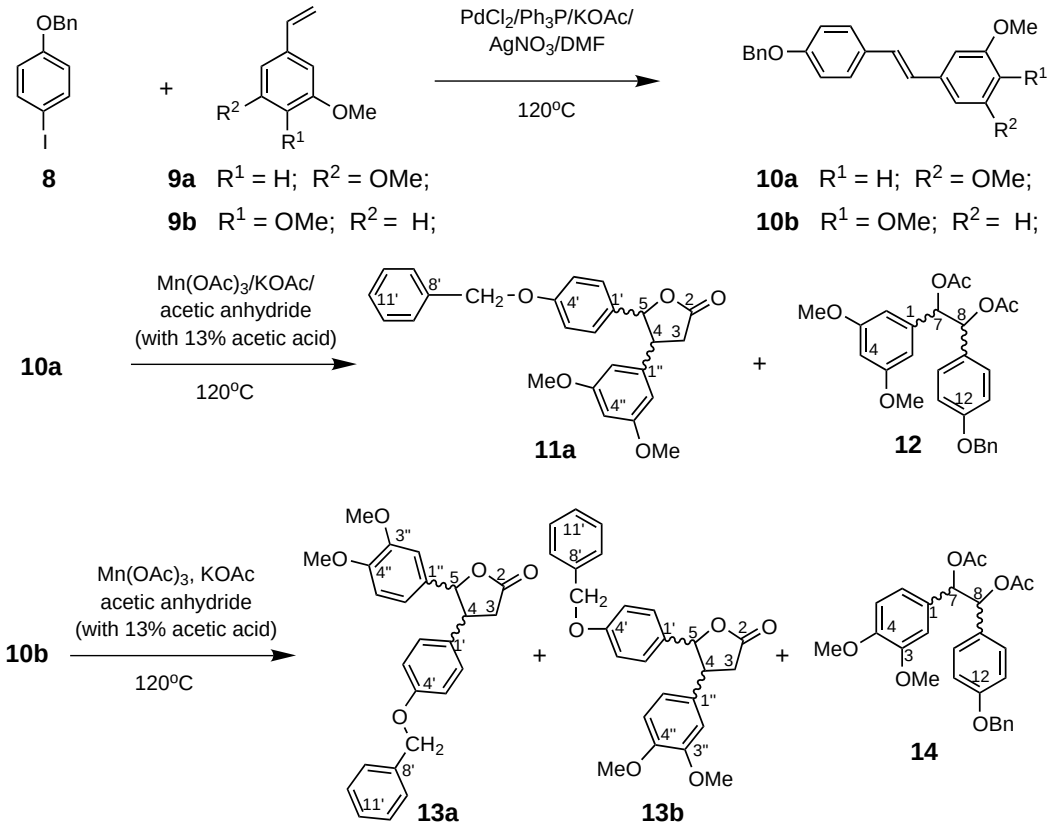
In contrast to the situation depicted in Scheme 3, for the 3,4-dimethoxystilbene **10b**, the two carbocationic intermediates are **19c** and **19d**. In this case stabilisation of the benzylic carbocations is equally efficient (Scheme 4), and thus **13a** and **13b** are formed in equal proportion. This would explain the 1:1 regioisomeric mixture observed in the $Mn(OAc)_3$/3,4-dimethoxystilbene transformation. The structures of **13a** and **13b** were also deduced from their HMBC spectra. The spectrum of **13a** showed the key $^3J_{C-H}$ correlation cross-peaks H-2′,6′/C-4′ and H-2″,6″/C-5, while **13b** was characterised by the H-2′,6′/C-5 and H-2″,6″/C-4 correlations. It is noteworthy that only one diastereoisomer of each regioisomer could be detected by NMR. Here also, the establishment of their relative stereochemistry is in progress.

In addition to the above mentioned lactones **11a** and **13**, the reaction mixtures also afforded the expected diacetates **12** and **14**.

## 3. Experimental

### 3.1. Synthesis of lactone 11

Stilbene **10a** (1.271 mmol), manganese triacetate (2.643 mmol), potassium acetate (13.448 mmol) and acetic anhydride/acetic acid (20 ml; 87:13 v/v) were refluxed under nitrogen until the dark brown colour of the Mn(III) had disappeared. The reaction mixture was then cooled, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate, dried (anhydrous $Na_2SO_4$) and concentrated. The crude product was purified by column chromatography to yield lactone **11** and diacetate **12** in 35% (as a single regioisomer but as a 3:1 mixture of diastereoisomers) and 10% (as a diastereoisomeric mixture) yields, respectively. This reaction was repeated on stilbene **10b** to yield lactone **13a** and **13b** and diacetate **14** in 13% (1:1 mixture of regioisomers) and 12% (as a diastereoisomeric mixture) yields, respectively.




**Scheme 2.** Synthesis of resveratrol analogues **10a** and **10b** and lactonisation of **10b**.

### 3.2. 4-(4′-Benzyloxyphenyl)-5-(3′,5′-dimethoxyphenyl)-furan-2-one 11a

Data for the major furan diastereomer: IR $\nu_{max}$ (NaCl) = 1783 cm$^{-1}$ (γ-lactone carbonyl). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 7.35 (m; 5H), 7.10 (d; $J$ = 8.8 Hz; 2H), 6.92 (d; $J$ = 8.8 Hz; 2H), 6.35 (t; $J$ = 2.2 Hz; 1H), 6.27 (d; $J$ = 2.0; 2H), 5.34 (d; $J$ = 8.5 Hz; 1H), 5.03 (s; 2H), 3.72 (s; 6H), 3.50 (ddd; 11.1, 8.5, 8.3 Hz; 1H), 3.00 (dd; $J$ = 17.6, 8.3 Hz; 1H), 2.86 (dd; $J$ = 17.6, 11.1 Hz; 1H). $^{13}$C NMR (100.4 MHz, $CDCl_3$) 140.16 (C-1), 105.49 (C-2,6), 161.18 (C-3,5), 99.17 (C-4), 50.44 (C-7), 87.00 (C-8), 129.94 (C-9), 127.31 (C-10,14), 114.96 (C-11,13), 158.93 (C-12), 70.02 (C-15), 136.68 (C-16), 127.42 (C-17,21), 128.58 (C-18,20), 128.02 (C-19), 55.31 (3-$OCH_3$, 4-$OCH_3$), 37.03 ($CH_2$-CO), 175.01 (C=O).

### 3.3. 4-(4-Benzyloxyphenyl)-5-(3′,4′-dimethoxyphenyl)-furan-2-one 13a and 13b

Irresolvable 1:1 mixture of regioisomers. IR: $\nu_{max}$ (NaCl): 1764 cm$^{-1}$ (γ-lactone carbonyl). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ ppm: 7.3–7.4 (m; 10H; **13a** and **13b**), 7.12 (d; $J$ = 8.6 Hz; 2H; **13a**) and 7.05 (d; $J$ = 8.5 Hz; 2H; **13b**), 6.92 (d; $J$ = 8.5 Hz; 4H; **13a** and **13b**), 6.82 (d; $J$ = 7.6 Hz; 1H; **13a** or **13b**) and 6.76 (d; $J$ = 7.6 Hz; 1H; **13a** or **13b**), 6.71 (dd; $J$ = 7.6, 2.0; 1H; **13b**) and 6.68 (dd; $J$ = 7.6, 2.0 Hz; 1H; **13a**), 6.69 (d; $J$ = 2.0 Hz; 1H; **13b**) and 6.55 (d; $J$ = 2.0 Hz; 1H; **13a**), 5.28 (d; $J$ = 8.9 Hz, 1H; **13a** or **13b**) and 5.26 (d; $J$ = 8.9 Hz; 1H; **13b** or **13a**), 5.03 (s; 4H; **13a** and **13b**), 3.84 (s; 6H; **13a** or **13b**), 3.83 (s; 6H; **13b** or **13a**), 3.51 (ddd; 17.4, 8.9, 8.3 Hz; 2H; **13a** and **13b**), 2.99 (dd; $J$ = 17.4, 8.3 Hz; 1H; **13a** or **13b**) and 2.97 (dd; $J$ = 17.4, 8.3 Hz; 1H; **13b** or **13a**), 2.90 (dd; $J$ = 17.4, 11.3 Hz; 1H; **13a** or **13b**) and 2.87 (dd; $J$ = 17.4, 11.3 Hz; 1H; **13b** or **13a**). $^{13}$C NMR (100.4 MHz, $CDCl_3$) $\delta$ ppm 175.25 (C-2; **13a** or **13b**), 175.28 (C-2; **13b** or **13a**), 37.00 (C-3; **13a** or **13b**), 37.16 (C-3; **13b** or **13a**), 55.84 and 55.86 ($CH_3O$-3″,4″; **13a** and **13b**), 50.07 (C-4; **13a**), 49.83 (C-4; **13b**), 87.44 (C-5; **13a**), 87.59 (C-5; **13b**), 129.83 (C-1′; **13a** and **13b**), 127.32 (C-2′, 6′; **13a**), 128.44 (C-2′,6′; **13b**), 115.29 (C-3′,5′; **13a**), 114.90 (C-3′,5′; **13b**), 159.02 (C-4′; **13a** or **13b**), 158.28 (C-4′; **13b** or **13a**), 70.00 (C-7′; **13a** or **13b**), 69.98 (C-7′; **13b** or **13a**), 136.65 (C-8′; **13a** or **13b**), 136.68 (C-8′; **13b** or **13a**), 128.00 (C-11′; **13a** and **13b**), 128.58 (C-10′,12′; **13a** and **13b**), 128.55 (C-9′,13′; **13a** or **13b**), 127.37 (C-9′,13′; **13b** or **13a**), 130.05 (C-1″; **13a**), 129.70 (C-1″; **13b**), 110.57 (C-2″; **13a**), 108.69 (C-2″; **13b**), 149.07 (C-3″; **13a**), 149.22 (C-3″; **13b**), 147.55 (C-4″; **13a**), 148.55 (C-4″; **13b**), 111.46 (C-5″; **13a** or **13b**), 110.92 (C-5″; **13b** or **13a**), 119.16 (C-6″; **13a**), 118.39 (C-6″; **13b**).

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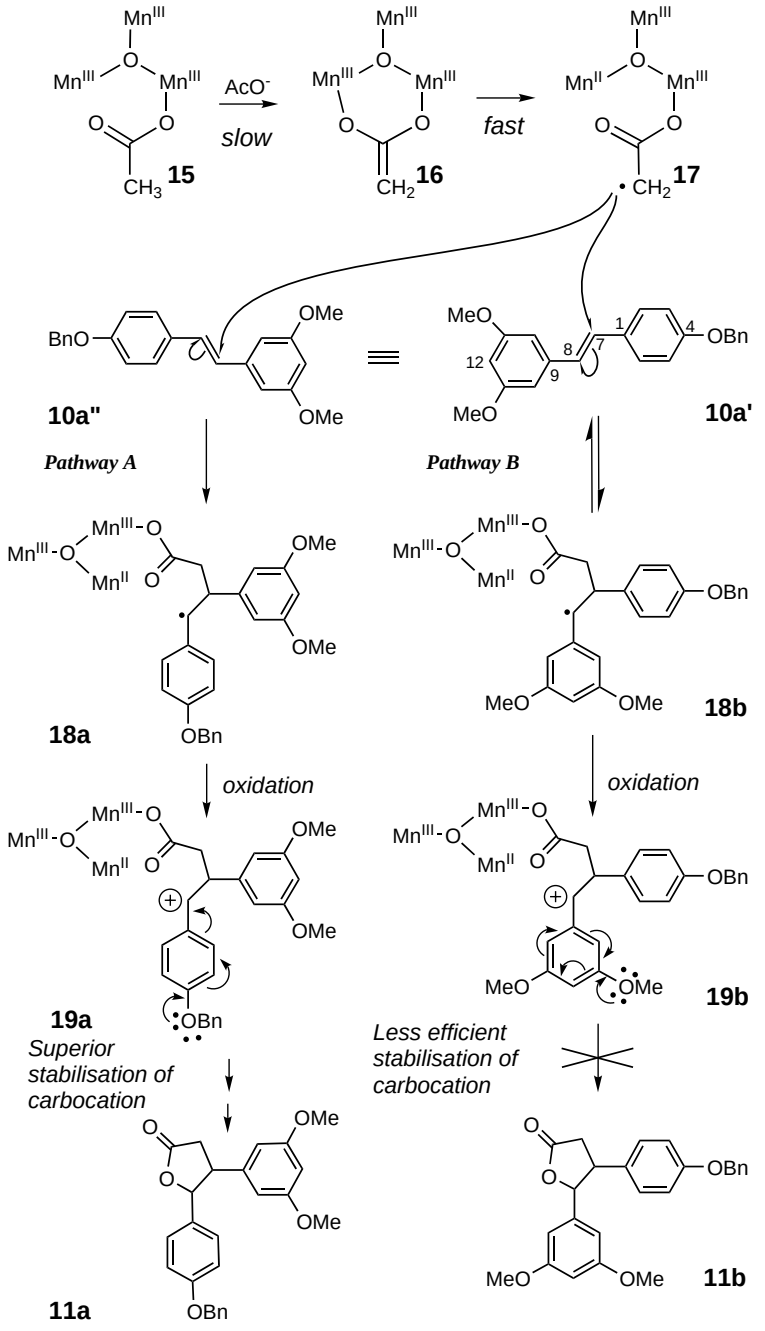
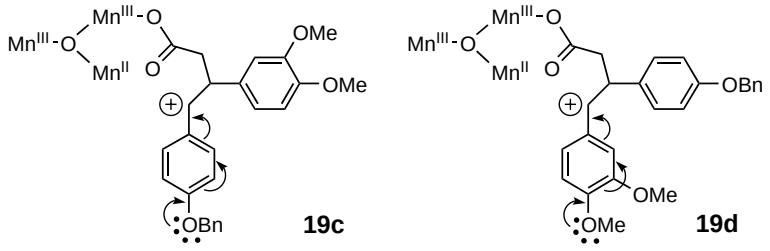



**Scheme 3.** Mechanistic pathways for the lactones **11**.




**Scheme 4.** Stability of carbocations **19c** and **19d**.

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