

Tandem pericyclic reactions in a new FeCl₃-promoted synthesis of catechol analogues of restrytisol C

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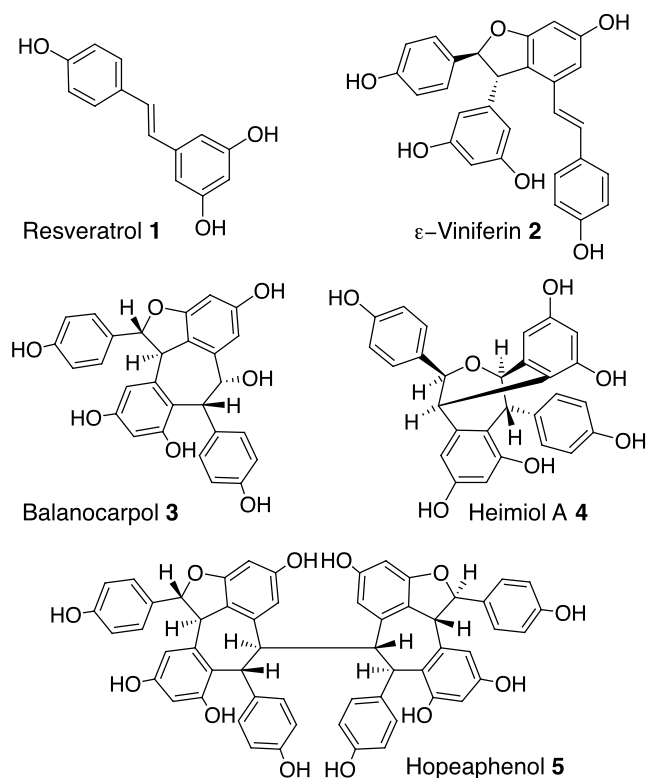
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Abstract—The uncommon stilbene, 3,4-dimethoxy-12-acetoxy stilbene, has been synthesised by Heck coupling methodology in three steps. Treatment of this stilbene with ferric chloride in dichloromethane (room temperature) gave the unnatural stilbenoid dimers; 8,8'-(12,12'-bisacetoxyphenyl)-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene and 8-(12-acetoxyphenyl)-8'-(12'-hydroxyphenyl)-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene. The structures of both stilbene dimers were unambiguously confirmed by 1D (¹H, ¹³C) and 2D NMR experiments (COSY, HMQC, HMBC and NOESY). This is the first report of a FeCl₃-promoted sequential pericyclic pathway leading to a highly oxygenated oligostilbenoid dimer (incorporating two asymmetric centres). The NMR spectroscopic evidence and a mechanistic interpretation consistent with these structures are discussed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

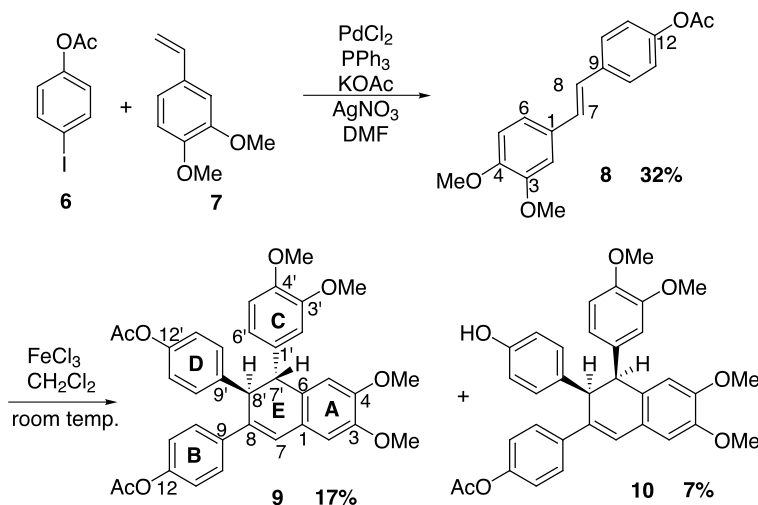
It is by now well established that resveratrol **1**, a stilbene, has significant antiplatelet¹ and antioxidant² properties. It is also the biosynthetic progenitor of the oligostilbenoid polyphenols³ such as ϵ -viniferin **2**, balanocarpol **3**, heimiol A **4** and hopeaphenol **5** (Scheme 1). Some of these are known to have interesting biological activities. Oligostilbenoid polyphenols are generated from resveratrol by oxidative phenolic coupling, and like resveratrol, possess the typical resorcinol arrangement. Stilbene monomer building blocks with the catechol arrangement are relatively infrequently used in oligostilbenoid biosynthesis. One can of course speculate on the reasons for this. Specific enzyme systems capable of binding efficiently to catechol stilbenes may be less common. The *ortho* dihydroxy substituents in such stilbenes tend to be protected for example as dimethyl ethers or as methylenedioxyethers.³ We have noticed that a significant proportion of these stilbenes lack the all important *trans* olefinic bond between the two benzene rings which must surely severely limit the options for complex phenol biosynthesis. Our previous work in the oligostilbenoids has included the isolation and structure



Scheme 1. Examples of oligostilbenoid polyphenols.

Keywords: stilbene; ferric chloride; pericyclic; dihydronaphthalene; restrytisol.

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Scheme 2. Synthesis of stilbene **8** and transformation of **8** to dihydronaphthalene stilbene dimers.

elucidation of a new oligostilbenoid heimiol **A** ⁴. Further investigation has resulted in our recent report of the regio controlled oxidative lactonisation of stilbenes using manganese triacetate.^{5–7} Since nature is able to construct complex polyphenols from unprotected stilbenes like resveratrol, we were keen to study oxidative coupling of our stilbenes with one electron oxidants such as manganese triacetate, vanadium oxytrichloride⁸ and FeCl_3 . This type of study has not received much attention.

2. Results and discussion

Stilbene **8** was prepared (Heck coupling),^{9,10} by heating a mixture of 4-iodoacetophenone **6** and 3,4-dimethoxystyrene **7** in the presence of palladium dichloride, triphenylphosphine, potassium acetate and silver nitrate in DMF for 7 days. We obtained the stilbene **8** in 32% yield (Scheme 2). Treatment of **8** with FeCl_3 in dichloromethane produced the two stilbene dimers; 8,8'-(12,12'-bisacetoxyphenyl)-7',8'-dihydro-naphthalene **9** in 17% yield and 8-(12-acetoxyphenyl)-8'-(12'-hydroxyphenyl)-7',8'-dihydro-naphthalene **10** in 7% yield. Both structures (**9** and **10**) were unambiguously assigned by means of 1D (^1H and ^{13}C) NMR, and extensive 2D NMR experiments (COSY, HMQC, HMBC and NOESY) and also high resolution mass spectral data.

8,8'-(12,12'-Bisacetoxyphenyl)-7',8'-dihydro-naphthalene **9** was obtained as a yellow oil. The spot on the TLC plate exhibited a strong blue fluorescence under UV (254 nm) which suggests that the *trans* stilbene chromophore has been retained. This is consistent with a structure in which the olefinic bond is at C7–C8 and not C8–C8' as in some natural analogues (see below). High resolution EI mass spectrum gave a molecular ion peak with accurate mass 594.2273 compatible with the molecular formula $\text{C}_{36}\text{H}_{34}\text{O}_8$ (calcd mass 594.2254, Δ 1.9 mmu) corresponding to two stilbene units **8** minus two protons. The ^1H NMR and ^1H – ^1H COSY spectra showed two sets of *ortho*-coupled aromatic protons in AA'/BB' spin systems assignable to two independent 4-acetoxyphenyl

rings B and D. These are 7.32 ppm, doublet $J=8.7$ Hz integrating for two protons (H-10, H-14); 6.94 ppm, doublet, $J=8.7$ Hz, integrating for two protons (H-11, H-13), 7.27 ppm doublet, $J=8.6$ Hz, corresponding to two protons (H-10', H-14') and 6.95 ppm, doublet $J=8.6$ Hz integrating for two protons (H-11', H-13'). Further examination of the ^1H spectrum reveals an ABM system for the catechol ring C (*ortho* and *meta* coupled protons with coupling constants of 8.3 and 1.9 Hz, respectively). The three singlets in the aromatic region (6.87, 6.52, 7.09 ppm) were identified as the isolated protons in rings A and E (H-2, H-5 and H-7, respectively) after examination of the HMBC spectrum. Apart from the aromatic region, the ^1H NMR spectrum also showed two broad singlets at 4.15 and 4.11 ppm corresponding to H-7' and H-8', four methoxy and two acetoxy singlets. The connection between protons and their corresponding carbons was established by HMQC. Correlations from 2D long distance heteronuclear NMR spectrum (HMBC, Fig. 1) allowed the assignment of all proton and carbon signals. Observation of a cross peak with 2J and 3J (two and three bond correlations) shown by H-7'/C-8', H-7'/C-2', H-7'/C-5, H-7'/C-9', H-7'/C-8, H-8'/C-7',

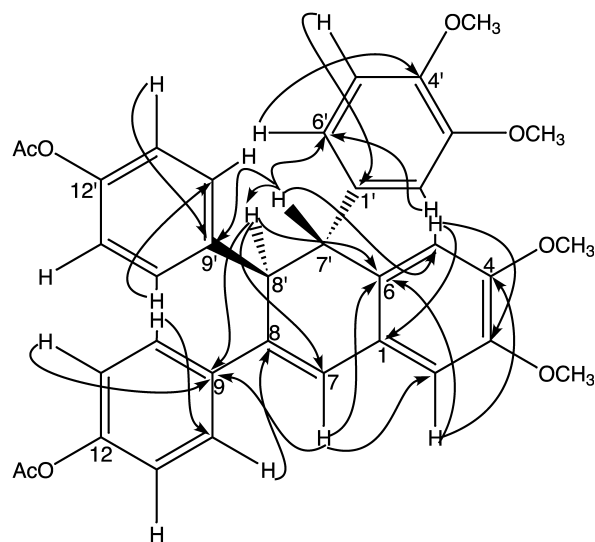


Figure 1. Main HMBC correlations in **9** (400 MHz, CDCl_3).

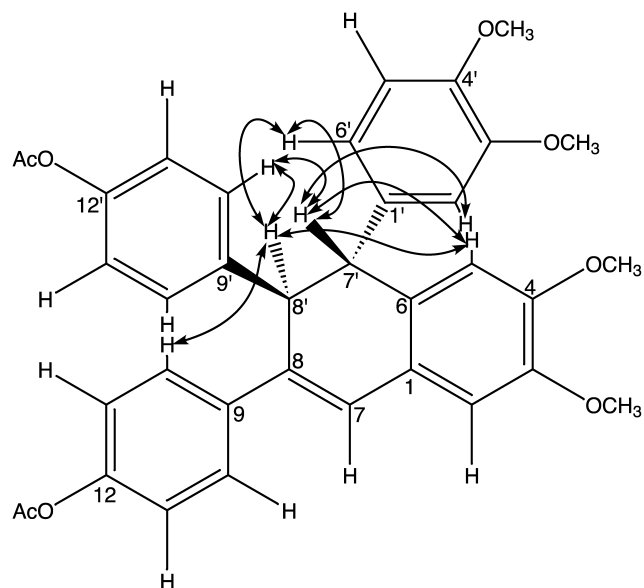


Figure 2. Main NOESY correlations in **9** (500 MHz, CDCl₃).

H-8'/C-1', H-8'/C-9', H-8'/C-7, H-7/C-6, H-7/C-8', H-7/C-2 and H-7/C-9 allowed us to establish the naphthalene structure of **9**. The relative configuration of **9** was deduced from the NOESY spectrum. The distinct correlation (Fig. 2) between H-8' with H-2'/6' and H-7' with H-10'/14' confirmed that protons H-7' and H-8' are in an *anti* configuration, a correlation not seen in compound **10** and confirming the latter's *syn* configuration (see Section 3.2.2).

8-(12-Acetoxyphenyl)-8'-(12'-hydroxyphenyl)-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene **10** was also obtained as a yellow oil. The appearance of a strong blue fluorescence spot under UV (254 nm) again suggested the retention of a *trans* stilbene chromophore in structure **10**. The high resolution mass spectrum (CI) gave an exact mass 553.2241 for the pseudomolecular ion [M+H]⁺, compatible with the molecular formula C₃₄H₃₂O₇ (calcd mass 553.2226, Δ 1.5 mmu) of a stilbene

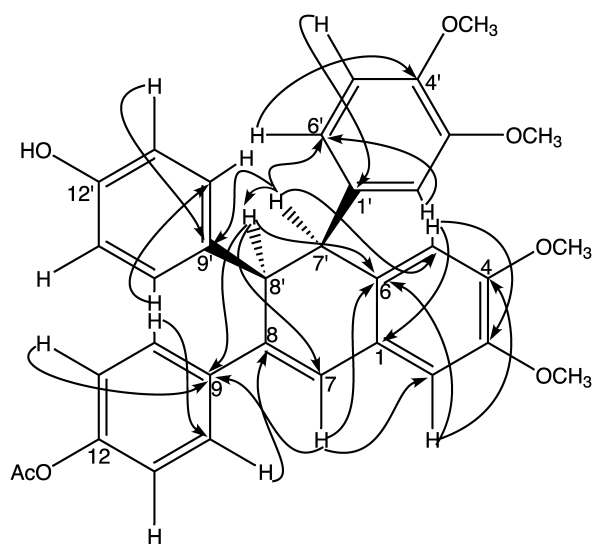


Figure 3. Main HMBC correlations in **10** (400 MHz, CDCl₃).

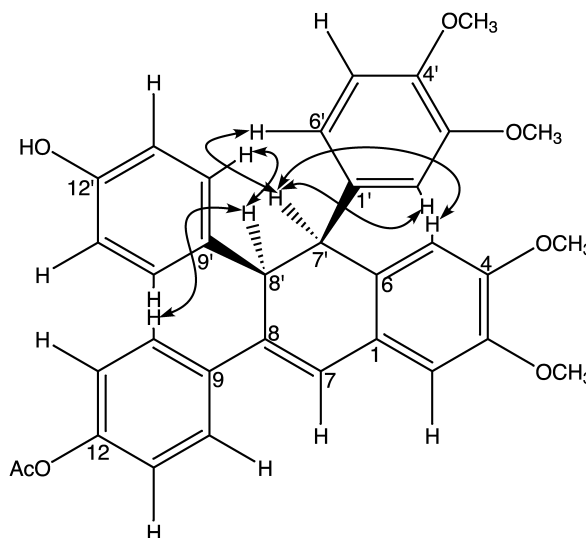
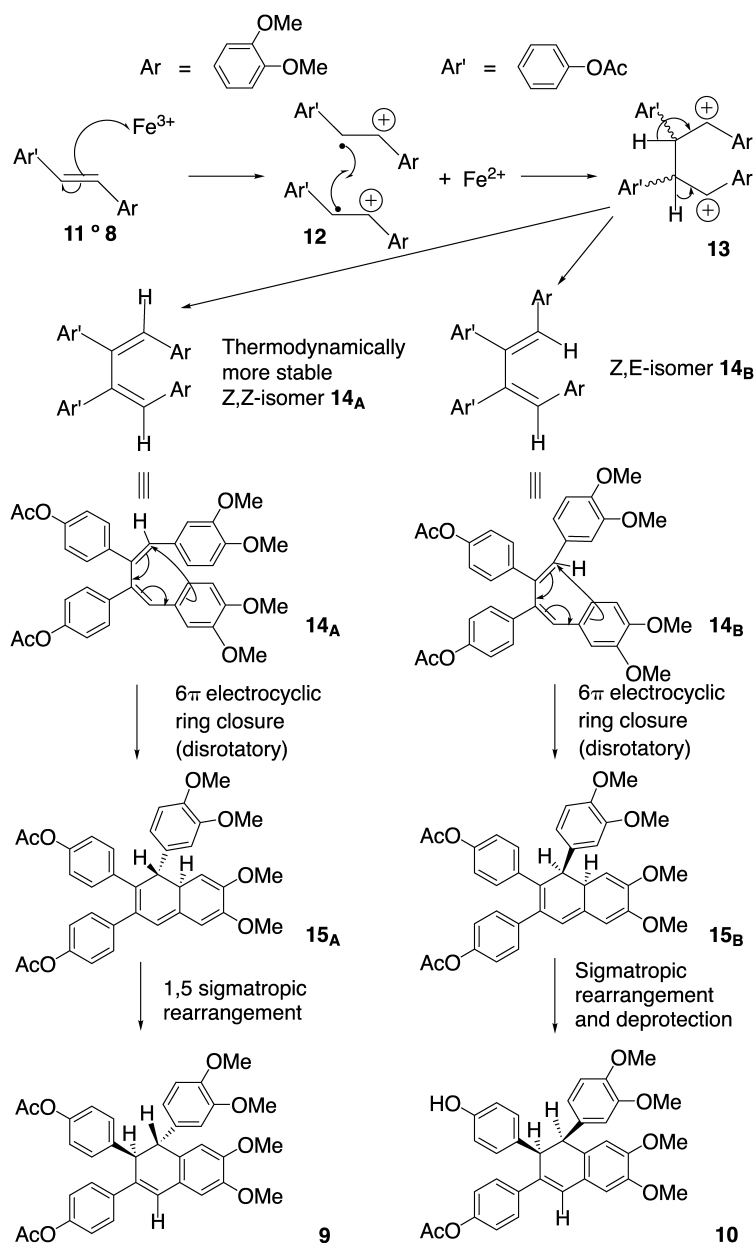


Figure 4. Main NOESY correlations in **10** (500 MHz, CDCl₃).

dimer. The ¹H and ¹³C NMR spectra of **10** were similar to compound **9** except for the replacement of an acetoxy group with a free hydroxy group at C-12'. The increased shielding of H-11',13' in **10** (6.69 ppm) compared to **9** (6.95 ppm) and increased deshielding of the C-12', 154.69 ppm (**10**) compared to 149.42 ppm (**9**) is consistent with the presence of a free hydroxy group at C-12', as opposed to an acetoxy in the case of **9**. This reflects the much greater 'carbonyl' character of the C-12' in **10** compared to **9**. The structure of **10** was further confirmed by 2D NMR HMQC, HMBC (Fig. 3) and NOESY (Fig. 4) spectral data. In the HMBC spectrum, observation of a cross peak with ²J and ³J (two and three bonds correlation) shown by H-7'/C-8', H-7'/C-2', H-7'/C-5, H-7'/C-9', H-7'/C-8, H-8'/C-7', H-8'/C-1', H-8'/C-9', H-8'/C-7, H-7/C-6, H-7/C-8', H-7/C-2 and H-7/C-9 led us to establish the structure of **10**. The NOESY spectrum confirms the *syn* configuration of H-7' and H-8' (Fig. 4).

The formation of compounds **9** and **10** can be explained by thermally allowed pericyclic transformations.¹¹ The mechanistic pathway is initiated by removal of an electron by Fe³⁺ (the oxidizing agent) from the olefinic system **11** (or **8**) to form a radical cation **12**. This is followed by coupling of two radical cationic species to produce **13**. Rapid deprotonation of **13** would yield the dienes **14_A** and **14_B** the *Z,Z*- and *Z,E*-isomers, respectively. 6π electrocyclic ring closure of **14_A** and **14_B** would give **15_A** and **15_B**, respectively. This is followed by sigmatropic rearrangements to provide **9** and **10** as shown in Scheme 3. Both *syn* and *anti* isomers were isolated from the reaction mixture. The *anti* isomer was the major compound. This may be due to its greater thermodynamic stability. Its predominance probably also reflects the fact that it is formed from the more abundant diene **14_A**.

The transformation of **14_A** to **9** and **14_B** to **10** can be explained by frontier orbital considerations, as shown in Schemes 4 and 5. Considering the Highest Occupied Molecular Orbital (HOMO) for both 6π system (hexatriene) **14_A** and **14_B**, disrotatory ring closure of **14_A** would provide the *anti* disposed hydrogen at the two new asymmetric centers **15_A** and then followed by [1,5] suprafacial hydride

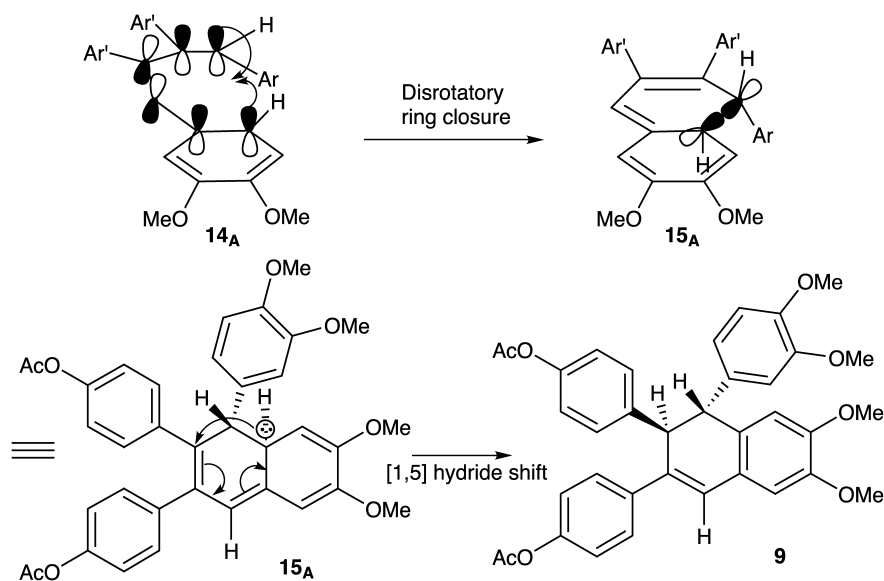


Scheme 3. Proposed mechanism for the formation of **9** and **10**.

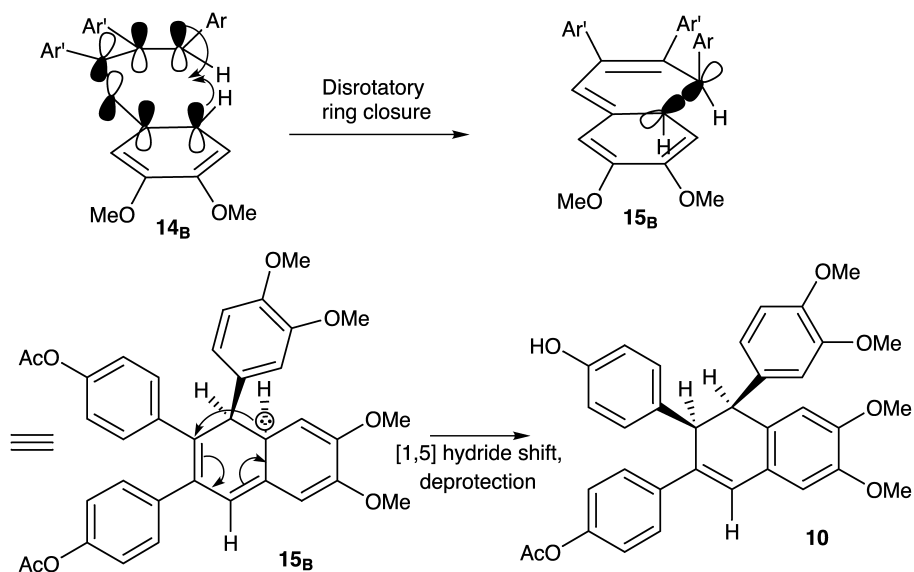
shifts to **9** (Scheme 4). By contrast disrotatory ring closure of **14_B** would produce the *syn* configuration shown in **15_B**. This is then followed by symmetry allowed [1,5] suprafacial hydride shifts and deprotection of the acetate leading to **10** as shown in Scheme 5.

In conclusion, we would like to point out that we are aware of recent reports regarding the isolation of cyphostemmins¹² and the *Botrytis cinerea* catalysed dimerisation of resveratrol¹³ to produce a mixture of compounds from which restrytol C **16** was isolated as the diastereoisomer shown. In the light of our mechanistic rationale, the biosynthesis of **16** could well involve pericyclic reactions (see Scheme 3), but intriguingly, the fact that the *cis* (*syn*) isomer is not formed in the *B. cinerea* catalysed transformation of resveratrol, could suggest that stereospecific requirements for these fungal pathogen enzymes, preclude formation of the *Z,E*-

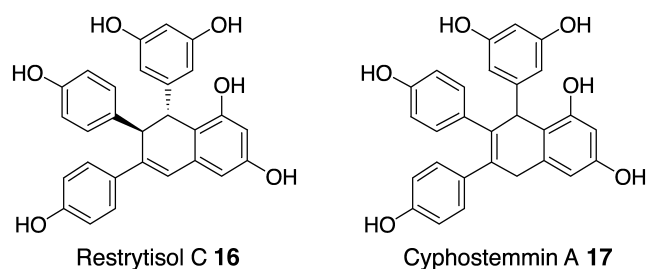
diene isomer related to our **14_B** (see Scheme 3). Our compounds (and **16**) are structurally related to the natural product cyphostemmin A **17** which incorporates the *cis* (rather than the *trans*) stilbene chromophore (Scheme 6). From a biosynthetic standpoint, it would appear that for **17** formation, the 1,5 sigmatropic rearrangement **15_A** to **9** (Scheme 3) is prohibited, and that a prototropic shift (non-concerted) involving the proton at C-6 is the favoured pathway. It is also noteworthy that the reported biomimetic synthesis of **16** by Kouzi et al. also describes a number of other compounds presumably arising from oxidative phenolic coupling (excluding we believe **16**). In our FeCl_3 reactions these oxidative phenolic compounds seem to be precluded, and pericyclic pathways leading to **9** and **10** predominate. The results of further synthetic and biosynthetic investigations from our group will be reported in due course.



Scheme 4. Thermally allowed 6π electron electro-cyclization leading to **9**.



Scheme 5. Thermally allowed 6π electron electro-cyclization leading to **10**.



Scheme 6. Natural dihydronaphthalenic stilbenoid dimmers.

3. Experimental

3.1. Synthesis of 3,4-dimethoxy-12-acetoxy stilbene **8**

4-Iodoacetoxybenzene **6** (3.59 g, 0.0134 mol) was dissolved

in dry DMF (50 mL). To this stirring solution palladium(II) chloride (0.238 g, 1.34 mmol), triphenylphosphine (0.703 g, 2.68 mmol), silver nitrate (2.28 g, 0.0134 mol), potassium acetate (1.63 g, 0.0166 mol) and 3,4-dimethoxy styrene **7** (2.20 g, 0.0134 mol) was added. The mixture was refluxed under nitrogen for a week. The reaction mixture was filtered and extracted with ethyl acetate and water. The combined ethyl acetate extracts were dried over anhydrous Na_2SO_4 . The crude was purified by column chromatography (ethyl acetate/hexane; 1:10) to gave 1.28 g (32% yield) of colourless crystals **8**.

3.1.1. 3,4-Dimethoxy-12-acetoxy stilbene 8. IR (film) ν_{max} : 3007, 2963, 2938, 1756 (acetate C=O), 1600, 1580, 1238, 1212, 1191, 1163, 1137, 1024; ^1H NMR (400 MHz, CDCl_3) δ ppm: 7.49 (d; $J=8.6$ Hz; 2H; H-10,14), 7.07 (d; $J=8.6$ Hz; 2H; H-11,13), 7.06 (d; $J=2.2$ Hz; 1H; H-2), 7.04 (dd; $J=8.0$, 2.2 Hz; 1H; H-6), 7.00 (d; $J=16.4$ Hz; 1H; H-7), 6.97 (d;

$J=16.4$ Hz; 1H; H-8), 6.86 (d; $J=8.0$ Hz; 1H; H-5), 3.95 (s; 3H; 3-OCH₃), 3.90 (s; 3H; 4-OCH₃), 2.31 (s; 3H; 12-OAc). ¹³C NMR (100.4 MHz, CDCl₃) δ ppm: 130.08 (C-1), 108.57 (C-2), 148.93 (C-3), 148.80 (C-4), 111.04 (C-5), 119.75 (C-6), 128.51 (C-7), 125.53 (C-8), 135.15 (C-9), 126.95 (C-10,14), 121.57 (C-11, 13), 149.61 (C-12), 169.28 (C=O), 55.71 (3-OCH₃), 55.65 (4-OCH₃), 20.91 (COCH₃).

3.2. Synthesis of stilbene dimer 9 and 10

To a stirring solution of stilbene **8** (0.4 g, 1.34 mmol) in dichloromethane (40 mL), FeCl₃·6H₂O (2 mL, 13.4 mmol) was added. The reaction was monitored by TLC. After 3 h, reaction mixture was worked up with MeOH. The crude product was purified by column chromatography (100% CHCl₃) and centrifugal chromatography (100% CHCl₃). Two pure compounds were isolated.

3.2.1. 8,8'-(12,12'-Bisacetoxypheyl)-7'-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene 9. The compound was isolated as yellow oil, 0.14 g (17% yield). HRMS-EI 594.2273; IR (film) ν_{\max} : 3020, 2937, 2835, 1760 (acetate C=O), 1604, 1505, 1296, 1238, 1199, 1167, 1019, 755; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.32 (d; $J=8.7$ Hz; 2H; H-10,14), 7.27 (d; $J=8.6$ Hz; 2H; H-10',14'), 7.09 (s; 1H; H-7), 6.95 (d; $J=8.6$ Hz; 2H; H-11',13'), 6.94 (d; $J=8.7$ Hz; 2H; H-11,13), 6.87 (s; 1H; H-2), 6.75 (d; $J=1.9$ Hz; 1H; H-2'), 6.73 (d; $J=8.3$ Hz; 1H; H-5'), 6.69 (dd; $J=8.3, 1.9$ Hz; 1H; H-6'), 6.52 (s; 1H; H-5), 4.15 (br s; 1H; H-8'), 4.11 (br s; 1H; H-7'), 3.96 (s; 3H; 3-OCH₃), 3.82 (s; 3H; 4'-OCH₃), 3.78 (s; 6H; 3'-OCH₃, 4-OCH₃), 2.27 (s; 6H; 12-OAc, 12'-OAc). ¹³C NMR (100.4 MHz, CDCl₃) δ ppm: 126.77 (C-1), 137.69 (C-1'), 110.14 (C-2), 110.81 (C-2'), 147.97 (C-3), 147.70 (C-3'), 148.89 (C-4), 148.80 (C-4'), 112.62 (C-5), 111.29 (C-5'), 127.20 (C-6), 119.31 (C-6'), 125.35 (C-7), 52.74 (C-7'), 134.95 (C-8), 51.17 (C-8'), 138.23 (C-9), 139.94 (C-9'), 126.45 (C-10,14), 128.48 (C-10',14'), 121.66 (C-11,13), 121.42 (C-11',13'), 149.74 (C-12), 149.42 (C-12'), 55.74 (3-OCH₃), 55.81 (3'-OCH₃, 4-OCH₃), 55.94 (4'-OCH₃), 21.05 (12-COCH₃)*, 21.00 (12'-COCH₃)*, 169.40 (C=O) (*—interchangeable).

3.2.2. 8-(12-Acetoxyphenyl)-8'-(12'-hydroxyphenyl)-7'-7'-(3',4'-dimethoxyphenyl)-3,4-dimethoxy-7',8'-dihydro-naphthalene 10. The compound was isolated as yellow oil, 0.052 g (7% yield); IR (film) ν_{\max} : 3439, 3020, 2935, 2837, 1756 (acetate C=O), 1607, 1512, 1241, 1200, 1167, 1026, 756; HRMS-CI [M+H]⁺ 553.2241; ¹H NMR (400 MHz, CDCl₃) δ ppm: 7.33 (d; $J=8.8$ Hz; 2H; H-10,14), 7.13 (d; $J=8.6$ Hz; 2H; H-10',14'), 7.07 (s; 1H; H-7), 6.93 (d; $J=8.8$ Hz; 2H; H-11,13), 6.69 (d; $J=8.6$ Hz; 2H; H-11',13'), 6.87 (s; 1H; H-2), 6.74 (d; $J=1.9$ Hz; 1H;

H-2'), 6.72 (d; $J=8.3$ Hz; 1H; H-5'), 6.68 (dd; $J=8.6$ Hz, 1.9 Hz; 1H; H-6'), 6.52 (s; 1H; H-5), 4.09 (br s; 1H; H-8'), 4.07 (br s; 1H; H-7'), 4.70 (br s; 1H; 12'-OH), 3.96 (s; 3H; 3-OCH₃), 3.82 (s; 3H; 4'-OCH₃), 3.78 (s; 3H; 3'-OCH₃)*, 3.77 (s; 3H; 4-OCH₃)*, 2.24 (s; 3H; 12-OAc); ¹³C NMR (100.4 MHz, CDCl₃) δ ppm: 126.96 (C-1), 137.88 (C-1'), 110.04 (C-2), 110.83 (C-2'), 147.83 (C-3), 148.71 (C-3'), 148.69 (C-4), 147.57 (C-4'), 112.58 (C-5), 111.24 (C-5'), 127.45 (C-6), 119.32 (C-6'), 124.99 (C-7), 53.07 (C-7'), 135.47 (C-8), 50.99 (C-8'), 138.48 (C-9), 134.30 (C-9'), 126.45 (C-10,14), 128.60 (C-10',14'), 121.30 (C-11,13), 115.54 (C-11',13'), 149.61 (C-12), 154.69 (C-12'), 55.73 (3-OCH₃), 55.79 (3'-OCH₃)*, 55.78 (4-OCH₃)*, 55.91 (4'-OCH₃), 21.04 (12-COCH₃), 169.61 (C=O) (*—interchangeable).

Acknowledgments

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