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Regio- and Stereoselective Biomimetic Synthesis of Oligostilbenoid Dimers from Resveratrol Analogues: Influence of the Solvent, Oxidant, and Substitution

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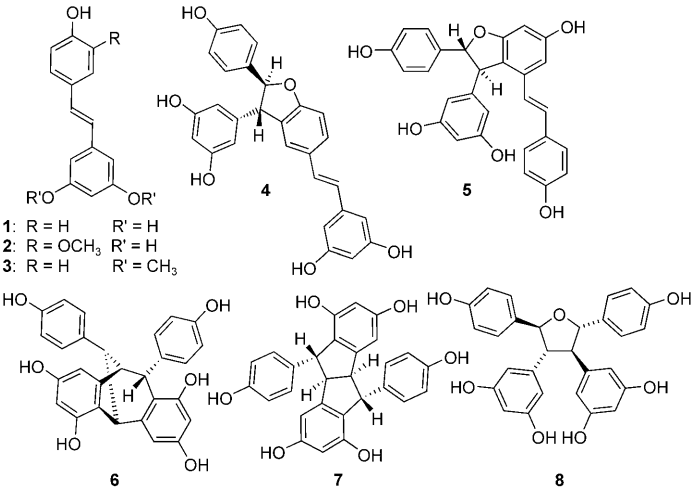
Abstract: Oligostilbenoids are polyphenols that are widely distributed in nature with multifaceted biological activities. To achieve biomimetic synthesis of unnatural derivatives, we subjected three resveratrol analogues to oligomerization by means of one-electron oxidants. Upon varying the metal oxidant (AgOAc, $CuBr_2$, $FeCl_3{\cdot}6H_2O$, $FeCl_3{\cdot}6H_2O$/NaI, PbO_2, VOF_3), the solvent (over the whole range of polarities), and the oxygenated substitution pattern of the starting material, stilbenoid oligomers with totally different carbon skeletons were obtained. Here we propose to explain the determinism of the type of skeleton produced with the aid of hard and soft acid/base concepts in conjunction with the solvating properties of the solvents and the preferred alignment by the effect of π stacking.

Keywords: biomimetic synthesis · hard/soft acids · oxidation · stacking interactions · stilbene dimers

Introduction

Oligostilbenoids form a group of polyphenolic compounds relatively small in number, but with significant economic impact, as they are constituents of a large portion of timber trees from South East Asia[1,2] as well as grapevine.[3] The biosynthesis of oligostilbenoids may impact the durability of timber, the manufacturing of paper and other wood products, and also wine palatability.[4] It is accepted that most of these compounds derive from resveratrol (**1**) and to a lesser extent, from its derivatives isorhapontigenin (**2**) or pterostilbene (**3**).[1,5] Some of the commonly encountered dimers include the benzofurans δ-viniferin (**4**)[6,7] and ε-viniferin (**5**),



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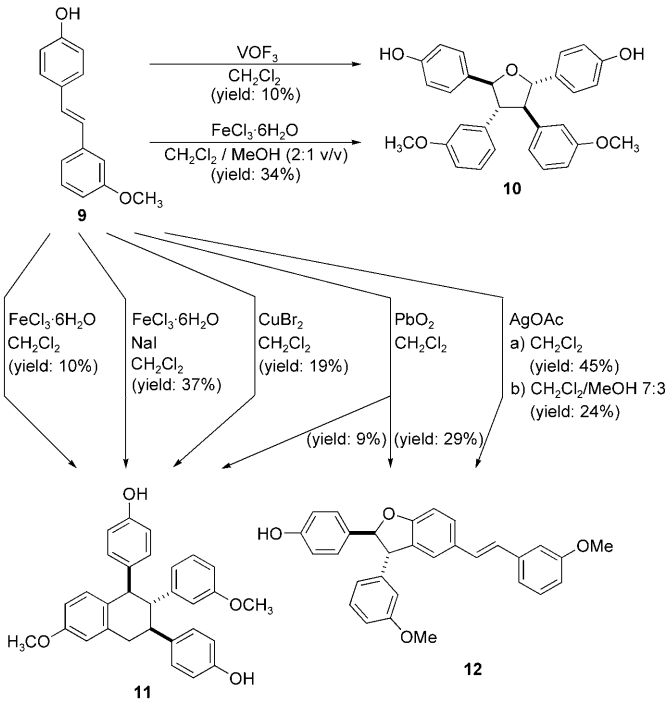
the dibenzocycloheptanoid ampelopsin F (**6**),[7] the dibenzooctahydropentalene pallidol (**7**),[8] and the tetraarylfuran tricuspidatol A (**8**).[9] In spite of the structural diversity and attractiveness of oligostilbenoids, only very few studies were undertaken to attempt their synthesis. A recent paper by Snyder et al.[10] describes elegant and versatile routes to a few dimeric species by adding and/or constructing additional rings onto a brominated stilbenes. Some key steps include intramolecular Friedel–Crafts alkylation. Few other groups attempted biomimetic syntheses from natural precursors. Niwa's group reported the biotransformation (with help of horseradish, soybean, and fungus peroxidase) and chemical conversion of oligostilbenes and resveratrol.[5,7,11] Sako et al. subjected resveratrol (**1**) and ε-viniferin (**4**) to a variety of one-electron oxidants ($K_3[Fe(CN)_6]$, Ag^I, Cu^I, Cu^I, and Mn^{II} derivatives).[12] Lin's group described the oxidative coupling of isorhapontigenin (**2**) by means of formic acid and one-electron oxidants (Ag_2O, $FeCl_3{\cdot}6H_2O$).[13] These researchers managed to obtain dimeric species of various natural skeletons, mainly of the δ- or ε-viniferin type. However, they did not provide convincing mechanisms that would both explain the selectivity of their reactions and the apparent discrepancies between all these results. Hou and co-workers dimerized a cleverly designed resveratrol derivative with help of the horseradish peroxidase.[14] The bulky substituents did not allow the enzyme to convert the substrate into a δ-viniferin analogue and subsequently quadrangularin A could be obtained. The interest we developed in these compounds was also triggered by the wide range of reported biological activities that include antimicrobial,[15] antifungal,[16] antioxidant,[17] hepato-protective,[18] anti-HIV,[19] cytotoxic,[20] anti-inflammatory,[21] and inhibition of DNA topoisomerase II.[22] These biological activities obviously originate from pharmacophores that are specific to each type of oligostilbenoid, in contrast with the majority of polyphenols, which derive from flavan-3-ols or polygalloyl glucose. However, we believe that their drugability should be improved notably by increasing their lipophilicity.

As a result of all the above, we embarked on the study of the dimerization of partially or fully protected hydroxystilbenes by means of $FeCl_3$[23] and other one-electron oxidants to obtain analogues of natural dimers. Such biomimetic approaches may not necessarily lead to high yields as several products might be formed during the reaction cascades. However, this should allow us to better understand the biogenesis of oligostilbenoids and possibly make some comparison with peroxidases[24] and laccases[25] that are involved in their biosynthesis and use Fe^{3+} as a cofactor.[26] More significantly, when the results presented below are combined with our own previous observations and those from Sako, Niwa, and Lin, it becomes possible to better understand some aspects of this chemistry.

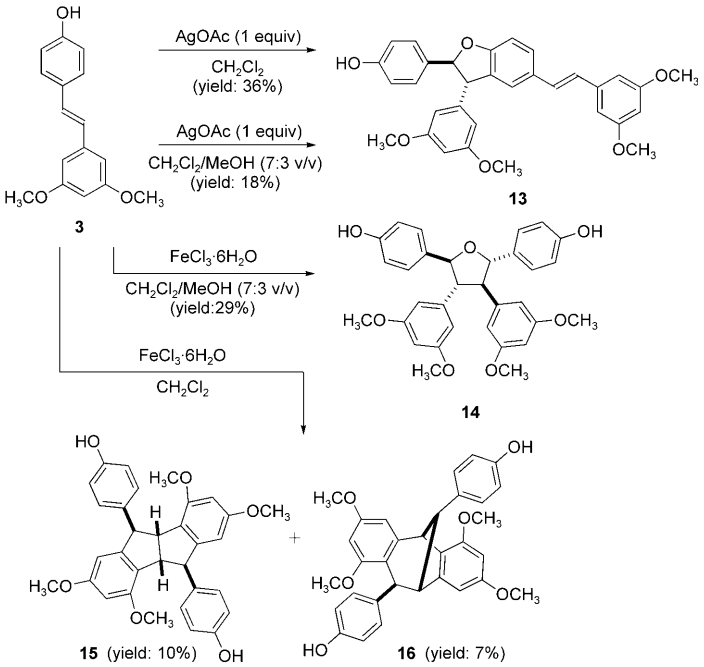
Results and Discussion

We have subjected a few stilbenoids to oligomerization by means of one-electron oxidants under various conditions. These starting materials were prepared by a modification of our previously published procedure.[27] All significant reaction products are reported herein. They were usually easily isolated by preparative TLC on silica gel. As a result, several stilbene dimers were identified that share their carbon skeleton with natural derivatives. The repeatability of these transformations was confirmed.

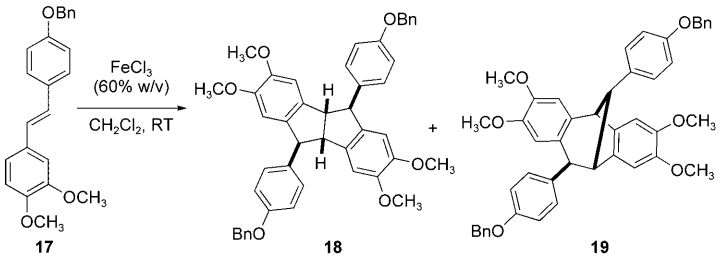
Dimerization of 12-hydroxy-3-methoxystilbene (demethoxypterostilbene) (9) and 12-hydroxy-3,5-dimethoxystilbene (pterostilbene) (3): We subjected **9** and **3** to oxidation by means of a series of one-electron oxidants and the major isolated products are described below (Schemes 1 and 2). When treated with AgOAc, **9** and **3** were converted into δ-viniferin analogues **12** and **13**, respectively. This is consistent with Sako's report of the isolation of δ-viniferin (**4**) and an unnatural tetrameric species by treatment of unprotected resveratrol with AgOAc in MeOH.[12] However, we observed a solvent effect: when the reaction is carried out in CH_2Cl_2, the yield is roughly twice the one obtained from CH_2Cl_2/MeOH (2:1 v/v). When the same compounds **9** and **3** were treated with $FeCl_3{\cdot}6H_2O$, the reaction outcome was different for each starting material and solvent. On the one hand, treatment of **3** with $FeCl_3{\cdot}6H_2O$ in CH_2Cl_2 produced some new analogues of ampelopsin F and pallidol, **16** and **15**, respectively. The addition of methanol to the



Scheme 1. Dimerization of demethoxypterostilbene **9** under various conditions.



Scheme 2. Dimerization of pterostilbene **3** by means of AgOAc and $FeCl_3$ under various conditions.



Scheme 3. Construction of **18** and **19** by dimerization of **17**.

$FeCl_3$·6H_2O/CH_2Cl_2 mixture gives rise to a new tricuspidatol A analogue **14**. On the other hand, exposure of **9** to $FeCl_3$·6H_2O in CH_2Cl_2/MeOH (2:1 v/v) gave rise to another tricuspidatol A analogue **10** (**10** is also produced by treatment of **9** with VOF_3 in CH_2Cl_2).[28] Treatment of **9** with $FeCl_3$·6H_2O in CH_2Cl_2 (in the absence of methanol) produced the tetrahydronaphthalene **11**. The addition of NaI[29] to the reaction mixture increased the yield very significantly from 10 to 37% (when NaF is used no reaction is observed at all). Similarly, **11** was obtained by treatment of **9** with $CuBr_2$[30] in CH_2Cl_2.

We have also observed that **9** can be converted to **11** and **12** by treatment with PbO_2[31] in CH_2Cl_2. As a result, the δ-viniferin skeleton is obtained by treatment of a 12-hydroxystilbenes **9** and **3** with AgOAc, regardless of substituents or solvent effects. Tricuspidatol A analogues **10** and **14** are formed from the same building blocks by using $FeCl_3$·6H_2O. However, this reaction is solvent dependent as it occurs only in a mixture of CH_2Cl_2/MeOH (7:3, v/v). When this reaction is performed in pure CH_2Cl_2, we observed the formation of compounds with structures that depend on the substitution pattern of the building blocks.

Dimerization of 12-benzyloxy-3,4-dimethoxystilbene (17): Treatment of **17** with a 60% aqueous solution of $FeCl_3$ (w/v) in dichloromethane produced the catechol oligostilbenoid dimers **18** (9%) and **19** (16%) related to pallidol (**7**) and ampelopsin F (**6**), respectively (Scheme 3).[32] We shall refer to **18** and **19** as 3,4-dimethoxypallidol or DMP and 3,4-dimethoxyampelopsin F or DMAF, respectively, to avoid confusion.

Parameters that were thought to influence the above results were studied by repeating the reaction on a small scale under carefully controlled conditions and by analyzing the reaction mixtures by HPLC following a standardized sample preparation procedure. The effects of some of them are summarized in Table 1. Others that were found to have some significant impact on the outcome of the reaction are discussed below.

Table 1. Effects of some parameters on the dimerization reaction of **17** by $FeCl_3$.

Reaction parameter	Observed effect
reaction duration	all starting material consumed in 5 h
illumination	negligible
presence of oxygen	negligible
concentration of the starting material	negligible in the range of 0.2–11 mg mL^{-1} (0.5–31 mM) of starting material. Decreased yield at 21 mg mL^{-1} (61 mM)

Effect of the quantity of the $FeCl_3$ solution: To standardized solutions of **17** in CH_2Cl_2 were added increasing volumes of a 60% w/v aqueous solution of $FeCl_3$, resulting in a fixed $FeCl_3$-to-water ratio. The maximum yields we have recorded in this reaction are 18% for DMP (**18**) and 24.5% for DMAF (**19**) (degree of transformation). The reaction is clearly not catalytic as the yields of **18** and **19** tended to decrease when less than 1.5 equivalents of $FeCl_3$ were used. In addition, the fact that some starting material was recovered is further evidence of the stoichiometric nature of the reaction. However, larger quantities of the reagent do not significantly improve its efficiency. No significant change was observed in the DMP/DMAF ratio within the studied range of 0.5 to 15 equivalents of $FeCl_3$.

Effect of the dilution of the $FeCl_3$ solution: To standardized solutions of **17** in CH_2Cl_2 were added decreasing volumes of a 60% w/v aqueous solution of $FeCl_3$. To maintain a constant volume of water (164 μL), increasing amounts of pure water were added. Unlike the previous experiment, the $FeCl_3$-to-water ratio was steadily decreased. We observed that diluting the $FeCl_3$ solution by half resulted in lower

yields of **18** (7%) and **19** (10%) and more than 80% of **17** was unreacted (Figure 1). This 32% w/v $FeCl_3$ solution corresponded to 7.5 equivalents, a quantity that was shown to produce maximum yields, as described above, when the solution was 60% w/v. Further dilution of $FeCl_3$ leads to only trace amounts of **18** and no **19**.

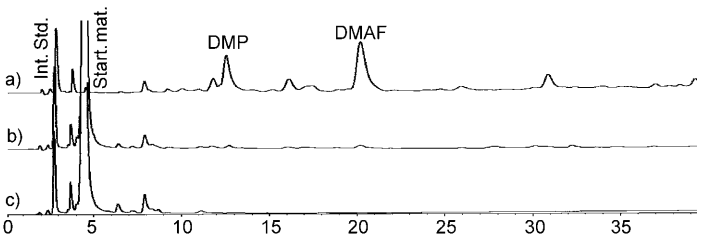


Figure 1. Effect of the dilution of the $FeCl_3$ solution on stilbene **17** dimerization. a) $FeCl_3$ 60% (w/v) (15 equiv); b) $FeCl_3$ 32% (w/v) (7.5 equiv); c) $FeCl_3$ 2.3% (w/v) (0.5 equiv).

Effect of the solvent: We compared the ferric chloride dimerization reaction in sixteen solvents covering the whole range of polarity indices with some surprising results (Figures 2 and 3). The dimerization reaction was completely inhibited when carried out in the following solvents: water, methanol, ethanol, 2-propanol, and DMF. No other peaks could be detected during the 40 minutes of our chromatographic analysis. Yet, only 3 to 36% of the starting material was recovered. This suggests that the starting material had polymerized into large insoluble compounds. Reactions carried out in acetone, ethylmethylketone (EMK), ethyl acetate, diethyl ether, THF, and acetonitrile show some common characteristics. Quite large amounts of starting material were recovered untransformed, especially in EMK and acetonitrile (83 and 60%, respectively). Interestingly enough in these reactions, we observed the appearance of two peaks at about 16 and 17 minutes, respectively, that is with retention times that are intermediate between those of DMP and DMAF. The yields of these latter products in these reactions were low. When the reaction was performed in nonpolar solvents, xylenes, toluene, and hexanes, the expected dimers were formed in moderate yields in addition to a number of unidentified compounds. The starting material was recovered in a comparatively low yield, which meant that in these experiments large insoluble compounds were formed. The most surprising results were obtained when we compared the dimerization of our starting material in dichloromethane and chloroform. The reactions resulted in very different chromatographic profiles. In dichloromethane, we obtained the expected compounds **18** and **19** as the major products, in 13.5 and 24.5% yields, respectively, the highest yields of all the experiments in this series, along with a small number of insignificant unidentified compounds. In contrast, for the reaction performed in chloroform, many more chromatographic peaks were observed that were similar to those previously observed for reactions in other solvents, such as toluene or acetone; however, the peaks were taller. By far, the largest peaks were those appearing at approximately 16 and 17 minutes.

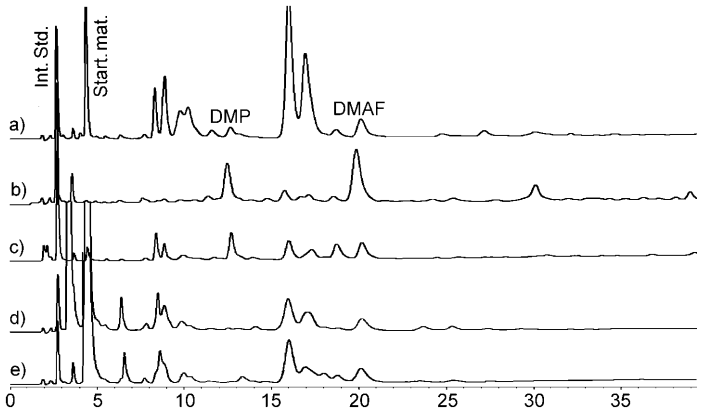


Figure 2. Chromatograms of the dimerization mixtures of stilbene **17** in various solvents: a) $CHCl_3$; b) CH_2Cl_2; c) toluene; d) EMK; e) acetone.

In summary, chloroform and dichloromethane appear to be the best solvents for generating small molecular weight products from our stilbene ferric chloride reactions. One critical point to be emphasized is that whereas in dichloromethane ferric chloride produces predominantly a mixture of **18** and **19**, in chloroform, it induces the formation of a wider array of compounds, in moderate to good yields, including the expected dimers.

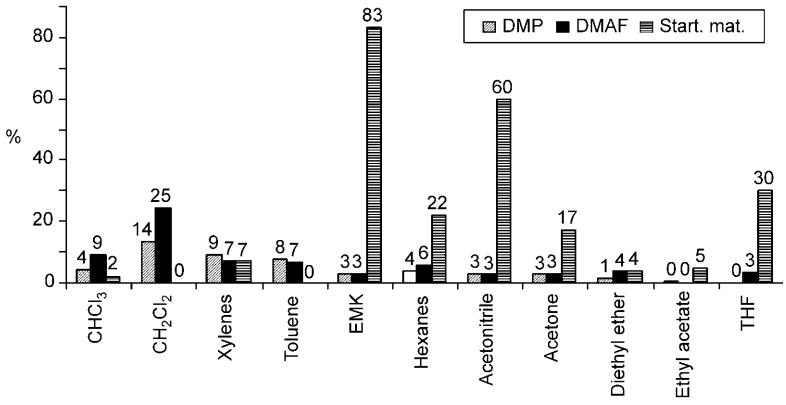


Figure 3. Effect of solvent on the dimerization of stilbene **17**. DMP: calculated yield of DMP (**18**); DMAF: calculated yield of DMAF (**19**); Start. mat.: % of remaining stilbene **17**.

We also investigated the oxidative coupling in varying mixtures of CH_2Cl_2 and MeOH (Figure 4). The resulting observations are summarized as follows: The yield of **18** decreases rapidly as the methanol proportion in the solvent mixture increases from 0 to 10% (v/v) unlike **19**, which is unaffected. For a methanol concentration in the solvent of 25% (v/v) and above, virtually no reaction

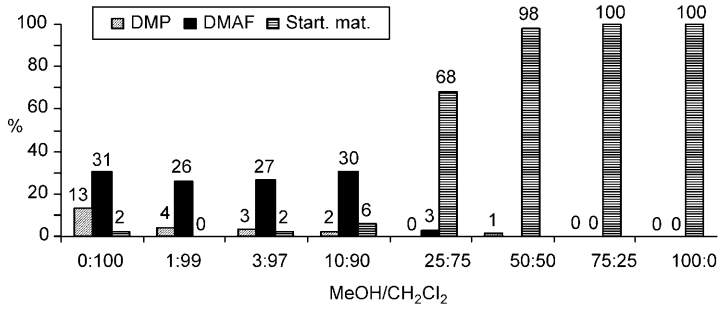


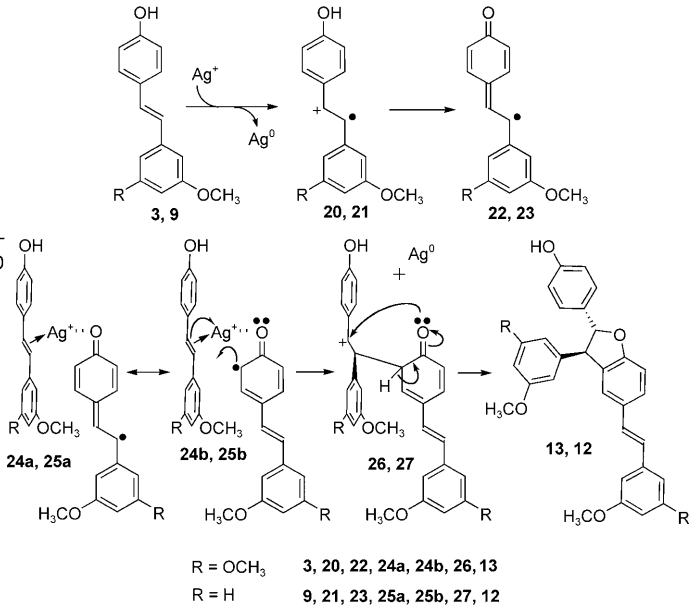
Figure 4. Effect of mixtures of methanol/dichloromethane on the dimerization of stilbene **17**. DMP: calculated yield of DMP (**18**); DMAF: calculated yield of DMAF (**19**); Start. mat.: % of remaining stilbene **17**.

product is obtained and most of the starting material is recovered unchanged. For a methanol concentration between 1 and 10% (v/v), we observed the formation of additional products with retention times identical to those of the compounds obtained from the reaction in chloroform (approximately 16 and 17 minutes). To summarize, when dichloromethane is mixed with small portions of methanol (3 to 10% v/v), the reaction proceeds in a similar way to that observed when the reaction carried out in chloroform (Figure 2a). Small quantities of methanol can be considered as modifying the dichloromethane properties so as to make them similar to those of chloroform.

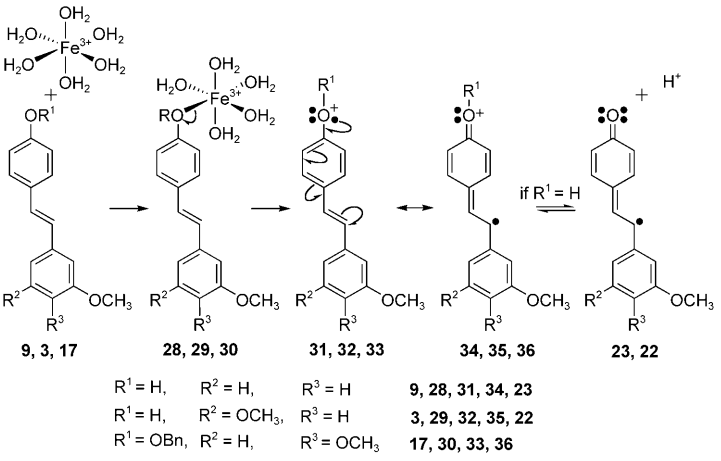
Mechanistic discussion: The above-mentioned results can be explained in terms of reagent hardness/softness, solvent, and substituent effects. All three parameters would affect the electronic distribution over the stilbenes and thus the π stacking[33] and relative orientation of the reacting species.

Silver acetate is a soft Lewis acid with back-bonding to olefin bonds (soft acid/soft base interactions).[34] As a result, it tends to form complexes with the olefinic bridges of stilbenes. Silver is also known to form complexes with the oxygen atom of carbonyl groups.[35] Oxidation of a 12-hydroxystilbene leads to a radical cation **20**/**21** that, after loss of a proton from the hydroxyl group, gives rise to stable quinone methide radical **22**/**23** (Scheme 4). The oxygen atom of the carbonyl then interacts with a silver ion coordinated to the olefinic bond of a native stilbene (species **24a**/**25a**). From resonance form **24b**/**25b**, a cascade of electron movements leads to **13**/**12**. The observed regioselectivity of this reaction arises from the fact that stable quinone methide species cannot be obtained from the 3- or 3,5-oxygenated ring. The lower yields observed for this reaction when a mixture of CH_2Cl_2/MeOH is used as the solvent instead of only CH_2Cl_2 is probably due to competing solvation of the silver ion by MeOH.

In contrast to the above, Fe^{3+} is a hard Lewis acid, and so are the oxygen atoms of the phenolic groups.[36] Therefore, when in presence of one another, these species preferably interact. However, for the oxygen atom of the hydroxyl to coordinate with Fe^{3+} from $FeCl_3{\cdot}6H_2O$, one molecule of water should be displaced from its coordination. Then oxidation can take place, leading eventually to quinone methide **23**/**22** (Scheme 5). This oxidized species will then react with a native stilbene.

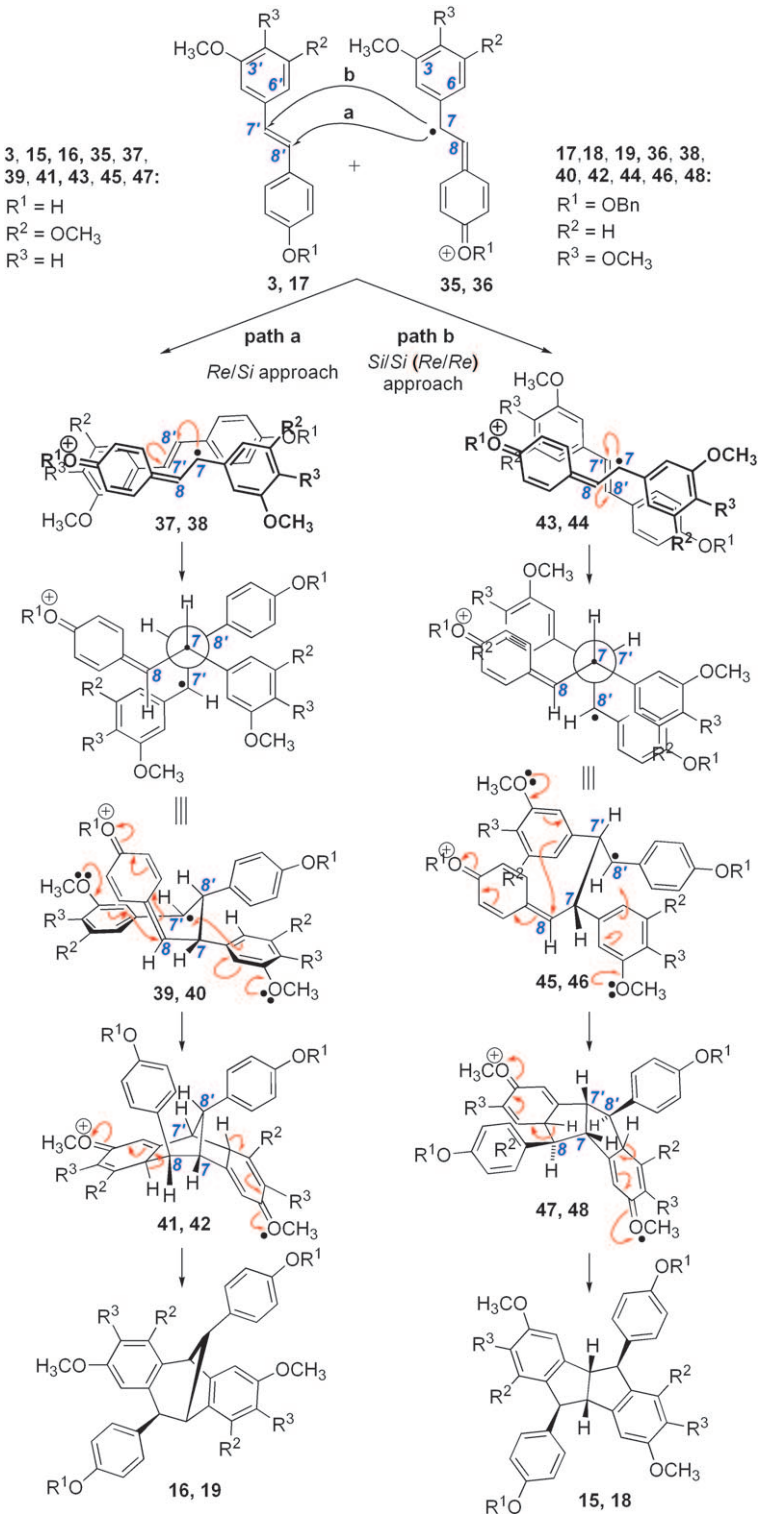


Scheme 4. Oxidation of **3** and **9** and alignment of the reacting species leading to **13** and **12**.



Scheme 5. Oxidation of **9**, **3**, and **17** by $FeCl_3{\cdot}6H_2O$.

The driving force that holds the quinone methide radical and the native stilbene together is believed to be π stacking.[37] The nearly symmetrical nature of stilbenes leads to two types of alignments, head-to-head and head-to-tail. When this reaction is carried out in CH_2Cl_2 by using **3** or **17** as the substrate, head-to-tail stacking seems to be the preferred arrangement (Scheme 6). Additionally, both species can approach each other either from opposite faces (*Re*/*Si* interactions) or from the same face (*Re*/*Re* or *Si*/*Si* interactions) leading to different reaction products. When the approach is *Re*/*Si*, the stacking is such that the lone electron of

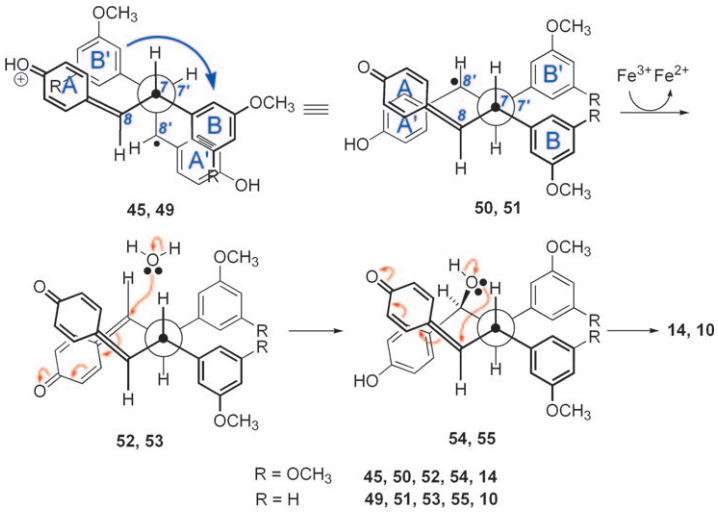


Scheme 6. *Re*/*Si* and *Re*/*Re* (or *Si*/*Si*) approaches of reacting species leading to ampelopsin F and pallidol analogues, respectively, in a one-pot reaction.

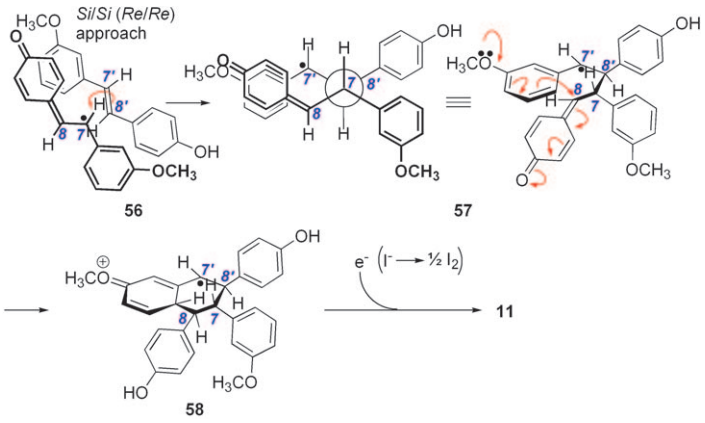
the quinone methide radicals **35**/**36** located on C7 attacks the C8′ atom of the native stilbene (path a). Yet, when the approach is *Re*/*Re* or *Si*/*Si*, then the lone electron on C7 of **35**/**36** is in a better position to attack the C7′ atom of **3**/**17** (path b). After the establishment of the bond between C7 and C8′ (**39**/**40**) or C7 and C7′ (**45**/**46**), two additional bonds are created by nucleophilic attack of the electron-rich C6 and C6′ atoms onto C8 and C7′ or C8 and C8′, respectively, to generate the fused ring systems. Standard rearomatization leads to ampelopsin F analogue **16**/**19** or to pallidol analogue **15**/**18**. As a result, whether **16**/**19** or **15**/**18** is produced depends solely on which faces the two species approach each other.

The addition of limited amounts of MeOH to CH_2Cl_2 as the solvent mixture (or the use of VOF_3 as the oxidizing agent) has some significant impact on the reaction outcome as analogues of tricuspidatol A are obtained (Scheme 7). The first bond to be established between the two stilbene units is a C7−C7′ bond. As discussed previously, the quinone methide radical stilbene **34**/**35** approaches the native stilbene **3**/**9** in a head-to-tail *Re*/*Re* or *Si*/*Si* manner leading to intermediate **45**/**49**. In this species, both C7 and C7′ are now sp^3 hybridized, and the stilbene moieties are no longer plane and parallel. The distances between the aromatic rings initially engaged in π stacking have increased. The rotation of one moiety around the C7−C7′ axis allows the rings B of both moieties to regain some closeness and re-establish π stacking while the cavity between the two rings A and A′ allows a molecule of water to enter and act as a nucleophile. Water originates from the $FeCl_3{\cdot}6H_2O$ complex after being displaced by MeOH or from the reduction of VOF_3 when this reagent is used.

The formation of the tetralin[38] derivative **11** from stilbene **9** can be easily explained by a slight variation of the mechanism of formation of **15** and **16** from **3** (Scheme 8). The first bond to be established is the C7−C8′ bond, with the quinone methide radical ap-



Scheme 7. Mechanism of the formation of tricuspidatol A analogues **14** and **10**.



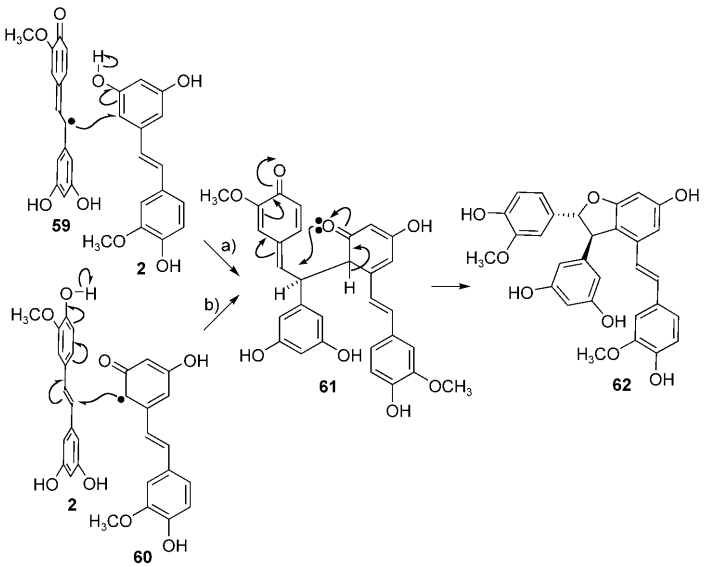
Scheme 8. Mechanism of the formation of tetralin **11**.

proaching the native stilbene **9** in a head-to-tail *Re*/*Re* or *Si*/*Si* manner. This alignment **56** is different from **43**/**44** as the substituent pattern is different and leads to the positioning of the dipoles at slightly different locations. As a result, the C7−C8′ bond can form easily leading to intermediate **57**. A ring-closure mechanism similar to the one above leads to intermediate **58** followed by the formation of **11**. Compound **11** differs from **16** just by removal of the C7−C6′ bond and the stereochemistry at C8′.

Disconnection of this bond from compound **16** leads to a triaryltetralin with a *trans*,*cis* configuration, whereas **11** is of *trans*,*trans* configuration, thus confirming a different relative orientation of the stilbene units stacked prior to the formation of **11**.

The cyclodimerization of 2,6-dimethoxy-4-methyl-stilbene by using boron tribromide in dichloromethane by Li and Ferreira[39] also produces a similar all-*trans* triaryltetralin derivative. This possibly means that the stilbene units in both cases adopted a similar alignment during the π-stacking step. These authors advocate a mechanism slightly different from the one proposed here, suggesting a BBr_3-induced protonation of one stilbene unit, reaction of this cation with a native species, and then cyclization followed by the loss of a proton. We believe that Lewis acids would rather generate stilbene radical cations (converted into radicals if a quinone methide formation is possible). This approach is supported by the significant increase in yield when NaI is added to the reaction mixture (from 10 to 37%). I^- is a reducer that is able to facilitate the final reduction step.

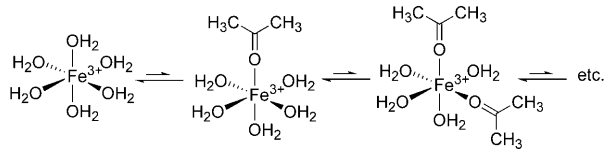
The principles mentioned above can be applied to explain the previous observations made independently by Sako,[12] Lin,[13,40,41] and Niwa.[5] Sako subjected resveratrol (**1**) to a number of soft acids, that is, AgOac, Ag_2O, Ag_2CO_3, $AgNO_3$, $Mn(OAc)_3$, CuOAc, $Cu(OAc)_2$, and $K_3[Fe(CN)_6]$.[12,42] δ-Viniferin (**4**) was very consistently obtained, although in varying yields. This result is fully consistent with the mechanism proposed above for soft acid reagents. Lin applied $FeCl_3{\cdot}6H_2O$ in water/acetone (3:2, v/v) to isorhapontigenin (**2**) and obtained the corresponding analogues of δ- and ε-viniferin as the major reaction products.[13b] As discussed above, $FeCl_3{\cdot}6H_2O$ is a hard acid and oxidizes hydroxystilbenes through their hydroxy groups. In the case of resveratrol (**1**) or isorhapontigenin (**2**), oxidation may occur at any of the three hydroxyls. Yet, it should take place preferably at the 12OH as the resulting radical would be better stabilized over an extended conjugated system through the formation of a quinone methide radical **59** (Scheme 9). Another important factor to consider in this reaction is the fact that the solvent, here a mixture of water and acetone, like other oxygenated solvents, solvates the starting material. Solvated stilbenes cannot arrange through π stacking the same way they do in dichloromethane. The preferred alignment, for steric reasons, should be perpendicular (T-shape) with the resorcinol moiety of the native stilbene coming at right angles to the ethylene radical bridge of



Scheme 9. Mechanism of the formation of bisisorhapontigenin A (**62**) from isorhapontigenin (**2**).

the oxidized species, as can be easily seen with simple Dreiding models. This perpendicular alignment is responsible for the stereoselectivity of the reaction. The intermediate species **61** will undergo a ring closure by nucleophilic attack on C8 from the oxygen atom of the carbonyl leading to bisisorhapontigenin A (**62**). The presence of δ-viniferin analogues shegansu B and bisisorhapontigenin B can be understood if the presence of acetone in that reaction mixture is taken into account.

Acetone is considered as a soft solvent.[43] Fe^{3+} will exchange partially its water ligands for acetone (Scheme 10). The resulting complex softens and induces reactions leading



Scheme 10. Acetone/water exchange in Fe^{3+} complex.

towards δ-viniferin skeletons. This effect is further supported by one of Niwa's observations that resveratrol (**1**), when treated at RT with anhydrous $FeCl_3$ with acetone as the only solvent, yields δ-viniferin (**4**) as the major product (97% DT) with only very small amounts of ε-viniferin **5** and pallidol **7** (0.9 and 1.5% DT, respectively).[5] On the other hand, when a hard solvent like methanol is used to convert resveratrol (**1**) (e.g., by Lin[40]), only ε-viniferin (**5**) is obtained.

Let us now apply the principles enunciated above to the dimerization of compound **17**. We should first notice the structural differences between **17** and the other stilbenes mentioned above. Compound **17** lacks the free hydroxyl at position 12 (replaced by a benzyloxy group) and possesses two methoxyls in an *ortho* relationship as opposed to *meta* substitution for the other compounds (except **4**). One can expect the alignment due to π stacking to be somewhat different. Indeed, when we compare the respective yields for ampelopsin F and pallidol analogues from the dimerization of **3** and **17** by $FeCl_3$ in CH_2Cl_2, we observe an inversion of the ratio of these reaction products: 10 and 7%, respectively, from **3**, as opposed to 9 and 16%, respectively, from **17** (isolated yields). Since these skeletons are believed to be the result of π stacking of stilbenes approaching each other from different faces, this reflects the relative stability of the different stacks in relation to the substitution pattern of the starting materials. For example, the aggregates **43** obtained from the stacking of stilbene **3** and its radical derivatives **35** approaching one another from the same faces (*Si*/*Si* or *Re*/*Re* alignment) are more stable than the stacks **37** obtained when these species approach one another from opposite faces (*Re*/*Si* alignment). As a result, pallidol analogue **15** is obtained in higher yields than ampelopsin F analogue **16**. However, when stilbene **17** is used this ratio is inverted. The solvent effects on the dimerization of **17** by $FeCl_3$, which seem to be inconsistent with the results obtained from similar reactions on hydroxylated stilbenes, could be interpreted by considering the properties of both the solvent and the stilbene. When high polarity solvents (water, alcohols, DMF) are used for the dimerization of highly lipophilic stilbene **17**, the reaction is inhibited mainly due to the poor solubility of the starting material. When these solvents are used for polyhydroxylated (and hence soluble) stilbenes, such as **1** and **2**, the ε-viniferin skeleton should be obtained provided a free OH is available at position 3 or 5. When **17** is reacted in other solvents, several factors must be considered, namely, the polarity of the solvent, the possible solvation of the oxygenated groups, and the availability of the oxygen source in the medium. The most intriguing effect is the large difference between the chromatographic profile obtained for reactions conducted in dichloromethane and chloroform. The fact that dimerization of **17** by $FeCl_3$ in chloroform yields very small amounts of DMP and DMAF can possibly be explained by the fact that chloroform is somewhat more polar than dichloromethane and that analytical grade chloroform, which was used without prior purification, contains small amounts of ethanol. The formation of DMP and DMAF might be inhibited by competing reactions in which solvation of the oxygenated groups plays a significant role.

Conclusion

When considering all the above results together with those accumulated by other groups, one can make the following observations. The dimerization of stilbenes by means of one-electron oxidants leads to low yields of dimeric products. Either the starting material is mostly recovered unmodified or is converted into large amounts of highly polymerized insoluble material. This does not seem so appealing to the organic chemist. Yet this biomimetic approach has the merit of shortness. Future challenges include improving the predictability power of the mechanistic rationalization provided above through molecular modeling of the π stacking of reactive species and finding ways to suppress indiscriminate polymerization of the starting material. In this respect, a detailed investigation of the effect of concentration, pH, and temperature, notably with help of microwaves could provide some answers. We shall take up these challenges and report our findings in due course.

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