

Full Paper

## Asymmetric Biomimetic Oxidations of Phenols: The Mechanism of the Diastereo- and Enantioselective Synthesis of Thomasidioic Acid

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**Abstract:** Enantiopure chiral amidic derivatives of sinapic acid were oxidised with hydrogen peroxide using horseradish peroxidase (HRP) as the catalyst to give the aryltetraline dilignol thomasidioic acid. *Trans*-diastereoselectivity and enantioselectivity in the formation of thomasidioic acid was observed. Computational methods show that the enantioselectivity is controlled by the  $\beta$ - $\beta$  oxidative coupling step, while the diastereoselectivity is controlled by the stability of the reactive conformation of the intermediate quinomethide.

**Keywords:** Diastereoselection, enantioselection, lignans, horseradish peroxidase, oxidative phenol coupling, conformational analysis, semiempiric calculations

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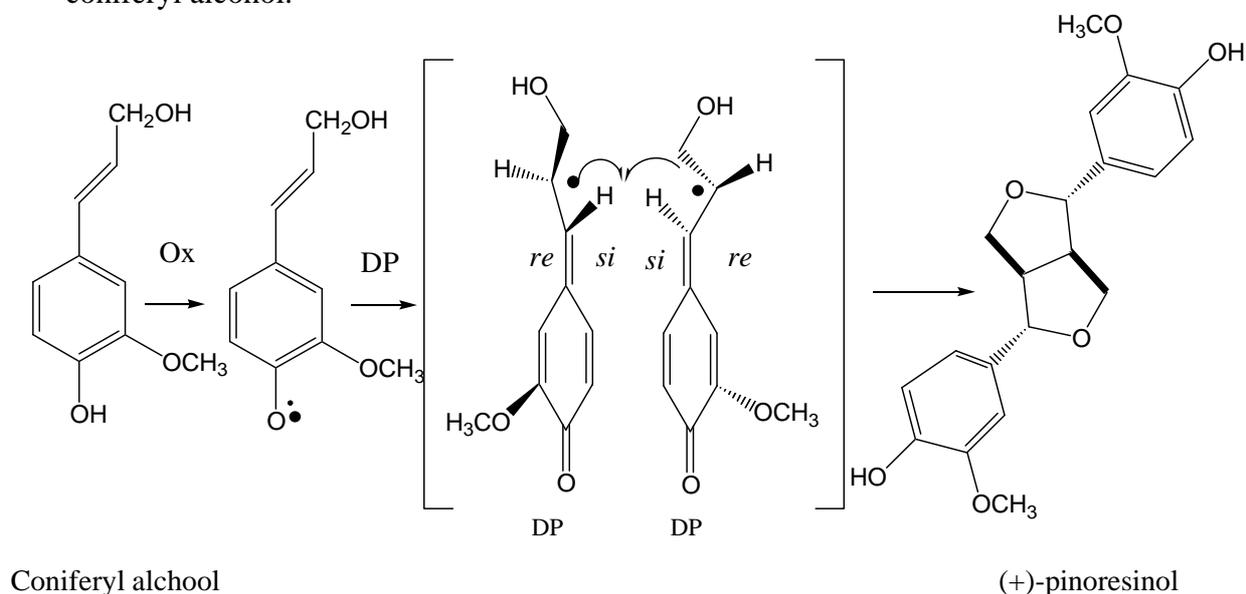
### Introduction

Organic compounds obtained from radical coupling of phenylpropenoidic phenols have an important biological role. In fact, they constitute organic polymers such as lignin [1], lignans [2], suberin [3] and algal cell walls [4].

The lignans represent a structurally very diverse class of vascular plant products. They are typically dimers and their primary physiological role in plants is in plant defense [5]. Some lignans have found application in medicine, such as podophyllotoxin in venereal wart treatment [6], or its semisynthetic derivatives etoposide, and teniposide in cancer therapies [7]. Stereoselective total syntheses of lignans can involve multistep procedures [8]. In particular Charlton's group has synthesized important podophyllotoxin analogs with applications in medicine. [9].

A bimolecular phenoxy radical coupling could be an alternative way to perform stereoselective syntheses of lignans, but, unlike most biological oxidations, the bimolecular phenoxy radical coupling reaction is not under a strictly regio- and stereospecific control [10]. This is due to the fact that phenoxy radicals are very persistent and the dimerization reaction is slow. Hence the stereogenic carbons formed in the oxidative phenol coupling reaction *in vitro* are racemic [11]. Sarkanen has studied the radical phenol coupling since 1973 and he has demonstrated that the  $\beta$ - $\beta$  coupling of phenols such as (*E*)-isoeugenol is remarkably stereospecific and produces exclusively *threo*-compounds, whereas the (*Z*)-isoeugenol gives *threo*- and *erythro*-coupling products in equal amounts. He has proposed that the differences in the probabilities of coupling modes in the oxidations of (*E*) and (*Z*)-isoeugenol must be considered to be due to the characteristics of these intermediate complexes rather than to the differences in spin densities [12]. A similar enzymatic oxidative coupling of ferulic acid derivatives was observed by us for the diastereoselective synthesis of benzo[*b*]phenylcoumarans [13].

**Scheme 1.** The formation of (+) pinoresinol by directing protein mediated coupling of coniferyl alcohol.



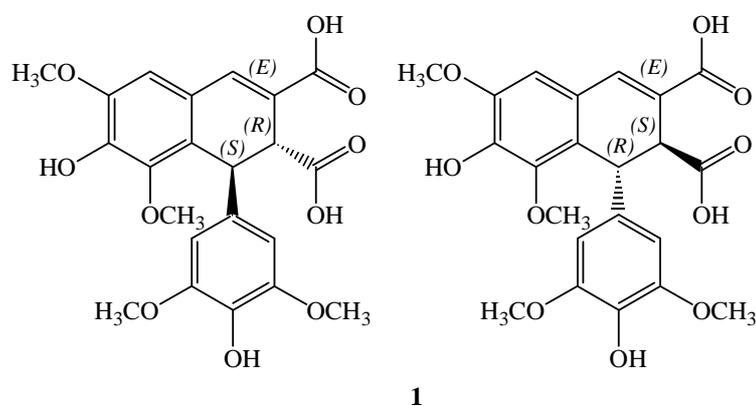
DP = directing protein

Recently Lewis has proposed a new biosynthetic pathway to enantiopure lignans. A protein isolated from *Forsythia* species is suggested to be responsible for the formation of enantiomeric pure pinoresinol from coniferyl alcohol [14]. In this case, the protein acts as a chiral inducer. The mechanism of stereoselective coupling of coniferyl phenoxy radical mediated by a directing protein

proposed by Lewis is shown in Scheme 1 [15]. The role of the directing protein is supposed to be at the level of  $\beta$ - $\beta$  coupling of phenols. Stereocontrol in enzymatic oxidative coupling of ferulic acid derivatives to enantioselectively give benzo[b]phenylcoumarans [16] has been recently shown to be possible in the oxidative phenol coupling reaction [17] using a chiral inducer and the horseradish peroxidase (HRP)-catalyzed oxidative coupling in presence of hydrogen peroxide as the oxidant. The chiral inducers were aminoacid ethyl esters, camphorsultam and aryloxazolidinones [18].

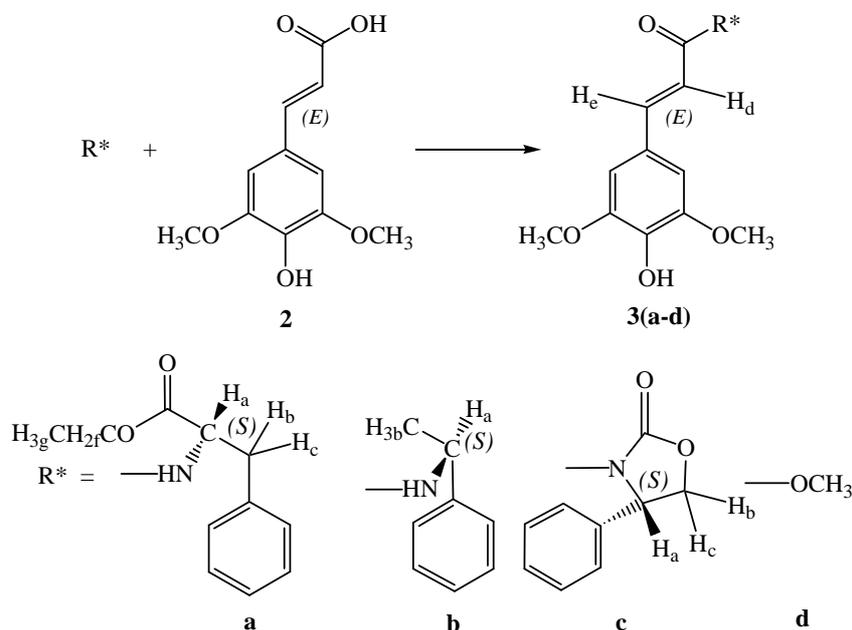
On these bases we focused our attention to thomasidioic acid (**1**, Figure 1). This lignan in the *trans* configuration was isolated for the first time from *Ulmus thomasi* in 1969 and shown to be cytotoxic [19]. Recently this acid has been shown to prevent the peroxynitrite-mediated protein nitration [20].

**Figure 1.**



Several synthetic methods have been developed to prepare racemic *trans* thomasidioic acid: Stobbe condensation of 3,4,5-trimethoxybenzaldehyde with dimethylsuccinate [21]; alkaline treatment of sinapic acid **2** [22], oxidative coupling of sinapic acid **2** [23] or of sinapic acid methyl ester **3d** [24] with ferric chloride in aqueous acetone (Scheme 2). Higher yields were obtained using hydrogen peroxide as the oxidant and horseradish peroxidase as the catalyst [25].

**Scheme 2.** Synthesis of amides from sinapic acid.

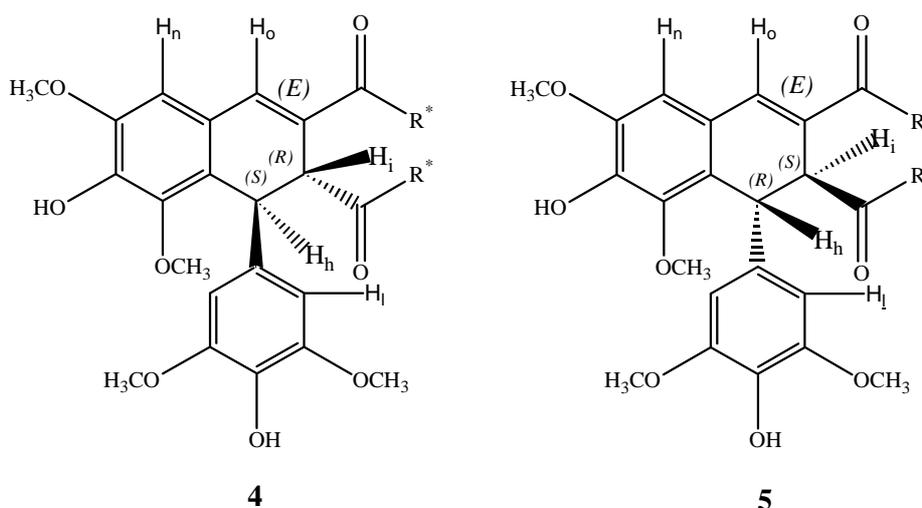


These reactions are important in food processing because sinapic acid **2** is a major constituent of canola oil [26]. This finding stimulated the question whether thomasidioic acid **1** is really a natural product. Charlton has demonstrated that *trans* thomasidioic acid can be formed also by air oxidation of sinapic acid at pH 13. On this basis and on the basis that “natural” *trans* thomasidioic acid is optically inactive, he suggested that this acid is not a real natural product of plant metabolism, but it is generated during the extraction procedure from basic aqueous extracts of *Ulmus thomasii* [27]. Chiral induction was obtained in a preliminary study showing that Me (*R*)-mandetyl sinapate could be dimerized diastereoselectively to give a 1,2-*trans* thomasidioate diester [28].

## Results and Discussion

Here we report an enantioselective biomimetic approach to synthesize thomasidioic acid (**1**). In order to achieve this result we performed a preliminary oxidation of methyl-(*E*)-sinapate **3d** catalyzed by horseradish peroxidase (HRP, EC 1.11.1.7), using hydrogen peroxide as the reactant. The best results of oxidative coupling were obtained in a dioxane 30%-buffer pH 4, 70% solution.

**Figure 2.**



The yield of racemic mixture of *trans*-thomasidioic acid dimethylesters **4d**, **5d** was 70%. In agreement with literature data it was no amounts of *cis*-thomasidioic acid dimethylester were observed. The enantioselective oxidative phenol coupling of sinapic acid derivatives **3(a-c)** having an amide bond with (*S*)-phenylalanine ethyl ester, (*S*)-methylbenzylamine, (*S*)-2-phenyloxazolidinone as chiral auxiliaries was performed using the same oxidation system. These sinapamides with the chiral auxiliaries were obtained in high yields in a one pot reaction from sinapic acid **2** (Scheme 2). The mixture of the two *trans* diastereoisomers **4**, **5** (Figure 2) was obtained with the diastereoisomeric excesses reported in Table 1.

**Table 1.** The enantioselective oxidative phenol coupling with chiral sinapamides.

Chiral auxiliary R*	Yields in 4 + 5 (%)	Yield in peak 1 (%)	Yield in peak 2 (%)	Diastereoisomeric excess (%)
( <i>S</i> )-phenylalanine ethyl ester	60	45	15	50
( <i>S</i> )-methylbenzylamine	50	35	15	40
( <i>S</i> )-2-phenyloxazolidinone	40	34	6	70

The diastereoisomeric excess was evaluated by RP-HPLC analysis of the crude reaction mixture. Separation by preparative RP-HPLC allowed to obtain the individual diastereoisomers which were characterized by <sup>1</sup>H-NMR.

The hydrolysis of the individual *trans*-thomasidioic acid amides **4** and **5** (Scheme 2) was performed with LiOOH in tetrahydrofuran (Table 2).

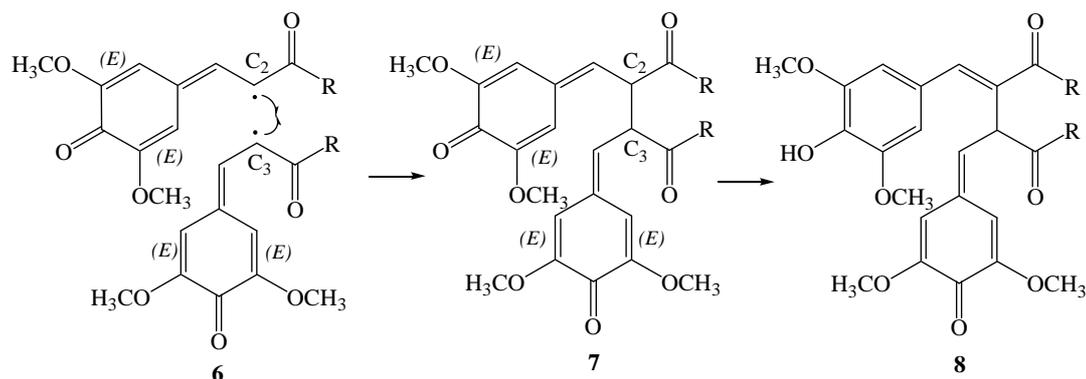
**Table 2.** The hydrolysis of thomasidioic acid derivatives.

Chiral auxiliary R*	Reactant	Solvent	Time (hours)	Yield of 1 (%)
( <i>S</i> )-Phenylalanine ethyl ester	LiOOH	THF	5	20
( <i>S</i> )-Methylbenzylamine	LiOOH	THF	4	10
( <i>S</i> )-2-Phenyloxazolidinone	LiOOH	THF	5	60

In order to account for the origin of the observed enantioselection and diastereoselection in the formation of thomasidioic acid derivatives **4**, **5**, the reaction mechanism has been investigated in detail by quantum-mechanical methods. As shown in Table 1 the chiral auxiliaries (*S*)-2-phenyloxazolidinone gave considerably higher selectivities (e.e. 70 %) compared to the (*S*)-phenylalanine ethyl ester and (*S*)-methylbenzylamine. Therefore, the compounds having (*S*)-2-phenyloxazolidinone as the chiral auxiliary were chosen for the theoretical study.

The proposed reaction pathway involves two steps; the first step is the β-β oxidative coupling of two quinomethide radicals **6** to give the bisquinomethide **7**, and the second step is the ring closure of **7** to give the final product (see Scheme 3). For this mechanism the absolute configuration of thomasidioic acid should be determined by the absolute configuration of the two stereogenic centers of the bisquinomethide **7** formed in the β-β oxidative coupling, and by the *trans* or *cis* ring closure of the bisquinomethide **7**.

The relative orientation of the two quinomethide radicals **6** in the β-β oxidative coupling determines the configuration of the stereogenic centres in **7**. In fact, coupling at the *re-re* and *si-si* face lead to the formation of *R,R*- and *S,S*-bisquinomethide **7**, while coupling at the *re-si* face results in the corresponding *R,S/S,R* mesoform. In this context, the preferred absolute configuration of **7** should be controlled by the different stabilities of the pre-reactive van der Waals complexes of dimers of **6**, and the corresponding transition states along the reaction path to give the bisquinomethide **7**.

**Scheme 3.** Radical coupling to form bisquinone methide **7** followed by aromatisation of one ring.

It should be noted that the computational study of the  $\beta$ - $\beta$  oxidative coupling is complicated by the diradical nature of the molecular system along the reaction path, which can only be modelled accurately by using the Configuration Interaction approach (CI). For this reason the semiempirical CI-PM3 level of theory has been adopted to investigate the  $\beta$ - $\beta$  oxidative coupling of quinomethide radicals **6**. Due to the large size of the molecular system only the frontier orbitals were included in the active space for the CI vector.

Initially, a conformational analysis of the quinomethide radical **6** has been performed in order to find the most stable conformations involved in the  $\beta$ - $\beta$  coupling. In this analysis two energy minimum conformers has been characterized, one in which the amide bond is *trans* (**6a**) and the other one in which the amide bond is *cis* (**6b**). The former is more stable than the latter by about 2 kcal·mol<sup>-1</sup>. Therefore, the conformer **6a** with *trans* amide bond was chosen for the study of the  $\beta$ - $\beta$  oxidative coupling.

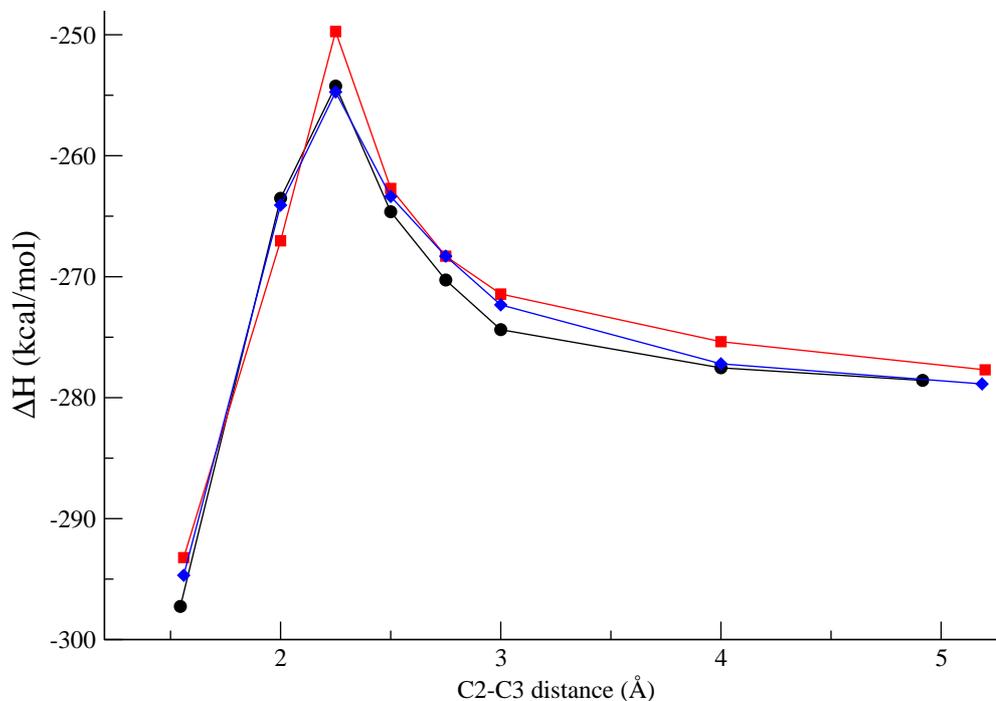
Figure 3 shows the computed profile along the reaction pathway for the  $\beta$ - $\beta$  coupling at the *re-re*, *si-si*, and *re-si* faces. In Figure 4 the molecular geometries of the pre-reactive van der Waals complexes and the corresponding bisquinomethide products in the first conformation after the formation of the C-C in the radical coupling are also shown. It is interesting to note that the energy barrier calculated for the *si-si* coupling is higher by more than 4 kcal·mol<sup>-1</sup> than that calculated for the *re-re* and *re-si* coupling. This result suggests that the formation of the *R,R* (from *re-re* coupling), and *R,S/S,R* (from *re-si* coupling) bisquinomethide **7** is preferred with respect to the formation of the *S,S* (from *si-si* coupling) bisquinomethide **7**.

Sarkanen *et al.* suggested that the excess of the *threo*  $\beta$ - $\beta$  coupling products over the *erithreo* ones, observed for some quinomethide derivatives such as syringylresinol and 2-propenylphenol [12] is due to the different stability of the *re-re*, *si-si* and *re-si* pre-reactive complexes. However, as shown in Figure 1, the pre-reactive complexes calculated in this work are almost isoenergetic, suggesting that for the bisquinomethide **7** the stereochemistry is not controlled by the formation of this pre-reactive complex.

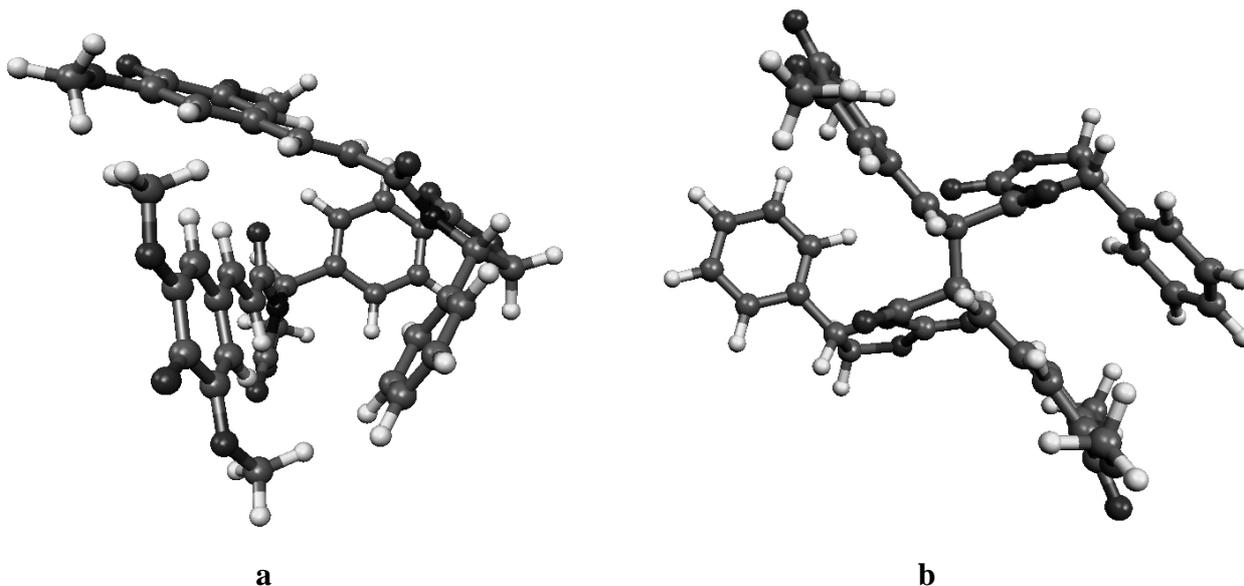
As discussed above, the second step of the reaction mechanism is the ring closure of the bisquinomethide **7** (see Scheme 2). The cyclization step determines the observed diastereoselection to the *trans* isomer. The diastereoselection should be controlled by the relative orientation of the two

quinomethide rings which should feature a preferred conformation in order to give the “correct” ring closure, as well as to the energy of the transition state along the reaction path to give the final product.

**Figure 3.** Reaction profile of the  $\beta$ - $\beta$  oxidative coupling of two quinomethide radicals **6** at the *re-re* (●-●), *si-si* (■-■), and *re-si* (◆-◆) faces.



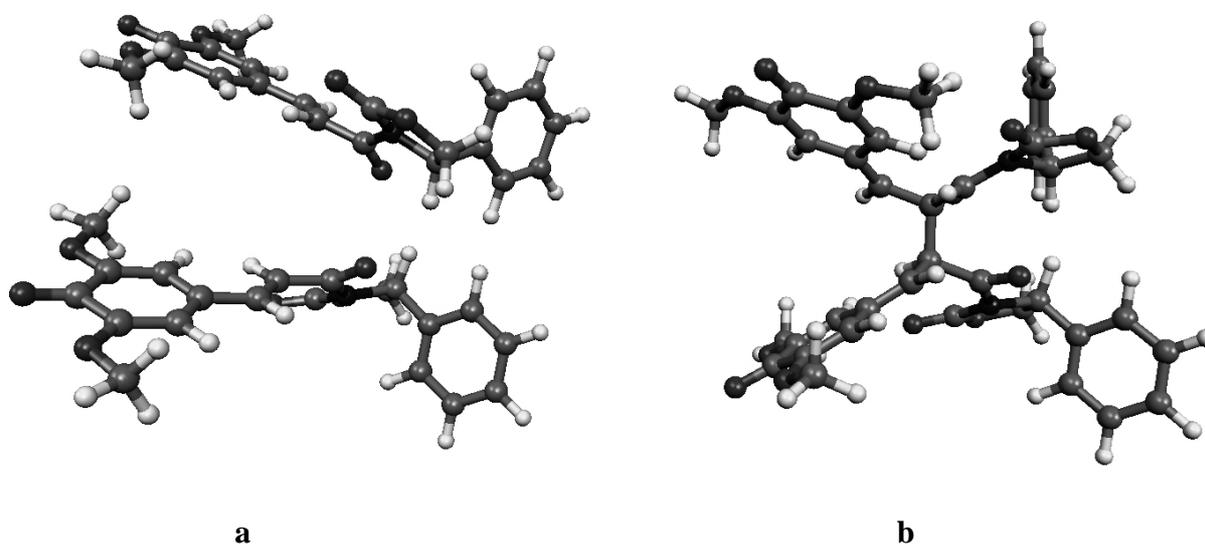
**Figure 4a.** Molecular geometry of the van der Waals pre-reactive complex with the monomers at the *re-re* face (a), and the corresponding bisquinomethide product (b).



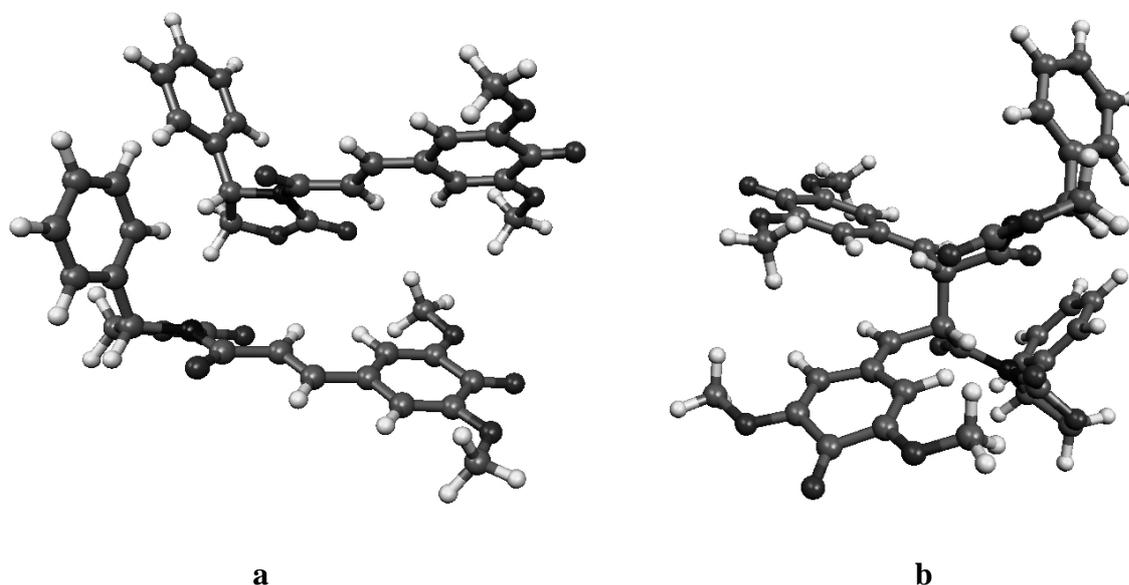
It should be noted that the cyclization should occur after the aromatization of one of the rings of bisquinomethide **7** with loss of one stereogenic center (Scheme 3, compound **8**). However, the carbon backbone of the intermediate **8** is much more rigid than in bisquinomethide **7**, possibly preventing

rearrangements to conformations with the rings in a different orientation. On the basis of this observation, the diastereoselection to the *trans* isomer should be controlled by the relative orientation of the two quinomethide rings in the most stable conformations of bisquinomethide **7**. The same assumption has been used by us to show that the observed *trans*-diastereoselectivity in the cyclization of ferulic acid derivatives to dihydrobenzo[*b*]furans [29] derives from thermodynamic control in the formation of diastereoisomeric quinomethide intermediates. These considerations prompted us to carry out a theoretical investigation of the potential energy surface (PES) of the quinomethide intermediate in the *R,R* enantiomer and *R,S* mesoforms.

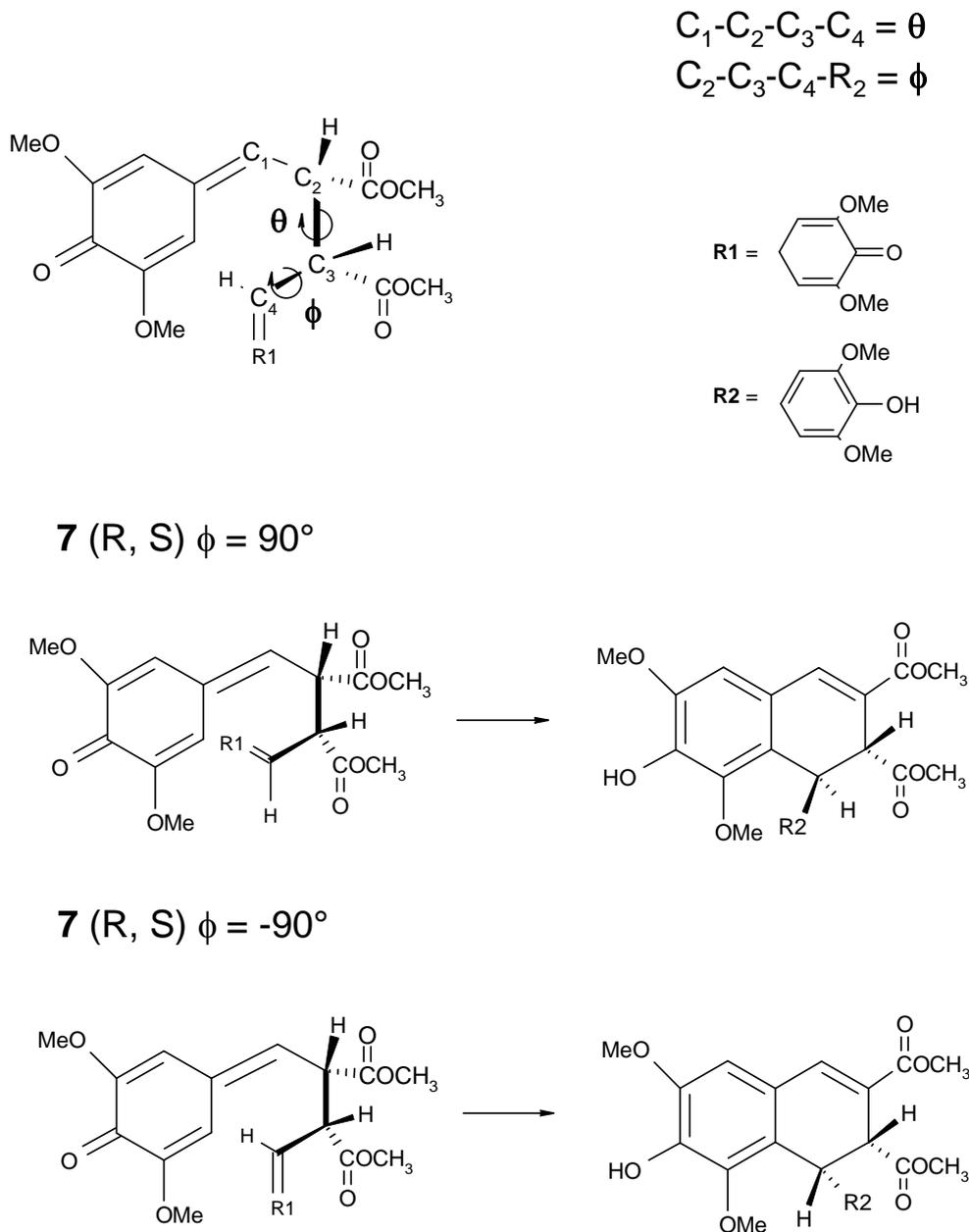
**Figure 4b.** Molecular geometry of the van der Waals pre-reactive complex with the monomers at the *si-si* face (a), and the corresponding bisquinomethide product (b).



**Figure 4c.** Molecular geometry of the van der Waals pre-reactive complex with the monomers at the *re-si* face (a), and the corresponding bisquinomethide product (b).



**Scheme 4.** Schematic representation of the  $\theta$  and  $\phi$  dihedral angles (on the top). For the mesoform  $2R,3S$  positive values of the  $\phi$  angle should lead to the formation of *trans*-thomasidioic acid **1**, while negative values the  $\phi$  angle should lead to the formation of *cis* isomer (on the bottom).



Because of the large number of degrees of freedom in the bisquinomethide **7** with the two chiral auxiliaries, we preliminarily performed an analysis of the PES for the bisquinomethide in which the chiral auxiliaries are replaced by  $-OCH_3$  groups **7d**, and for which, diastereoselection to the *trans* isomer is also observed. The PES of the quinomethide **7d** has been calculated as a function of the  $\phi$  and  $\theta$  dihedral angles as shown in Scheme 4.

An inspection of the molecular structure of the quinomethide **7** shows that for the  $R,S$  mesoform, conformations with *positive* dihedral angle  $\phi$  are expected to lead to the formation of thomasidioic acid **1** in the *trans* configuration, while conformations with *negative* dihedral angle  $\phi$  should lead to the

formation of compound **1** in the *cis* configuration. The contrary holds true for the *R,R* enantiomer, in which *negative* and *positive* values of the dihedral angle  $\phi$  lead to the formation of *trans*- and *cis*-compound **1**, respectively (see Table 3).

In addition, the two carbon atoms involved in the ring closure approach to each other for values of the  $\theta$  angle around  $0^\circ$ , while they are at the maximum distance for a value of  $\theta$  angle equal to about  $180^\circ$ . The PES computed at the semiempirical PM3 level of theory for the quinomethide **7** *R,S* mesoform and *R,R* enantiomer are shown in Figures 5a and 5b, respectively. In Table 3 the values of the heat of formation corresponding to the local minima identified on the PES are reported.

**Table 3.** Energy minima on the PES of the quinomethides **7** calculated as a function of the  $\theta$  and  $\phi$  dihedral angles (see Scheme 3) at the semiempirical PM3 level of theory.

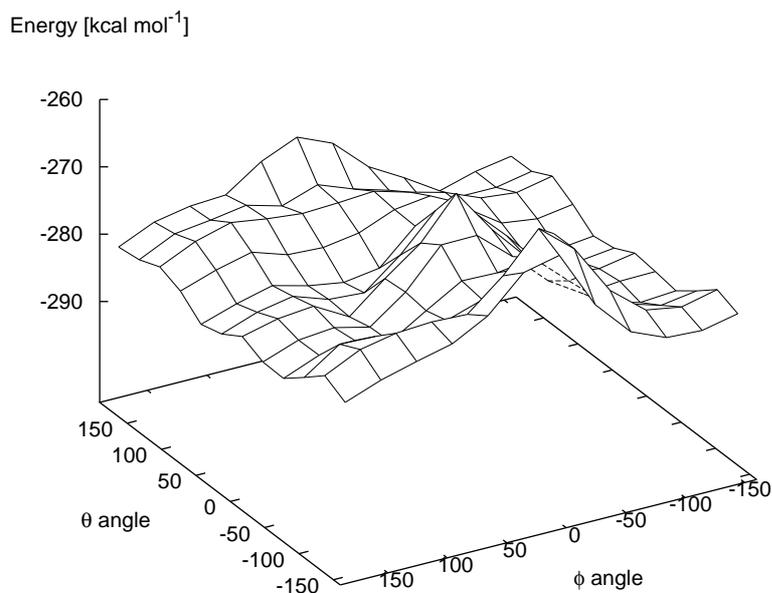
Quinomethide <b>7</b>	$\theta$ (Degrees)	$\phi$ (Degrees)	Heat of formation (kcal·mol <sup>-1</sup> )	Thomasidic acid ( <b>1</b> ) (predicted)
<i>R,S</i>	180	120	-286.6	1 <i>R</i> ,2 <i>S</i> /1 <i>S</i> ,2 <i>R</i> <i>trans</i>
<i>R,S</i>	60	120	-284.8	1 <i>R</i> ,2 <i>S</i> /1 <i>S</i> ,2 <i>R</i> <i>trans</i>
<i>R,S</i>	-60	120	-284.3	1 <i>R</i> ,2 <i>S</i> /1 <i>S</i> ,2 <i>R</i> <i>trans</i>
<i>R,S</i>	180	-60	-286.1	1 <i>R</i> ,2 <i>R</i> /1 <i>S</i> ,2 <i>S</i> <i>cis</i>
<i>R,S</i>	60	-90	-279.9	1 <i>R</i> ,2 <i>R</i> /1 <i>S</i> ,2 <i>S</i> <i>cis</i>
<i>R,S</i>	-60	-90	-279.4	1 <i>R</i> ,2 <i>R</i> /1 <i>S</i> ,2 <i>S</i> <i>cis</i>
<i>R,R</i>	180	-90	-285.3	1 <i>R</i> ,2 <i>S</i> <i>trans</i>
<i>R,R</i>	60	-120	-286.0	1 <i>R</i> ,2 <i>R</i> <i>trans</i>
<i>R,R</i>	-60	-120	-284.6	1 <i>R</i> ,2 <i>S</i> <i>trans</i>
<i>R,R</i>	60	30	-282.1	1 <i>R</i> ,2 <i>R</i> <i>cis</i>

In the case of the *R,S* mesoform a total of six local minima have been located on the PES; three, with positive values, and three with negative values of  $\phi$ . Two almost isoenergetic minima are characterized by a value of  $\theta$  of about  $180^\circ$  and values of  $\phi$  of about  $120^\circ$  ( $-286.5$  kcal·mol<sup>-1</sup>) and  $-60^\circ$  ( $-286.1$  kcal·mol<sup>-1</sup>). However, as noted above, in these conformations the two carbon atoms involved in the ring closure are at their maximum distance. The other local minima are located along the reaction coordinate corresponding to the rotation of the  $\theta$  angle from  $180^\circ$  to  $0^\circ$ , for which the two carbon atoms are close to each other. It is interesting to note that the two minima characterized by a positive value of  $\phi$  ( $\theta = 60^\circ$ ,  $\phi = 120^\circ$   $\Delta H = -284.8$ ;  $\theta = -60^\circ$ ,  $\phi = 120^\circ$   $\Delta H = -284.3$ ) are lower in energy by about 5 kcal·mol<sup>-1</sup> with respect to those characterized by negative values of  $\phi$  ( $\theta = 60^\circ$ ,  $\phi = -90^\circ$   $\Delta H = -279.9$ ;  $\theta = -60^\circ$ ,  $\phi = -90^\circ$   $\Delta H = -279.4$ ). This clearly indicates that the most stable conformation in the region of the PES where the two carbon atoms are close enough to give rise ring closure predicts for the formation of *trans*-(1*S*,2*R*, or 1*R*,2*S*) thomasidic acid **1**.

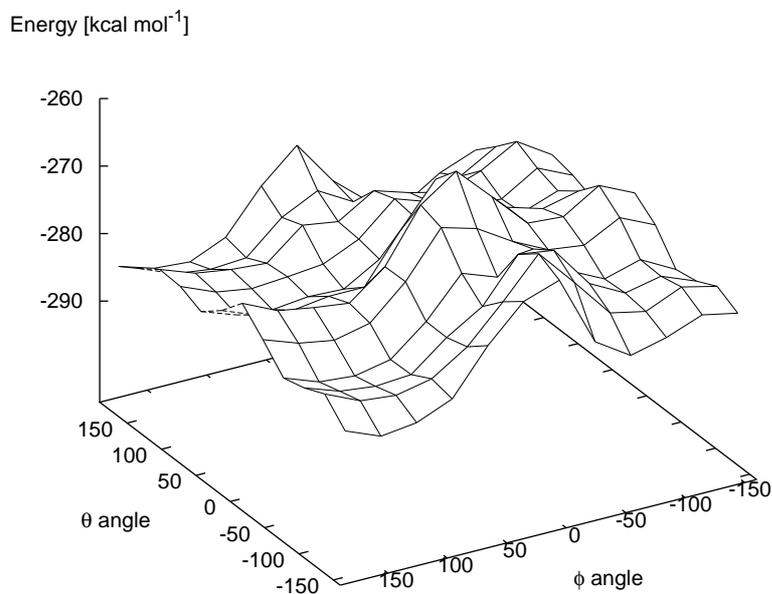
In the case of the *R,R* enantiomer only four local minima have been located on the PES; three with negative values, and one with a positive value of  $\phi$ . The lowest energy minimum is characterized by a value of  $\theta$  of about  $60^\circ$  and a value of  $\phi$  of about  $-120^\circ$  ( $-286.0$  kcal·mol<sup>-1</sup>). This minimum is located along the reaction coordinate which leads to the ring closure with the formation of *trans*-thomasidic acid **1**.

acid **1**. The only local energy minimum which should lead to the formation of *cis*-thomasidioic acid (**1**) ( $\theta = 60^\circ$ ,  $\phi = 30^\circ$ ,  $\Delta H = -282.1$ ) is about 4 kcal·mol<sup>-1</sup> higher in energy. Again, the most stable conformation in the region of the PES where the two carbon atoms are close enough to give rise to ring closure predicts for the formation of *trans*-(*1S,2R*, or *1R,2S*) thomasidioic acid (**1**).

**Figure 5.** Potential energy surface as a function of the  $\theta$  and  $\phi$  angles of quinomethide **7** with the *R,R* (a) and *R,S* (b) absolute configurations.



(a)



(b)

The same conformational analysis is then performed in order to predict the enantioselectivity in the formation of *trans*-thomasidioic acid **1** from quinomethides having a (*S*)-2-phenyloxazolidinone chiral

auxiliary group. Table 1 shows the enantioselectivity obtained experimentally. Three diastereoisomers are possible for this intermediate; a) *R,R*, *SS*; b) *S,S*, *SS*; c) *S,R*, *SS/R,S*, *SS* (mesoform). As for the case of the compound free of auxiliary groups, the conformational analysis was performed at the PM3 level by rotating the  $\theta$  and  $\phi$  angles (see Scheme 3). Conformations corresponding to energy minima on the PES was then fully optimized. For the three isomers the energies of the most stable conformations, and the corresponding  $\theta$  and  $\phi$  angles are reported in Table 4.

The relative stabilities of the different conformations allows to predict the amount of each quinomethide **7** isomer at the equilibrium. In this respect, we note that all energy minimum conformations calculated for the *2S,3S*, *SS* isomer are significantly less stable than that calculated for the *R,R*, *SS* and *R,S*, *SS* isomers (see Table 4). The low stability observed for the *S,S*, *SS* isomer is due to a larger steric hindrance between the two phenyl groups in the chiral auxiliary group. On the other hand, the energies of the *R,R*, *SS* and *R,S*, *SS* isomers are very similar, both for the conformation with the  $\theta$  angle near to  $180^\circ$  (in which the two carbon atoms involved in the ring closure are at the maximum distance), and for the conformation with the  $\theta$  angle near to  $0^\circ$  (in which the two carbon atoms involved in the ring closure are at the minimum distance). As discussed for the compounds free of auxiliary groups, in the case of the *R,R*, *SS* isomer conformations with *positive* dihedral angle  $\phi$  are expected to lead to the formation of thomasidioic acid **1** in the *cis* configuration, while conformations with *negative* dihedral angle  $\phi$  should lead to the formation of compound **1** in the *trans* configuration (see Table 4).

**Table 4.** Energy minima on the PES of the quinomethides **7** calculated as a function of the  $\theta$  and  $\phi$  dihedral angles (see Scheme 3) at the semiempirical PM3 level of theory.

Quinomethide <b>7</b>	R*	$\theta$ (Degrees)	$\phi$ (Degrees)	Heat of formation (kcal·mol <sup>-1</sup> )	Thomasidioic acid ( <b>1</b> ) (predicted)
		67	-117	-294.6	1 <i>S</i> , 2 <i>R</i> <i>trans</i>
<i>R,R</i> (isomer 1)	( <i>S</i> )-2- phenyloxazolidinone	50	66	-290.1	1 <i>R</i> , 2 <i>R</i> <i>cis</i>
		180	91	-286.4	---
		-175	-95	-295.5	---
		47	73	-294.1	1 <i>R</i> , 2 <i>S</i> / 1 <i>S</i> , 2 <i>R</i> <i>trans</i>
<i>R,S/S,R</i> (mesoform)	( <i>S</i> )-2- phenyloxazolidinone	-61	-88	-287.6	1 <i>R</i> , 2 <i>S</i> / 1 <i>S</i> , 2 <i>R</i> <i>cis</i>
		-84	-113	-293.2	---
		-178	94	-288.2	---
		-80	-118	-291.5	1 <i>R</i> , 2 <i>S</i> <i>trans</i>
<i>S,S</i> (isomer 2)	( <i>S</i> )-2- phenyloxazolidinone	-59	128	-286.3	1 <i>S</i> , 2 <i>S</i> <i>cis</i>
		161	117	-281.9	---
		172	-94	-276.2	---

Notably, the conformation with a negative value of  $\phi$  is about 4 kcal·mol<sup>-1</sup> more stable than that with a positive value of  $\phi$ , indicating that the ring closure to give the *trans* 1*S*,2*R* absolute configuration thomasidioic acid **1** should be preferred to the ring closure to the *cis* 1*R*,2*R* absolute configuration. In the case of the *R,S* mesoform, the ring closure to give the *trans* configuration is still significantly preferred with respect to that which give the *cis* configuration. However, in this case the reaction of the two non equivalent prochiral carbon atoms present at the quinomethide double bonds with the two ortho carbons of the phenyl ring can give both the *trans* 1*S*,2*R* and, *trans* 1*R*,2*S* absolute configurations.

In Table 5 are also reported the stabilities of conformers of the aromatic intermediate **8** for two different values of the  $\phi$  angle (see Scheme 3). The conformations have been obtained by the geometry optimization of stable conformers of bisquinomethide **7** in which the two rings approach to each other. As discussed above, the conformational analysis of **8** is simpler than that of **7**, due to the loss of one stereogenic centre and to the rigidity of the carbon backbone. For both the *R, SS* and *S, SS* isomers the two conformers are characterized by a negative and positive value of  $\phi$ , respectively. Interestingly the trend discussed above for the bisquinomethide **7** is fully confirmed. In fact, for the *R, SS* isomer, the conformer with a negative  $\phi$  angle is more than 10 kcal·mol<sup>-1</sup> stable than the conformer with a positive  $\phi$  angle, while the opposite is true in the case of the *S, SS* isomer. The ring closure starting from the most stable conformations of the *R, SS* and *S, SS* isomers leads in both cases to the thomasidioic acid **1** in the *trans* configuration, with the 1*S*, 2*R* and 1*R*, 2*S* absolute configuration, respectively.

**Table 5.** Heat of formation of conformers of the aromatic intermediate **8**, obtained for two different values of  $\phi$  angle (see Scheme 3), and of the corresponding Thomasidioic acid amide obtained after the ring closure computed at the semiempirical PM3 level of theory.

Aromatic intermediate <b>8</b>	$\phi$ (Degrees)	Heat of formation (kcal·mol <sup>-1</sup> )		Thomasidioic acid amide	Heat of formation (kcal·mol <sup>-1</sup> )
<i>R</i>	-121	-300.2	→	1 <i>S</i> , 2 <i>R</i> <i>trans</i>	-326.6
<i>R</i>	16	-287.3	→	1 <i>R</i> , 2 <i>R</i> <i>cis</i>	-321.2
<i>S</i>	130	-299.3	→	1 <i>R</i> , 2 <i>S</i> <i>trans</i>	-320.8
<i>S</i>	-106	-291.3	→	1 <i>S</i> , 2 <i>S</i> <i>cis</i>	-329.4

The results reported above, show that the diastereoselection to the *trans* thomasidioic acid **1** begin at the level of bisquinomethide **7** where the conformers that leads to the ‘correct’ ring closure are more stable with respect to the conformers that leads to the *cis* isomer. The difference in stability is even larger after the aromatization of **7** to give the intermediate **8**. Finally, it should be noted that *trans*-thomasidioic acid amides **4**, **5** are more stable than the corresponding *cis* isomers by about 5 kcal·mol<sup>-1</sup> (see Table 5). If the assumption is made that the energy of activation for the ring closure of **8** is correlated to the stability of the products, we can predict that the energy barrier of the cyclization to the *trans* thomasidioic acid is also lower than the energy barrier to the *cis* isomer. The larger stabilities of **7** and **8** conformers which can give ring closure to the *trans* isomer, and the lower energies of the corresponding transition states along the cyclization pathway clearly explain the total diastereoselectivity to the *trans* thomasidioic acid **1**.

## Conclusions

In summary, our computational investigation of the  $\beta$ - $\beta$  oxidative coupling of quinomethide radical **6** shows that the *R,R*, *S,S* and *R,S*, *S,S* isomers of bisquinomethide **7** should be formed in larger amounts with respect to the *S,S*, *S,S* isomer. The former, after aromatization preserves only one *R* centre that gives ring closure to the *trans* 1*S*,2*R* absolute configuration, while the latter after aromatization can preserve both an *R* or *S* centre, giving ring closure to both the *trans* 1*S*,2*R*, and 1*R*,2*S* absolute configurations. Hence, the still unknown configuration of thomasidioic acid (**1**) from the enantioselective synthesis here reported is predicted to be 1*S*,2*R*. Work is in progress towards the determination of the crystal structure of the synthetic material.

## Acknowledgments

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## Experimental

### General

All chemicals were from Sigma-Aldrich. IR spectra were recorded with a FT-IR Jasco spectrophotometer in KBr pellets. Mass spectra were determined by the direct injection system mode with positive electron impact using a VG 7070 EQ instrument.  $^1\text{H-NMR}$  spectra were recorded at 300 MHz with a Bruker AMX 300 instrument (in  $\text{CDCl}_3$  solutions). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. HPLC analyses were performed using a Waters 600 E instrument equipped with a HP 1040 Diode Array Detector and a column Agilent XDB-C18 (5  $\mu\text{m}$ , 4.6 x 250 mm) was used. Water-acetonitrile (1:1) was used as a mobile phase. The total flow was 1 mL/min and the injection volume was 20  $\mu\text{L}$ .

### Preparation of compound **3a**

To a solution of (*S*)-phenylalanine ethyl ester hydrochloride (1.00 g, 4.35 mmol) in anhydrous tetrahydrofuran (100 mL), triethylamine (0.6 mL, 4.35 mmol) were added dropwise. After solubilisation of the salt, sinapic acid **2** (0.97 g, 4.35 mmol) and dicyclohexylcarbodiimide (DCC, 0.90 g, 4.35 mmol) were added under stirring and the mixture was stirred for further 4 h at room temperature. A few drops of acetic acid were then added, the urea was filtered off and the resulting solution was evaporated under reduced pressure to give a residue which was dissolved in ethyl acetate (50 mL), washed with water saturated with NaCl (60 mL) and dried over  $\text{Na}_2\text{SO}_4$ . The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography (eluent ethyl acetate-petroleum ether 7:3). Compound **3a** was obtained in 50% yield. Anal. calc. for  $\text{C}_{22}\text{H}_{25}\text{NO}_6$  (399.44): C 66.15%, H 6.31%, N 3.51%, O 24.03%; found: C 66.17%, H 6.29%, N 3.49%; MS: 399.4 ( $\text{M}^+$ );  $^1\text{H-NMR}$ :  $\delta_{\text{H}}$  1.12 (3 H, t,  $J=8.0$ ,  $\text{H}_{\text{g}}$ ), 2.95 (1 H, dd,  $J=15.0-8.0$ ,  $\text{H}_{\text{b}}$ ), 3.20 (1 H, dd,

$J=15.0-4.0$ ,  $H_c$ ), 3.60 (2 H, q,  $J=8.0$ ,  $H_f$ ), 3.75 (6 H, s,  $OCH_3$ ), 4.55 (1 H, ddd,  $J=12.0-8.0-4.0$ ,  $H_a$ ), 5.62 (1 H, s, O-H), 5.78 (1 H, d,  $J=12.0$  N-H) 6.55 (1 H, d,  $J=15.0$ ,  $H_e$ ), 7.20 (2 H, s, Ar-H), 7.30 (1 H, d,  $J=15.0$ ,  $H_d$ ), 7.35-7.50 (5 H, m, Ar-H); FT-IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3347 (N-H), 3161 (O-H), 1661 (C=O), 1603 (C=C), 1109 (O-CH<sub>3</sub>).

#### Preparation of compound 3b

To a solution of sinapic acid (**2**, 1.00 g, 4.46 mmol) in anhydrous dichloromethane (100 mL), *N*-methylmorpholine (0.50 mL, 4.46 mmol) and isobutylchloroformate (0.80 mL, 4.46 mmol) were added. The mixture was stirred at 0° C for 1 h, then *N*-methylmorpholine (0.50 mL) and (*S*)-methylbenzylamine (0.60 mL) were added. The mixture was stirred at room temperature for 2 h. The resulting solution was washed with a pH 4 solution of aqueous HCl (60 mL), with a 10% aqueous NaHCO<sub>3</sub> solution (60 mL), with saturated brine (60 mL) and finally dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography, (eluent ethyl acetate and petroleum ether 7:3). The yield was 40% to give **3b**. Anal. calc. for C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub> (327.34): C 69.71%, H 6.47%, N 4.28%, O 19.55%; found: C 69.65%, H 6.50%, N 4.31%; MS: 327.3 (M<sup>+</sup>); <sup>1</sup>H-NMR:  $\delta_H$  1.50 (3 H, d,  $J=6.8$ ,  $H_b$ ), 3.75 (6 H, s,  $OCH_3$ ), 5.20 (1 H, m,  $J=6.8-12.0$ ,  $H_a$ ), 5.62 (1 H, s, O-H), 5.78 (1 H, d,  $J=12.0$ , N-H), 6.55 (1 H, d,  $J=15.5$ ,  $H_e$ ), 6.80 (2 H, s, Ar-H), 7.30 (1 H, d,  $J=15.5$ ,  $H_d$ ), 7.20-7.40 (5 H, m, Ar-H); FT-IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3345 (N-H), 3155 (O-H), 1665 (C=O), 1602 (C=C), 1111 (O-CH<sub>3</sub>).

#### Preparation of compound 3c

Sinapic acid **2** (1 g, 4.46 mmol), 2-chloro-1-methylpyridine iodide (0.52 g, 4.46 mmol) and (*S*)-2-phenyloxazolidinone (0.35 g, 4.46 mmol) was dissolved in 20 ml of dry CH<sub>2</sub>Cl<sub>2</sub> under nitrogen atmosphere. A solution of triethylamine (0.7 mL, 5.6 mmol), dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (4 mL) was added dropwise for 15 min. The mixture was stirred at room temperature for 120 hours, then a saturated aqueous NaCl solution (20 mL) was added. The organic phase was separated, then washed with a pH 4 solution of aqueous HCl (20 mL), with a 10% aqueous NaHCO<sub>3</sub> solution (20 mL), with water saturated with NaCl (20 mL) and finally dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography, (eluent CH<sub>2</sub>Cl<sub>2</sub>-acetone 7:3). Compound **3c** was obtained in 40% yield. Anal. calc. for C<sub>20</sub>H<sub>19</sub>NO<sub>6</sub> (369.37): C 65.03%, H 5.18%, N 3.79%, O 25.99%; found: C 65.10%, H 5.15%, N 3.80%; MS: 369.4 (M<sup>+</sup>); <sup>1</sup>H-NMR:  $\delta_H$  3.75 (6 H, s,  $OCH_3$ ), 4.20 (1 H, dd,  $J=9.0-9.0$ ,  $H_a$ ), 4.73 (1 H, dd,  $J=9.0-9.0$   $H_b$ ), 4.97 (1 H, dd,  $J=9.0-9.0$ ,  $H_c$ ), 5.62 (1 H, s, O-H), 6.55 (1 H, d,  $J=15.0$ ,  $H_e$ ), 7.20 (2 H, s, Ar-H), 7.30 (1 H, d,  $J=15.0$ ,  $H_d$ ), 7.20-7.40 (5 H, m, Ar-H); FT-IR (KBr,  $\nu_{max}$ ,  $cm^{-1}$ ): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>).

#### Horseradish Peroxidase (HRP)-catalyzed oxidative phenol coupling methyl synapate 3d

A solution of **3d** (1.0 mmol) in dioxane (14 mL) and 0.02 M phosphate/citric acid buffer pH 3.5 (4.0 mL) was added of a 0.86 M aqueous hydrogen peroxide solution (0.60 mL, 0.5 mmol) and

aqueous HRP (0.93 mL, 837 U) at 0 °C in small portions over 15 minutes. The mixture was then stirred at 0 °C. After 4 hours a saturated aqueous NaCl solution (20 mL) was added. The organic phase was then evaporated under reduced pressure and the resulting solution was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with 10% aqueous NaHCO<sub>3</sub> (25 mL), then with water saturated with NaCl (25 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was chromatographed on a silica gel flash column with hexane-ethyl acetate (gradient mode, from 4:1 to 1:1) yielding a racemic mixture of *trans* thomasidioic methyl ester (**4-5d**), yield = 70%. Racemic mixture of **4-5d** had: m.p. 203 °C; <sup>1</sup>H-NMR: δ<sub>H</sub> 3.69 (6 H, s, OCH<sub>3</sub>), 3.70 (3 H, s, OCH<sub>3</sub>), 3.75 (6 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 3.99 (1 H, s, H<sub>i</sub>), 4.99 (1 H, s, H<sub>h</sub>), 5.00 (1 H, s, OH), 5.40 (1 H, s, OH), 6.21 (2 H, s, H<sub>l</sub>), 6.58 (1 H, s, H<sub>n</sub>), 7.60 (1 H, s, H<sub>o</sub>); MS: 474 (M<sup>+</sup>); FT-IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3300 (O-H), 1730 (C=O), 1700 (C=O), 1110 (O-CH<sub>3</sub>)

### *Horseradish Peroxidase (HRP)-catalyzed oxidative phenol coupling with compounds 3(a-c)*

A solution of **3(a-c)** (1.0 mmol) in dioxane (14 mL) and 0.02 M phosphate/citric acid buffer pH 3.5 (4.0 mL) was added of a 0.86 M aqueous hydrogen peroxide solution (0.60 mL, 0.5 mmol) and aqueous HRP (0.93 mL, 837 U) at 0 °C in small portions over 15 minutes. The mixture was then stirred at 0 °C. After 4 hours a saturated aqueous NaCl solution (20 mL) was added. The organic phase was then evaporated under reduced pressure, and the resulting solution was extracted with ethyl acetate (4 x 20 mL). The combined organic extracts were washed with 10% aqueous NaHCO<sub>3</sub> (25 mL), then with water saturated with NaCl (25 mL), and dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure, and the residue was purified with preparative RP-HPLC to obtain the individual diastereoisomers, named peak1 and peak 2 in eluative order. The diastereoisomeric excess was calculated by HPLC (Table 1). Compounds **4a**, **5a** had: **Peak 1**: Anal. calc. for C<sub>44</sub>H<sub>48</sub>N<sub>2</sub>O<sub>12</sub> (796.86): C 66.32%, H 6.07%, N 3.52%, O 24.09%; found: C 66.30%, H 6.05%, N 3.55%; MS: 796.9 (M<sup>+</sup>); FT-IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> = -160.27°; <sup>1</sup>H-NMR: δ<sub>H</sub> 1.12 (3 H, t, J=8.0, H<sub>g</sub>), 1.30 (3 H, t, J=8.0, H<sub>g</sub>), 3.08 (2 H, d-d, J=6.0-15.0, H<sub>b</sub>), 3.15 (2 H, d-d, J=8.0-15.0 H<sub>c</sub>), 3.69 (3 H, s, OCH<sub>3</sub>), 3.70 (1 H, s, H<sub>i</sub>), 3.75 (6 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 4.05 (2 H, q, J=8.0, H<sub>f</sub>), 4.20 (2 H, q, J=8.0, H<sub>f</sub>), 4.69 (1 H, d-d, J=6.0-8.0, H<sub>a</sub>), 4.87 (1 H, d-d, J=6.0-8.0, H<sub>a</sub>), 4.99 (1 H, s, H<sub>h</sub>), 5.00 (1 H, s, OH), 5.40 (1 H, s, OH), 6.21 (2 H, s, H<sub>l</sub>), 6.58 (1 H, s, H<sub>n</sub>), 6.75 (1 H, d, J=8.0 Hz, N-H), 7.00-7.20 (10 H, m, Ar-H), 7.60 (1 H, d, J=8.0 Hz, N-H), H<sub>o</sub> is in the aromatic zone. **Peak 2**: Anal. calc. for C<sub>44</sub>H<sub>48</sub>N<sub>2</sub>O<sub>12</sub> (796.86): C 66.32%, H 6.07%, N 3.52%, O 24.09%; found: C 66.30%, H 6.05%, N 3.55%; MS: 796.9 (M<sup>+</sup>); FT-IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> = +127.88°; <sup>1</sup>H-NMR: δ<sub>H</sub> 1.15 (3 H, t, J=8.0, H<sub>g</sub>), 1.20 (3 H, t, J=8.0, H<sub>g</sub>), 3.08 (2 H, d-d, J=6.0-15.0, H<sub>b</sub>), 3.15 (2 H, d-d, J=8.0-15.0 H<sub>c</sub>), 3.69 (3 H, s, OCH<sub>3</sub>), 3.70 (1 H, s, H<sub>i</sub>), 3.75 (6 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 4.10 (2 H, q, J=8.0, H<sub>f</sub>), 4.15 (2 H, q, J=8.0, H<sub>f</sub>), 4.70 (1 H, d-d, J=6.0-8.0, H<sub>a</sub>), 4.80 (1 H, d-d, J=6.0-8.0, H<sub>a</sub>), 5.02 (1 H, s, H<sub>h</sub>), 5.00 (1 H, s, OH), 5.40 (1 H, s, OH), 6.21 (2 H, s, H<sub>l</sub>), 6.58 (1 H, s, H<sub>n</sub>), 6.75 (1 H, d, J=8.0 Hz, N-H), 7.00-7.20 (10 H, m, Ar-H), 7.60 (1 H, d, J=8.0 Hz, N-H), H<sub>o</sub> is in the aromatic zone. Compounds **4b**, **5b** had: **Peak 1**: Anal. calc. for C<sub>38</sub>H<sub>40</sub>N<sub>2</sub>O<sub>8</sub> (652.73): C 69.92%, H 6.18%, N 4.29%, O 19.61%; found: C 69.88%, H 6.21%, N 4.34%; MS: 652.7 (M<sup>+</sup>); FT-IR (KBr, ν<sub>max</sub>, cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1110 (O-CH<sub>3</sub>); [α]<sub>D</sub><sup>25</sup> = -80.21°; <sup>1</sup>H-NMR: δ<sub>H</sub>

1.15 (3 H, d,  $J=5.0$  Hz,  $H_b$ ), 1.40 (3 H, d,  $J=5.0$  Hz,  $H_b$ ), 3.45 (6 H, s, OCH<sub>3</sub>), 3.65 (1 H, s,  $H_i$ ), 3.67 (3 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 4.72 (1 H, m,  $J=5.0$  Hz,  $H_a$ ), 4.92 (1 H, s,  $H_h$ ), 5.15 (1 H, m,  $J=5.0$  Hz,  $H_a$ ), 5.30 (1 H, s, OH), 5.73 (1 H, s, OH), 6.21 (2 H, s,  $H_i$ ), 6.52 (1 H, d,  $J=8.0$  Hz, N-H), 6.58 (1 H, s,  $H_n$ ), 7.02-7.20 (10 H, m, Ar-H), 7.55 (1 H, d,  $J=8.0$  Hz, N-H),  $H_o$  is in the aromatic zone. **Peak 2:** Anal. calc. for C<sub>38</sub>H<sub>40</sub>N<sub>2</sub>O<sub>8</sub> (652.73): C 69.92%, H 6.18%, N 4.29%, O 19.61%; found: C 69.88%, H 6.21%, N 4.34%; MS: 652.7 (M<sup>+</sup>); FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>);  $[\alpha]_D^{25} = +51.63^\circ$ ; <sup>1</sup>H-NMR:  $\delta_H$  1.35 (3 H, d,  $J=5.0$  Hz,  $H_b$ ), 1.45 (3 H, d,  $J=5.0$  Hz,  $H_b$ ), 3.65 (6 H, s, OCH<sub>3</sub>), 3.72 (1 H, s,  $H_i$ ), 3.75 (3 H, s, OCH<sub>3</sub>), 3.81 (3 H, s, OCH<sub>3</sub>), 4.88 (1 H, m,  $J=5.0$  Hz,  $H_a$ ), 4.92 (1 H, s,  $H_h$ ), 5.08 (1 H, m,  $J=5.0$  Hz,  $H_a$ ), 5.30 (1 H, s, OH), 5.73 (1 H, s, OH), 6.21 (2 H, s,  $H_i$ ), 6.52 (1 H, d,  $J=8.0$  Hz, N-H), 6.58 (1 H, s,  $H_n$ ), 7.02-7.20 (10 H, m, Ar-H), 7.55 (1 H, d,  $J=8.0$  Hz, N-H),  $H_o$  is in the aromatic zone. Compounds **4c**, **5c** had: **Peak 1:** Anal. calc. for C<sub>40</sub>H<sub>36</sub>N<sub>2</sub>O<sub>12</sub> (736.72): C 65.21%, H 4.93%, N 3.80%, O 26.06%; found: C 65.25%, H 4.90%, N 3.77%; MS: 736.7 (M<sup>+</sup>); FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>); <sup>1</sup>H-NMR: 3.65 (3 H, s, OCH<sub>3</sub>), 3.69 (1 H, s,  $H_i$ ), 3.75 (6 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 4.10 (1 H, dd,  $J=9.0-9.0$ ,  $H_a$ ), 4.20 (1 H, dd,  $J=9.0-9.0$ ,  $H_a$ ), 4.61 (1 H, dd,  $J=9.0-9.0$ ,  $H_b$ ), 4.73 (1 H, dd,  $J=9.0-9.0$ ,  $H_b$ ), 4.85 (1 H, dd,  $J=9.0-9.0$ ,  $H_c$ ), 4.97 (1 H, dd,  $J=9.0-9.0$ ,  $H_c$ ), 4.99 (1 H, s,  $H_h$ ), 5.00 (1 H, s, O-H), 5.40 (1 H, s, O-H), 6.21 (2 H, s,  $H_i$ ), 6.58 (1 H, s,  $H_n$ ), 7.00-7.20 (10 H, m, Ar-H),  $H_o$  is in the aromatic zone. **Peak 2:** Anal. calc. for C<sub>40</sub>H<sub>36</sub>N<sub>2</sub>O<sub>12</sub> (736.72): C 65.21%, H 4.93%, N 3.80%, O 26.06%; found: C 65.25%, H 4.90%, N 3.77%; MS: 736.7 (M<sup>+</sup>); FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>); <sup>1</sup>H-NMR: 3.65 (3 H, s, OCH<sub>3</sub>), 3.69 (1 H, s,  $H_i$ ), 3.75 (6 H, s, OCH<sub>3</sub>), 3.90 (3 H, s, OCH<sub>3</sub>), 4.10 (1 H, dd,  $J=9.0-9.0$ ,  $H_a$ ), 4.20 (1 H, dd,  $J=9.0-9.0$ ,  $H_a$ ), 4.61 (1 H, dd,  $J=9.0-9.0$ ,  $H_b$ ), 4.73 (1 H, dd,  $J=9.0-9.0$ ,  $H_b$ ), 4.85 (1 H, dd,  $J=9.0-9.0$ ,  $H_c$ ), 4.97 (1 H, dd,  $J=9.0-9.0$ ,  $H_c$ ), 4.99 (1 H, s,  $H_h$ ), 5.00 (1 H, s, O-H), 5.40 (1 H, s, O-H), 6.21 (2 H, s,  $H_i$ ), 6.58 (1 H, s,  $H_n$ ), 7.00-7.20 (10 H, m, Ar-H),  $H_o$  is in the aromatic zone.

#### *LiOOH hydrolysis of aryltetralines*

To a solution of aryltetralin **4 peak 1** (0.171 mmol) in tetrahydrofuran (20 mL) containing 30% hydrogen peroxide (1 mL), LiOH (69 mg, 2.87 mmol) dissolved in water (3 mL) was added and the solution was stirred at room temperature for 18 h. The resulting suspension was then cooled at 0 °C and a saturated solution of sodium bisulphite was added until peroxides were completely reduced, then concentrated under reduced pressure, acidified with a HCl solution pH 5 and extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulphate, then evaporated at reduced pressure to give thomasidioic acid **1**. Anal. calc. for C<sub>22</sub>H<sub>22</sub>O<sub>10</sub> (446.40): C 59.19%, H 4.97%, O 35.84%; found: C 59.22%, H 5.00%; MS: 446.4 (M<sup>+</sup>); FT-IR (KBr,  $\nu_{\max}$ , cm<sup>-1</sup>): 3155 (O-H), 1750 (C=O), 1659 (C=O), 1605 (C=C), 1110 (O-CH<sub>3</sub>); <sup>1</sup>H-NMR:  $\delta_H$  3.65 (6 H, s, OCH<sub>3</sub>), 3.70 (3 H, s, OCH<sub>3</sub>), 3.81 (3 H, s, OCH<sub>3</sub>), 4.03 (1 H, s,  $H_i$ ), 4.95 (1 H, s,  $H_h$ ), 5.30 (1 H, s, O-H), 5.75 (1 H, s, O-H), 6.20 (2 H, s,  $H_i$ ), 6.62 (1 H, s,  $H_n$ ), 7.57 (1 H, s,  $H_o$ );  $[\alpha]_D^{25} = -90.27^\circ$

*Computational details*

All calculations have been performed at the semiempirical PM3 level [30] of theory using Gaussian 03 [31] and Mopac2000 [32] suite of programs.

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