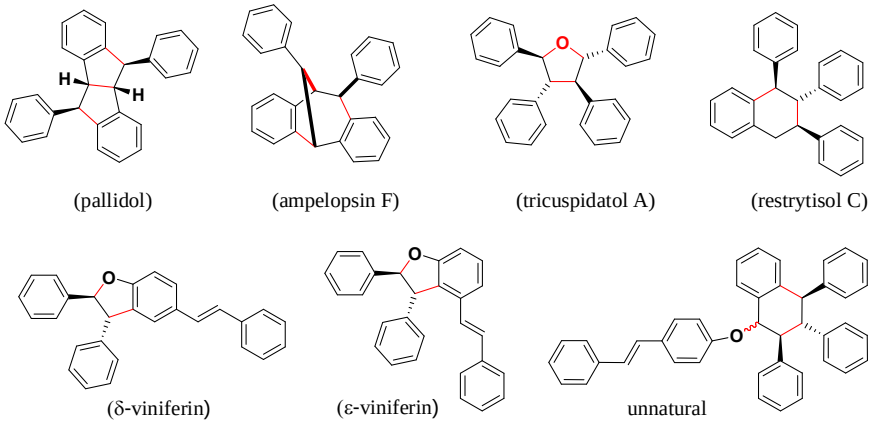
CHAPTER 6. CONCLUSION

Tandem one-pot reaction procedures have been developed to prepare regio- and stereoselectively by chemical oxidation ten oligostilbenoids with five natural skeletons, namely of pallidol, ampelopsin F, tricuspidatol A, restrytisol C (tetralin and trimer) and viniferin (δ- and ε-viniferin) types. Three different types of interstilbene linkages were constructed, C-C, C-O and C-O-C bonds leading to skeletons with fused 5-, 6- and 7-membered rings as well as benzofuran and furan rings.



(pallidol) (ampelopsin F) (tricuspidatol A) (restrytisol C)

(δ-viniferin) (ε-viniferin) unnatural

This undertaking is the continuation of work carried out previously by various groups on oligostilbenoids syntheses. Elegantly designed non biomimetic syntheses allowed preparing various oligostilbenoids in a targeted manner but through a relatively long route. On the other hand, short one-pot biomimetic reactions using enzymatic coupling, chemical oxidation or acid catalysis led to a number of oligostilbenoids in an unpredictable manner. The authors have opted to rationalize their observations through the standard phenolic oxidative coupling *via* the generation of quinone methide radical intermediates. This rationalization was found insufficient

to understand the selectivity of the reactions and the apparent discrepancies between all these results.

As mentioned in introduction, our initial intention was to synthesize a complex molecule, namely hopeaphenol. To materialize this intention, we undertook to analyze all observations from previous researchers. A series of additional experiments were designed and carried out in the quest for a common trend. As a result, two key hypotheses able to unify all the different mechanistic issues are proposed. These are a) the influence of the hardness or softness of the oxidant/solvent in stilbene oligomerisation, this hypothesis considers the interactions between the metal oxidant (in combination with the solvent) and the stilbene through the application of Pearsonôs principle of Hard and Soft Acid Base (HSAB principle). Accordingly, solvent-metal oxidant combinations can be categorized into hard, soft and borderline acids and interact either with oxygenated substituent (hard base) or with olefinic bond (soft base). It is remarkable to observe that all these soft reagents produce stilbene dimers with the δ-viniferin skeleton when resveratrol is employed, while the hard reagents generate various skeletons like Ů-viniferin, pallidol, ampelopsin F, restrytisol C and tricuspidatol A types involving mainly C7-C7 or C7-C8 bond formations and b) intermolecular self-assembly of stilbenes through non-covalent interactions (π–π interactions and hydrogen bonding) prior to its coupling, which then would determine the type of skeleton produced. On the one hand, stilbenes can be aligned in a parallel displaced manner with *Re*/*Re* or *Re*/*Si* approach. The first approach lead to compounds like pallidol, ampelopsin F, restrytisol C and tricuspidatol A types, while the later approach form the ampelopsin F skeleton. On the other hand, when stilbenes are aligned in a T-shape manner, δ-viniferin or ε-viniferin type will result. The alignments of stilbenes are basically modulated by the electronic distribution over stilbenes and

factors contributing to this modulation are the solvent, substitution pattern and metal oxidant coordination.

The proposed hypotheses were consistent with the preliminary results obtained from calculations, which support the occurrence of hydrogen bonding, π-π interactions and metal coordination between stilbenes in the system. The understanding of this supramolecular chemistry involved in stilbene oxidative coupling should enable chemists now to achieve the preparation of complex oligostilbenoid structures like hopeaphenol in a targeted manner through a one-pot biomimetic approach. This could be achieved by considering a template-directed synthesis. Biomimetically patterned syntheses of oligostilbenoids should provide some better understandings on their biosynthetic pathways. Additionally, they would provide short access to series of derivatives and analogues for drug development purpose.