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# Stereoselective cyclization of stilbene derived carbocations

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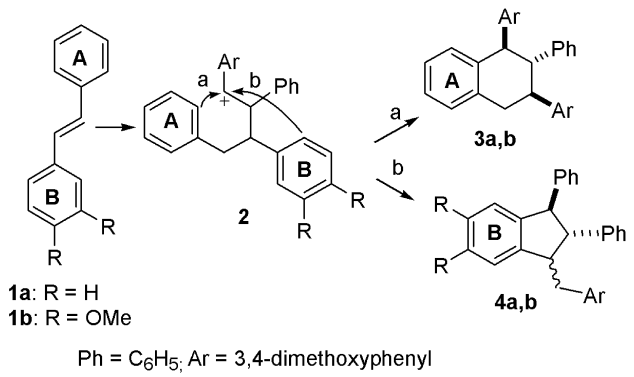
**Abstract**—Cyclodimerization of 2,6-dimethoxy-4-methylstilbene under acidic conditions affords the rotationally restricted 1,3-bis-(2,6-dimethoxy-4-methylphenyl)-2-phenyl-1,2,3,4-tetrahydronaphthalene. Nucleophilic addition of this stilbene to 1,4-benzoquinone and maleic anhydride, respectively, followed by an intramolecular cyclization yields dihydrobenzofuran derivatives and a trisubstituted butanolide, respectively. These stereoselective cyclizations involving stilbene derived carbocations apparently biomimic the cyclization of naturally occurring stilbenes during oxidative oligomerization. 

## 1. Introduction

Cyclodimerizations of stilbenes under acidic conditions to form tetralins and/or indanes have been studied extensively.[1,2] Hiscock et al.[1] suggested that the mechanism for the Lewis acid ($SbCl_3$) promoted formation of the tetralin **3a** and indane **4a** from symmetric *trans*-stilbene (**1a**) involved a dimeric stilbene carbocation (**2**) as the key intermediate (Scheme 1). Recently, Aguirre et al.[2,3] attempted to demonstrate the stereoselective nature of the cyclodimerization of *N*-1,2-diarylethylamides where formation of the carbocationic intermediate related to stilbene **1b** is catalyzed by ethyl polyphosphate (Scheme 1). In the course of our synthesis of antifungal styryl 1,4-benzoquinones, attempted *O*-demethylation of the intermediate 2,6-dimethoxy-4-methylstilbene (**5**) using the Lewis acid, boron tribromide in dichloromethane,[4] yielded a sterically congested cyclodimerization product, 1,3-bis-(2,6-dimethoxy-4-methylphenyl)-2-phenyl-1,2,3,4-tetrahydronaphthalene (**6**). The non-symmetric nature of **5** renders this reaction an ideal model to examine the stereochemical course of the cyclodimerization of stilbenes. In addition, we describe the reactions of a stilbene derived carbocation with selected dienophiles.




**Scheme 1.** Proposed mechanism for the formation of tetralins **3a**, **b** and indanes **4a**, **b** from stilbenes.

## 2. Results and discussion

Reaction of 2,6-dimethoxy-4-methylstilbene (**5**), available via *n*-butyllithium induced reaction of 3,5-dimethoxytoluene and phenylacetaldehyde followed by dehydration, with $BBr_3$ as Lewis acid in $CH_2Cl_2$ at −78°C for 50 min gave compound **6** in 34% yield. The molecular formula of **6**, $C_{34}H_{36}O_4$, which was established by a combination of high resolution ESI-MS and $^{13}C$ NMR spectral data indicated that it is a dimerization product of **5**. In the $^1H$ NMR spectrum of **6**, an aromatic methoxy signal appeared at $\delta$ 3.29 (3H, s), along with three other methoxyls at $\delta$ 3.62, 3.75, and 3.77 (3H each, s) resonating in the normal range of aromatic methoxy protons ($\delta$ 3.6–4.0). The appearance of four instead of two methoxy signals, in the $^1H$- and $^{13}C$ NMR spectra indicated that **6** was rotationally restricted. The presence of five coupled aliphatic proton signals at $\delta$ 4.91 (d, $J$=10.7 Hz), 4.38 (dd, $J$=10.7, 11.6 Hz), 4.27 (ddd, $J$=12.0, 11.6, 4.0 Hz), 3.82 (dd, $J$=16.0, 12.0 Hz) and 2.87 (dd, $J$=16.0, 4.0 Hz) in the $^1H$ NMR spectrum, which was supported by a DQF-COSY, suggested that **6** possessed a 1,2,3-trisubsititued tetrahydronaphthalene (tetralin) skeleton.[1,2] The protonated carbon signals were further assigned by an HMQC spectrum. Using an HMBC experiment,[5] the long-range H/C correlations, e.g. H-1/C-1′,2′,6′, H-2/C-1″, 2″,6″, and H-3/C-1‴,2‴,6‴, were established. Thus, the

*Keywords*: stereoselective cyclization; stilbene; tetrahydronaphthalene; dihydrobenzofuran; butanolide.

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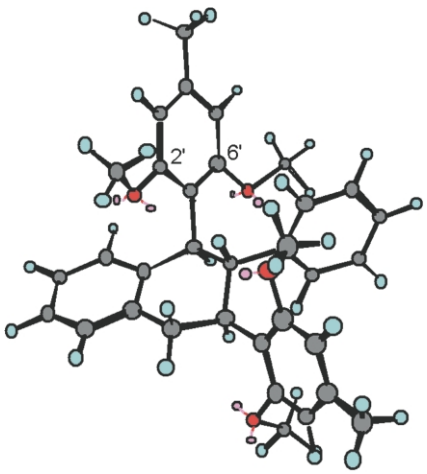



**Figure 1.** Steric view of compound **6**.

NMR data indicated that the structure of **6** is 1,3-bis-(2,6-dimethoxy-4-methylphenyl)-2-phenyl-1,2,3,4-tetrahydronaphthalene. The coupling constants of the five aliphatic protons as well as the NOE correlations (H-1/H-3; H-2/H-4β) suggested that **6** possessed a 1,2-*trans*-2,3-*trans* relative stereochemistry with a pseudo-chair conformation. The 3D-structure of **6**, which was generated by Chem3D Pro™ 5.0 and energy-minimized by MM2, showed that the MeO-2′ was located directly above the plane of the aromatic ring of the tetrahydronaphthalene moiety, explaining the significant shielding of the methoxy protons (Fig. 1), such a conformation presumably being stabilized by attracting π-alkyl interactions.[6] The NOE correlation of MeO-2′ with H-3′ further permitted complete NMR assignments of this more rotationally restricted 2,6-dimethoxy-4-methylphenyl moiety compared to the unit at C-3 (Table 1). The benzene ring at C-2 should be able to rotate freely, as was evidenced by the equivalent chemical shifts of H/C-2″,6″ and H/C-3″,5″ as well as the NOE correlations of H-2″,6″ with both H-1 and H-3.

**Table 1**. NMR data for compound **6** in $CDCl_3$ (δ, ppm; *J*, Hz)

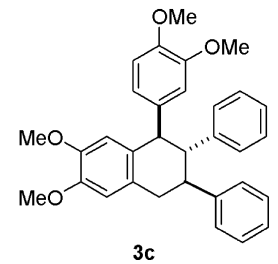
| C/H | $\delta_C$ | $\delta_H$ | NOESY |
|---|---|---|---|
| 1 | 44.4 | 4.91 d (10.7) | H-3,8,2″,6″ |
| 2 | 47.6 | 4.38 dd (10.7, 11.6) | H-4β,2″,6″ |
| 3 | 36.7 | 4.27 ddd (16, 11.6, 4.0) | H-1,4α,2″,6″ |
| 4 | 35.4 | 3.82 dd (16, 12.0)…4β | H-2 |
| | | 2.87 dd (16, 4.0)…4α | H-3,5 |
| 5 | 128.2 | 7.12 d (7.4) | H-4α |
| 6 | 124.7 | 7.06 t (7.4) | – |
| 7 | 125.5 | 6.98 t (7.4) | – |
| 8 | 127.8 | 6.80 d (7.7) | H-1 |
| 9 | 142.2 | – | – |
| 10 | 138.2 | – | – |
| 1′ | 120.3 | – | – |
| 2′ | 158.9 | – | – |
| 3′ | 105.8 | 6.17 s | MeO-2′, Me-4′ |
| 4′ | 137.2 | – | – |
| 5′ | 107.0 | 6.35 s | MeO-6′, Me-4′ |
| 6′ | 159.0 | – | – |
| MeO-2′ | 56.4 | 3.29 s | H-3′ |
| MeO-6′ | 56.1 | 3.62 s | H-5′ |
| Me-4′ | 22.3 | 2.29 s | H-3′,5′ |
| 1″ | 145.6 | – | – |
| 2″,6″ | 128.6 | 6.93 br d (8.8) | H-1,2,3 |
| 3″,5″ | 126.8 | 6.91 br t (7.6) | – |
| 4″ | 125.1 | 6.85 br t (7.0) | – |
| 1‴ | 118.4 | – | – |
| 2‴ | 159.4[a] | – | – |
| 3‴ | 105.3[b] | 6.19 s[a] | MeO-2‴ |
| 4‴ | 136.9 | – | – |
| 5‴ | 105.6[b] | 6.20 s[a] | MeO-6‴ |
| 6‴ | 158.1[a] | – | – |
| MeO-2‴ | 55.4[b] | 3.78 s[b] | H-3‴ |
| MeO-6‴ | 56.3[b] | 3.75 s[b] | H-5‴ |
| Me-4‴ | 22.1 | 2.21 s | H-3‴,5‴ |

[a,b] Signals may be interchangeable within each column.

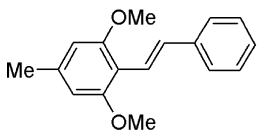
Table 1). The benzene ring at C-2 should be able to rotate freely, as was evidenced by the equivalent chemical shifts of H/C-2″,6″ and H/C-3″, 5″ as well as the NOE correlations of H-2″,6″ with both H-1 and H-3.

The cyclodimerization of **5** was optimized with different acidic reagents and a remarkable yield (95%) was achieved in trichloroacetic acid/MeOH at room temperature for 4 days. As could be anticipated only one pair of enantiomers was obtained from the dimerization reaction, hence the reaction being stereoselective.

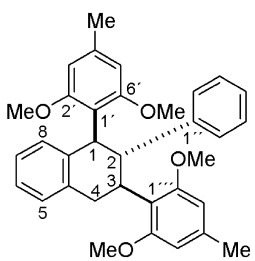
The mechanism for the formation of **6** (Scheme 2) shows that in this type of reaction the carbocation **12** is exclusively generated at the position α to the more electron-rich aromatic ring. The dimeric carbocation **13** will then intramolecularly alkylate the aromatic rings A and/or B, depending on the nucleophilicity of the *ortho*-carbons of each aromatic ring, to form indanes and/or tetralins (also refer to Scheme 1), the latter compounds arising via aromatization of intermediate **15**. In the case of stilbene **5**, tetralin **6** is the only product since the *ortho*-positions of the A-ring are blocked by the methoxy groups. The stereoselective control of this reaction is the key step forming the relatively low-energy 2,3-*trans* intermediate **13**. An alternative 2,3-*cis* intermediate **16** would impose a higher degree of steric congestion than **13**. Intermediate **13** will then



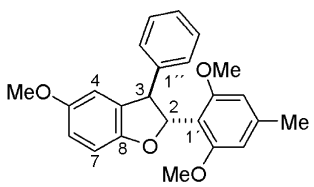

**3c**



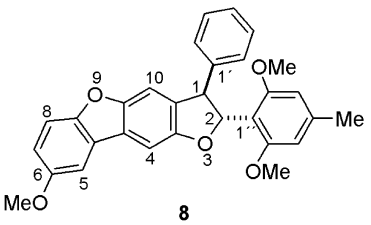

**5**



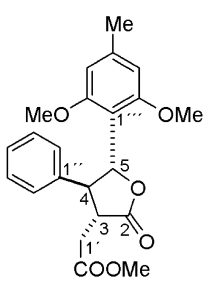

**6**



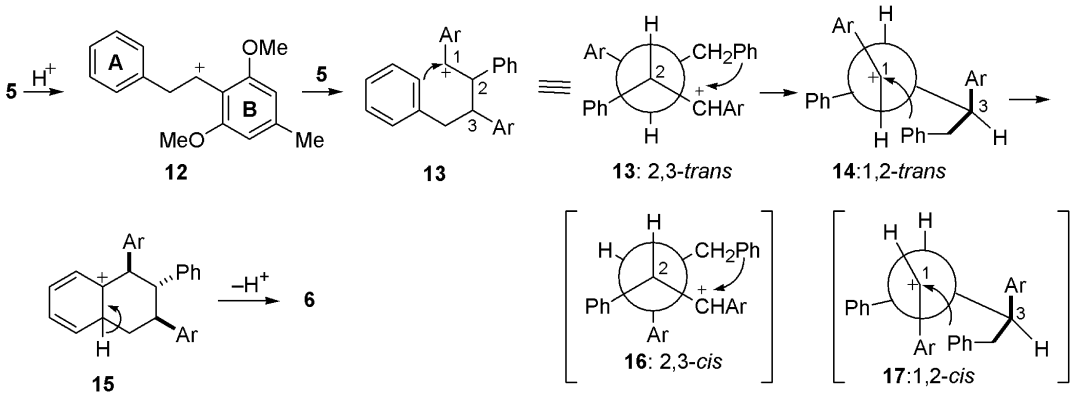

**7**



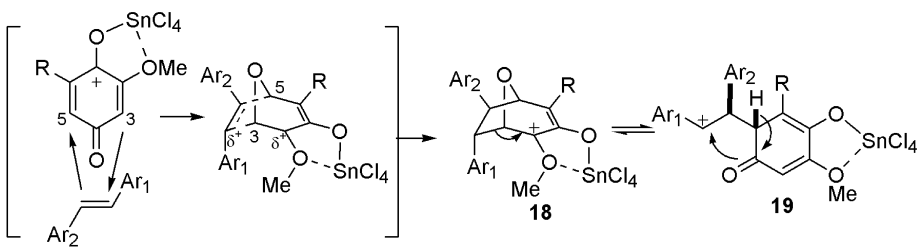

**8**




**11**



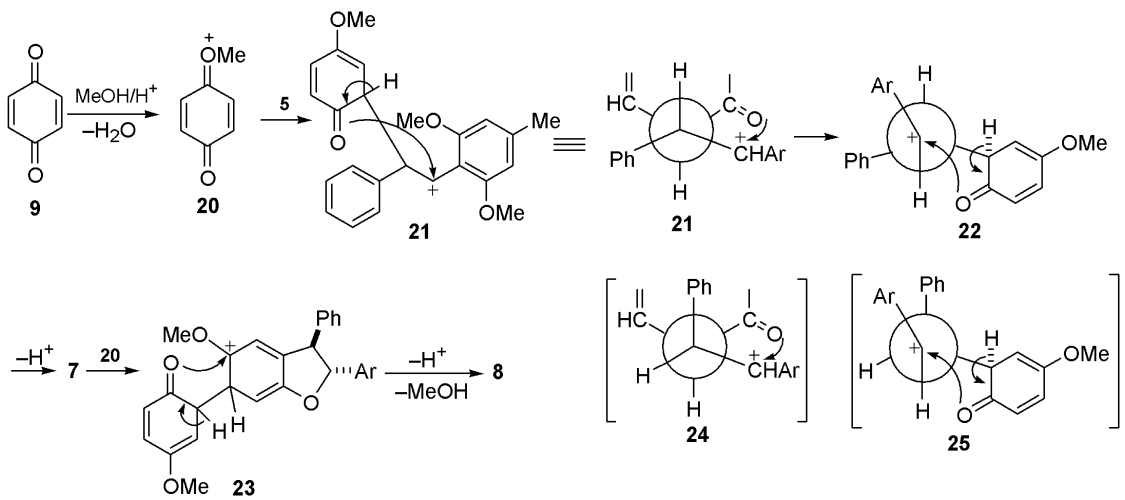
**Scheme 2.** Stereoselective formation of **6**.



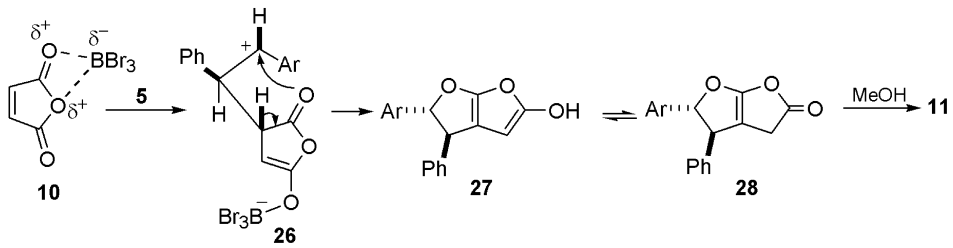
**Scheme 3.** Proposed [5+2]-cycloaddition of stilbenes with benzoquinones.[7]

determine a 1,2-*trans* conformation for the carbocation **14** in the final intramolecular cyclization step, since a 1,2-*cis* conformation **17** would impose considerable steric hindrance between the 2,6-dimethoxy-4-methylphenyl moiety at C-1 and the two benzene rings.

Reaction of **5** with 1,4-benzoquinone (**9**) under acid catalysis (HCl/MeOH or $Cl_3CCOOH$/MeOH) afforded products **7** and **8**. The structure of **7** was established as 2,3-*trans*-2-(2,6-dimethoxy-4-methylphenyl)-5-methoxy-3-phenyl-2,3-dihydrobenzofuran by ESI-MS and NMR including COSY, HMQC, and HMBC. The *trans*-stereochemistry of the dihydrobenzofuran was confirmed by a NOESY experiment, which showed NOE correlations between H-2 and H-2″/-6″ of the benzene ring. Similar reactions of stilbenes with 2-substituted 1,4-benzoquinone derivatives under Lewis acid catalysis have been reported[7–9] and the stereoselective formation of 2,3-*trans*-dihydrobenzofuran was proposed 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 of intermediate **18** into dienone **19** (Scheme 3).[7] However, this mechanism seems inapplicable to our case since the 1,4-benzoquinone (**9**) would not be able to stabilize the carbocation formed as indicated in intermediate **18** (Scheme 3). We assume that the mechanism for the formation of **7** is simply via generation of the stablized carbocation **21** that originates by addition of **5** to the 'activated' benzoquinone **20** (Scheme 4). Stereoselective formation of 2,3-*trans* stereochemistry of the



**Scheme 4.** Stereoselective formation of **7** and **8**.

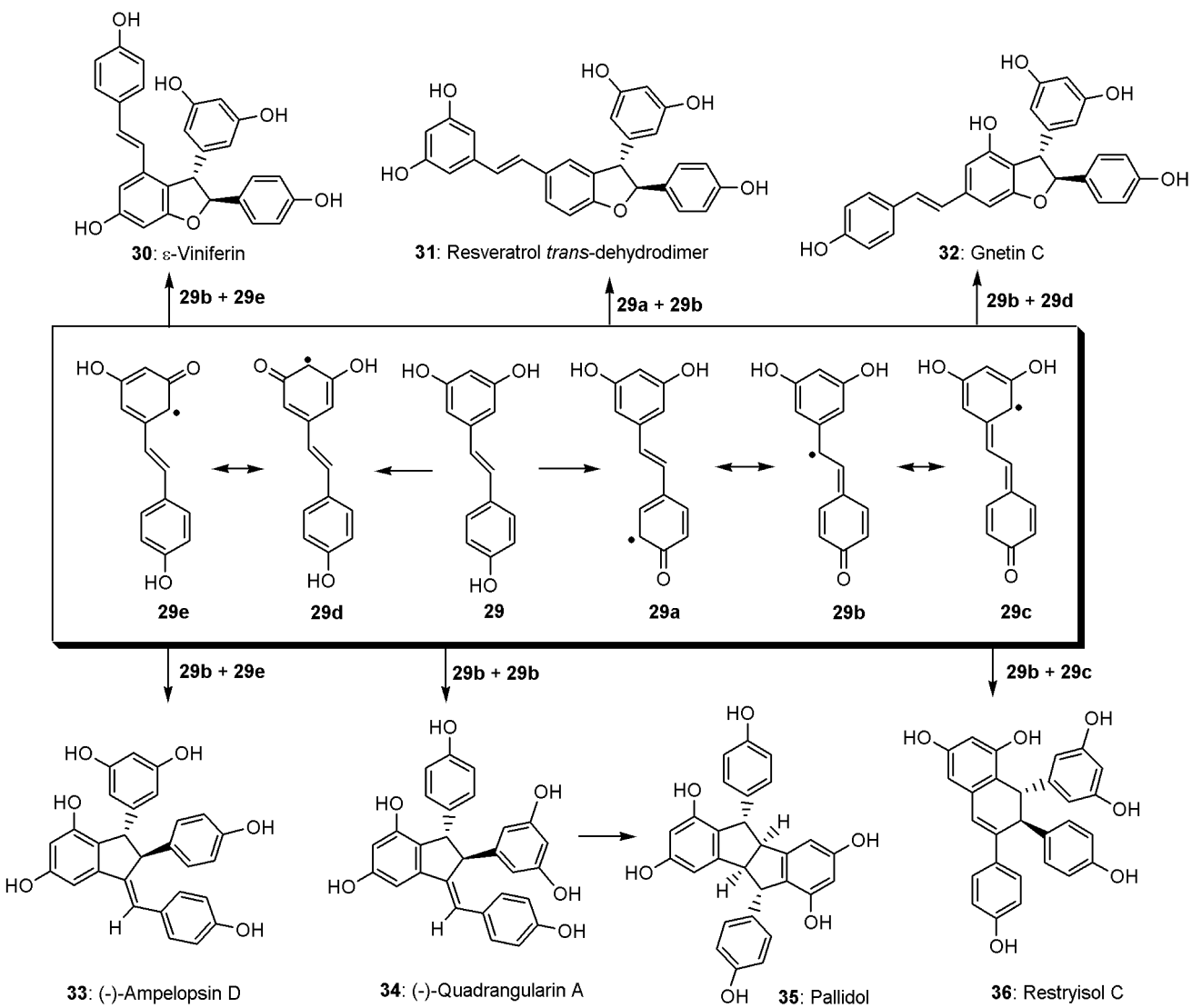



**Scheme 5.** Stereoselective formation of **11**.

dihydrobenzofuran ring is then determined by the lower degree of steric hindrance of the aromatic rings in intermediates **21** and **22**, compared to **24** and **25**, respectively. Compound **7** is susceptible to further acid-catalyzed reaction with intermediate **20** to give compound **8** via cyclization of intermediate **23**.

The NMR spectra of compound **8** showed close resemblance with those of **7** except for an additional aromatic ring. Using an HMBC spectrum, the structure of **8** was established as 2-(2,6-dimethoxy-4-methylphenyl)-6-methoxy-1-phenyl-1,2-dihydro-3,9-dioxacyclopenta[*b*]fluorene. The mechanism for the formation of this product (Scheme 4) is supported by previously reported reactions of resorcinol with 1,4-benzoquinone.[10] It is interesting to note that the ESI-MS of **8** exhibited a strong fragmentation ion peak of [M−COMe−CO], characteristic for 2-methoxydibenzofuran derivatives as shown in their EI-MS spectra,[11] without giving the molecular ion peak. Both compounds **7** and **8** were again obtained as the 2,3-*trans* racemates.

Reaction of stilbene **5** with maleic anhydride (**10**) in




**Scheme 6.** Possible biosynthetic pathways of resveratrol dimers.

$BBr_3/CH_2Cl_2$ at −78°C for 30 min followed by work-up in the presence of MeOH afforded, in addition to the cyclodimerization product **6**, a novel butanolide **11**. The molecular formula of **11** was determined as $C_{22}H_{24}O_6$ by a combination of HRESI-MS and $^{13}C$ NMR spectral data. The presence of a phenyl group and a 2,6-dimethoxyl-4-methylphenyl moiety was readily confirmed by the $^1H$- and $^{13}C$ NMR spectra. DQF-COSY of **11** showed five coupled aliphatic protons of one spin-network at $\delta$ 6.06 (1H, d, $J$=9.4 Hz), 3.96 (1H, dd, $J$=11.5, 9.4 Hz), 3.43 (1H, ddd, $J$=11.5, 7.4, 6.0 Hz), 2.94 (1H, dd, $J$=15.6, 5.9 Hz), and 2.58 (1H, dd, $J$=15.6, 7.5 Hz). These protons were correlated with respective carbons by an HMQC spectrum. Additionally, two carbonyl groups at $\delta$177.1 and 171.8 and one methoxy group at $\delta$ 52.2 appeared in the $^{13}C$ NMR spectrum. In conjunction with the HMBC analysis, the structure of **11** was established as methyl [5-(2,6-dimethoxy-4-methylphenyl)-2-oxo-4-phenyltetrahydrofuran-3-yl]-acetate. Since the coupling constants between protons of the γ-lactone ring may not be reliable for assigning their relative stereochemistry,[7,12] a NOESY experiment was performed. The key NOE correlations between H-2″/6″ of the benzene ring and both H-3 and H-5 indicated a *trans*,*trans*-relative stereochemistry of H-3, H-4, and H-5. Such assignments were further supported by the weak NOE correlation between H-3 and H-5.

The mechanism for the formation of racemic **11** is similar to the aforementioned genesis of dihydrobenzofurans **7** and **8**. Nucleophilic addition of **5** to the $BBr_3$ activated maleic anhydride complex generates the stilbene derived carbocation **26**, which undergoes an intramolecular cyclization to form the bicyclic intermediate **27/28** (Scheme 5). Methanolysis of the intermediate gives the final product **11**. The stereoselectivity of this reaction is also similar to that depicted in Scheme 4. Formation of the 3,4-*trans* configured heterocyclic ring is determined by steric control of the benzene ring and the C-3 side chain.

It is interesting to note that the aforementioned reactions seem to mimic the oligocyclizations of naturally occurring stilbenes, e.g. resveratrol (**29**), which is widely distributed in the plant kingdom and well-known for its important biological activities.[13,14] The difference is, however, that dimerizations or oligomerizations of resveratrol catalyzed by enzymes in organisms presumably involve phenol oxidative coupling via stilbene derived radicals (**29a**–**e**). The possible biosynthetic routes for the formations of a few representative resveratrol dimers (**30**–**36**)[15–20] are proposed as shown in Scheme 6. This may explain the natural occurrence of ampelopsin D (**33**),[18] the structure of which had been questioned[19] but was later confirmed by chemical and spectral evidence.[21]

In conclusion, the formation of stilbene-derived carbocations in the reactions of stilbene derivatives with acidic reagents has been clearly defined. Similar to the intramolecular cyclizations of naturally occurring stilbenes which contribute to their fascinating oligomerization chemistry, the susceptibility of the stilbene-derived carbocations to stereoselective cyclizations may be useful for preparation of stilbene derivatives. The proposed biosynthetic routes of resveratrol dimers (Scheme 6) can be used as an additional tool in characterizing complex naturally occurring stilbene oligomers.[22–24]

## 3. Experimental

### 3.1. General

Melting points were measured on a Thomas Hoover capillary melting point apparatus and are uncorrected. UV spectra were measured on a Hewlett Packard 8453 spectrometer. IR spectra were recorded on an ATI Mattson Genesis Series FTIR Spectrometer. NMR spectra were recorded on Bruker Avance DPX-300 (300 MHz), DRX-400 (400 MHz) or DRX-500 (500 MHz) NMR spectrometers. Chemical shifts are expressed relative to the deuterated solvent ($CDCl_3$: $\delta_H/\delta_C$, 7.26/77.4). COSY, HMQC, HMBC ($J$, 10 Hz), NOESY (mixing time, 800 ms) spectra were performed with standard pulse programs. GC–MS was run on an Hewlett–Packard (HP) 5890 Series II Plus Gas Chromatograph interfaced to a HP 5970B Mass Selective Detector: DB-1 minibore capillary column (0.18 mm ID, 20 m), column temperature 100⟶280°C (10°C/min⟶25 min), He (45 psi). ESI-FTMS were measured on a Bruker-Magnex BioAPEX 30es ion cyclotron high-resolution HPLC-FT spectrometer by direct injection into an electrospray interface. Column chromatography was run on silica gel (40 μm, J. T. Baker). TLC was performed on silica gel sheets (Alugram® Sil G/$UV_{254}$, Macherey-Nagel, Germany). All the reagents were purchased from Aldrich (Milwaukee, WI).

**3.1.1. 2,6-Dimethoxy-4-methylstilbene (5).** According to the procedure for preparation of similar compounds,[25,26] *n*-butyllithiuim (10.3 mL of a 2.5 M solution in hexane, 25.75 mmol) was slowly added to a cold (0°C) solution of 3,5-dimethoxytoluene (2.61 g, 17.17 mmol) in dry $Et_2O$ (50 mL) under an argon blanket. After 30 min stirring at 0°C, the formation of a white precipitate was observed. The mixture was further stirred at room temperature for 24 h. The resulting suspension was cooled again to 0°C and phenylacetylaldehyde (3 mL, 25.75 mmol) was added dropwise over 10 min. After 1 h stirring at 0°C, the cloudy reaction mixture was quenched by the addition of ammonium chloride solution (15 mL). The $Et_2O$ layer was separated, and the aqueous layer was extracted with $Et_2O$ (15 mL×3). The organic layers were combined and washed with brine, dried ($MgSO_4$), and concentrated to give an oily residue. To this oil was added 250 mL of MeOH and 4 mL of concentrated HCl. After stirring at room temperature for 24 h, the solution was neutralized with 6% NaOH, concentrated to half volume, and extracted with $Et_2O$ (100 mL×4). The $Et_2O$ layer was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (200 g) eluting with a mixture of hexane and $CH_2Cl_2$ (3:1, 1.5 L, 1:2, 500 mL) and $CH_2Cl_2$ (500 mL) to yield compound **5** (1.2 g, 28%) as a viscous oil, UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 208 (4.33), 230 (sh, 4.04), 320 (4.16), 338 (sh, 3.98) nm; IR (KBr) $\nu_{max}$ 3077–2836 (multiple peaks), 1609, 1584, 1474, 1417, 1197, 1120, 971, 950, 748, 699 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz) $\delta$: 7.64 (1H, d, $J$=17.0 Hz), 7.63 (2H, d, $J$=7.0 Hz), 7.55 (1H, d, $J$=17.0 Hz), 7.41 (2H, t, $J$=7.5 Hz), 7.28 (1H, t, $J$=7.3 Hz),

6.48 (2H, s), 3.94 (6H, s), 2.43 (3H, s); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$: 158.6 (2C), 139.7, 138.6, 131.4, 128.6 (2C), 126.9, 126.4 (2C), 120.2, 112.2, 105.1 (2C), 55.8 (2C), 22.3; GC–MS ($t_R$=13.26 min) *m/z* 254 [M, base beak]$^+$.

**3.1.2. 1,2-*trans*-2,3-*trans*-1,3-Bis-(2,6-dimethoxy-4-methylphenyl)-2-phenyl-1,2,3,4-tetrahydronaphthalene (6).** To a stirred solution of **5** (67 mg, 0.264 μmol) in dry $CH_2Cl_2$ (5 mL) at −78°C under argon, $BBr_3$ in $CH_2Cl_2$ (1 M, 0.53 mL, 0.53 μmol) was added dropwise. After stirring at −78°C for 50 min, the mixture was warmed to room temperature and quenched with saturated aqueous ammonium chloride (2 mL) and $H_2O$ (10 mL). The mixture was stirred for 1 h, the organic layer was separated and the aqueous layer was extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layers were concentrated to dryness, and the residue was chromatographed on silica gel eluting with a mixture of hexane and $CHCl_3$ to give recovered **5** (22 mg) and compound **6** (31 mg, 34%) as colorless needles, mp 214°C, UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 210 (4.45), 238 (sh, 3.76), 270 (2.86) nm; IR (KBr) $\nu_{max}$ 3077–2835 (multiple peaks), 1608, 1584, 1465, 1417, 1237, 1206, 1124, 972, 816, 742, 697, 584 cm$^{-1}$; $^1$H (500 MHz) and $^{13}$C (125 MHz) NMR data in $CDCl_3$, see Table 1; HRESI-MS *m/z* 509.2696 (calcd for $[M(C_{34}H_{36}O_4)+H]^+$, 509.2686); GC–MS ($t_R$= 26.02 min) *m/z* 508 [M]$^+$, 417, 356, 265, 223 (base peak), 165, 91.

Cyclodimerization of **5** was performed under different conditions: (a) HCl/MeOH, rt/2 days; (b) $Cl_3CCOOH/CH_2Cl_2$, rt/4 days; (c) $Cl_3CCOOH$/EtOH, rt/2 days; and (d) $Cl_3CCOOH$/MeOH, rt/4 days. The formation of **6** with a 95% isolated yield was achieved under the conditions in d with complete consumption of **5**.

**3.1.3. 2,3-*trans*-2-(2,6-Dimethoxy-4-methylphenyl)-5-methoxy-3-phenyl-2,3-dihydrobenzofuran (7) and 2-(2,6-dimethoxy-4-methylphenyl)-6-methoxy-1-phenyl-1,2-dihydro-3,9-dioxacyclopenta[*b*]fluorene (8).** A solution of **5** (36 mg, 0.142 μmol), **9** (36 mg, 0.333 μmol) and concentrated HCl (0.5 mL) in MeOH (5 mL) was stirred at room temperature for 2 days. The mixture was neutralized with $NaHCO_3$. After adding $H_2O$ (10 mL), the mixture was extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel eluting with a mixture of hexane and $CH_2Cl_2$ to give compounds **6** (5 mg, 10%), **7** (8 mg, 23%) and **8** (6 mg, 14%) with a recovery of **5** (12 mg).

Similarly, a solution of **5** (36 mg, 0.142 μmol), **9** (28 mg, 0.259 μmol) and $Cl_3CCOOH$ (35 mg, 0.214 μmol) in MeOH (5 mL) was stirred at room temperature for 4 days. Work-up and chromatography on silica gel eluting with a mixture of hexane and $CH_2Cl_2$ gave compounds **7** (22 mg, 50%) and trace amount of **8** (~1 mg) with a recovery of **5** (6 mg). Cyclodimerization of **5** to form **6** was not detected under these conditions.

Compound **7**: colorless needles, mp 140°C, UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 210 (4.88), 238 (sh, 4.18), 302 (2.79) nm; IR (KBr) $\nu_{max}$ 3080–2823 (multiple peaks), 1609, 1586, 1486, 1465, 1204, 1118, 1033, 952, 814, 740, 702 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$: 7.30 (2H, br t, *J*=7.3 Hz, H-3″,5″), 7.24 (1H, br t, *J*=7.3 Hz, H-4″), 7.20 (2H, br d, *J*=7.3 Hz, H-2″,6″), 6.77 (1H, d, *J*=7.0 Hz, H-7), 6.73 (1H, dd, *J*=7.0, 2.2 Hz, H-6), 6.59 (1H, br s, H-4), 6.40 (2H, s, H-3′,5′), 6.16 (1H, d, *J*=9.4 Hz, H-2), 5.05 (1H, d, *J*=9.0 Hz, H-3), 3.74 (3H, s, MeO-5), 3.63 (6H, s, H-2′,6′), 2.35 (3H, s, Me-4′); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$: 159.7 (2C, s, C-2′,6′), 155.2 (s, C-8), 154.2 (s, C-5), 143.3 (s, C-1″), 140.7 (s, C-4′), 132.8 (s, C-9), 128.9 (2C, d, C-3″,5″), 128.8 (2C, d, C-2″,6″), 127.1 (s, C-4″), 113.5 (d, C-6), 113.3 (s, C-1′), 111.2 (d, C-4), 106.2 (2C, C-3′,5′), 85.3 (d, C-2), 56.4 (2C, q, MeO-2′,6′), 54.4 (2C, C-3 and MeO-5), 22.6 (q, Me-4′); ESI-MS *m/z* 399 $[M(C_{24}H_{26}O_5)+Na]^+$, 377 $[M+H]^+$; GC–MS ($t_R$=18.89 min) *m/z* 376 [M]$^+$, 345 [376−OMe]$^+$.

Compound **8**: white powder, mp 170–172°C, UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 210 (4.90), 238 (sh, 4.12), 310 (3.93) nm; IR (KBr) $\nu_{max}$ 3070–2838 (multiple peaks), 1608, 1585, 1477, 1419, 1216, 1121, 955, 815, 738, 699 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 7.31 (2H, br t, *J*=7.6 Hz, H-3′,5′), 7.25 (1H, br t, *J*=7.6 Hz, H-4′), 7.19 (2H, br d, *J*=7.6 Hz, H-2′,6′), 6.96 (1H, d, *J*=7.8 Hz, H-8), 6.91 (1H, d, *J*= 2.9 Hz, H-5), 6.82 (s, H-4), 6.78 (1H, dd, *J*=8.9, 2.9 Hz, H-7), 6.68 (1H, d, *J*=0.6 Hz, H-10), 6.41 (2H, s, H-3″,5″), 6.19 (1H, d, *J*=8.7 Hz, H-2), 4.98 (1H, d, *J*=8.7 Hz, H-1), 3.78 (3H, s, MeO-6), 3.65 (6H, s, H-2″,6″), 2.37 (3H, s, Me-4″); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 159.6 (2C, s, C-2″,6″), 154.9 (s, C-3a), 154.1 (s, C-6), 145.9 (s, C-8a), 145.6 (s, C-9a), 143.0 (s, C-1′), 141.0 (s, C-4″), 132.7 (s, C-10a), 128.9 (2C, d, C-3′,5′), 128.6 (2C, d, C-2′,6′), 127.2 (d, C-4′), 120.3 (s, C-5a), 118.5 (s, C-4a), 117.0 (d, C-8), 114.9 (d, C-7), 114.5 (d, C-5), 113.0 (s, C-1″), 112.8 (d, C-10), 109.1 (d, C-4), 106.1 (2C, d, C-3″,5″), 85.7 (d, C-2), 56.4 (2C, q, MeO-2″,6″), 56.3 (q, MeO-6), 54.1 (d, C-1), 22.5 (q, Me-4″); ESI-MS *m/z* 397 $[M(C_{30}H_{26}O_5)-COMe-CO+2H]^+$; GC–MS ($t_R$=20.69 min) *m/z* 466 [M]$^+$, 396 $[M-COMe-CO+H]^+$, 365 [396−OMe]$^+$.

**3.1.4. Methyl [5-(2,6-dimethoxy-4-methylphenyl)-2-oxo-4-phenyltetrahydrofuran-3-yl]-acetate (11).** To a stirred solution of **5** (57 mg, 0.224 μmol) and **10** (31 mg, 0.316 μmol) in dry $CH_2Cl_2$ (5 mL) at −78°C under argon $BBr_3$ in $CH_2Cl_2$ (1 M, 0.3 mL, 0.3 μmol) was added dropwise. After stirring at −78°C for 30 min, the mixture was warmed to room temperature and quenched with saturated aqueous ammonium chloride (5 mL) and 50% aqueous MeOH (10 mL). The organic layer was separated, the aqueous layer was diluted with $H_2O$ and then extracted with $CH_2Cl_2$ (10 mL×3). The combined organic layers were concentrated to dryness. The residue was chromatographed on silica gel eluting with a mixture of hexane and $CHCl_3$ to give compounds **11** (14 mg, 20%) and **6** (6 mg, 7%) with a recovery of **5** (11 mg). **11**: colorless needles, 143°C, UV (MeOH) $\lambda_{max}$ (log $\varepsilon$) 210 (4.88), 238 (sh, 4.19), 284 (2.57) nm; IR (KBr) $\nu_{max}$ 3080–2840 (multiple peaks), 1766 (lactone), 1730 (ester), 1611, 1585, 1463, 1420, 1245, 1179, 1115, 989, 827, 755, 705 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 500 MHz) $\delta$: 7.30 (2H, br t, *J*=7.2 Hz, H-3″,5″), 7.24 (1H, br t, *J*=7.2 Hz, H-4″), 7.20 (2H, br d, *J*=7.2 Hz, H-2″,6″), 6.36 (2H, s, H-3‴,5‴), 6.06 (1H, d, *J*=9.4 Hz, H-5), 3.96 (1H, dd, *J*=11.5, 9.4 Hz, H-4), 3.70 (6H, s, MeO-2‴,6‴), 3.47 (3H, s, MeO-2′), 3.43 (1H, ddd, *J*=11.5, 7.4, 6.0 Hz, H-3), 2.94 (1H, dd, *J*=15.6, 5.9 Hz, H-1′a), 2.58 (1H, dd,

$J$=15.6, 7.5 Hz, H-1′b), 2.33 (3H, s, Me-4‴); $^{13}$C NMR ($CDCl_3$, 125 MHz) $\delta$: 177.1 (s, C-2), 171.8 (s, C-2′), 159.4 (2C, s, C-2‴,6‴), 141.5 (s, C-4‴), 138.8 (s, C-1″), 129.0 (2C, d, C-3″,5″), 128.2 (2C, d, C-2″,6″), 127.9 (d, C-4″), 110.7 (s, C-1‴), 106.1 (2C, d, C-3‴,5‴), 78.7 (d, C-5), 56.5 (2C, s, MeO-2‴,6‴), 52.2 (s, MeO-2′), 52.1 (d, C-4), 22.6 (s, Me-4‴); HRESI-MS $m/z$ 385.1661 (calcd for [M($C_{22}H_{24}O_6$)+H], 385.1646), 407.1439 (calcd for [M($C_{22}H_{24}O_6$)+Na], 407.1465).

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