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Asymmetric biomimetic oxidations of phenols using oxazolidines as chiral auxiliaries: the enantioselective synthesis of (+)- and (−)-dehydrodiconiferyl alcohol†

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ABSTRACT: Stereoselective bimolecular radical coupling reactions of phenylpropenoid phenols are described. Evans's 2-oxazolidinone **11a–d** derivatives of ferulic acid were prepared and oxidized to give dimeric benzofuran neolignan structures **12–13a–d** in 40–50% overall yields. The chiral phenols were dimerized either enzymatically with hydrogen peroxide and horseradish peroxidase (HRP) or with silver oxide. The enantioselectivity after reductive cleavage of the chiral auxiliaries to give dehydrodiconiferyl alcohol ranged from 18% to 62% enantiomeric excess. The conformational analysis and the activation energy using semiempirical PM3 calculations on the intermediate quinomethides is used to explain the observed stereoselectivity. Copyright © 2006 John Wiley & Sons, Ltd.

KEYWORDS: enantioselection; lignans; horseradish peroxidase; oxidative phenol coupling; conformational analysis; semiempiric calculations

INTRODUCTION

Ferulic acid derivatives **1** are dimerized to dehydrodimers **7** and **8** (Scheme 1) to give almost exclusively the racemic trans isomer if *R* is achiral.[1] This has been suggested recently to be the result of diastereocontrol in the cyclization of the intermediate quinomethide[2,3] deriving from the dimerization of a persistent phenoxy radical.[4,5] An initial single electron transfer from the starting ferulic acid derivative **1** gives the intermediate π-complex **2**, which undergoes carbon–carbon bond formation in a reversible way[6,7] to give the isomeric quinomethides **3–6**, possessing, respectively, the (*E*) and (*Z*) configuration at the exocyclic quinonoid double bond and the (*R*) and (*S*) configuration at the stereogenic C-3 carbon.

We demonstrated recently that stereocontrol in enzymatic oxidative coupling reactions of phenylpropenoidic phenols is possible. In fact, ferulic acid amides with chiral amino acids were oxidized with hydrogen peroxide in the presence of horseradish peroxidase (HRP) as the catalyst to give the dehydrodimers **7** and **8**(R = —C(O)—NH—CH(COOH)—C_6H_5) in different amounts. Chromatographic separation and hydrolysis allowed to show that 65% enantioselectivity had been obtained.[8]

Moderate stereoselectivity had been observed by Charlton *et al.*[9] in the reaction of chiral sinapate esters with $FeCl_3$ to give aryltetralin lignan structures. Moreover, the biosynthetic pathway to enantiopure (+)-pinoresinol lignan has been elucidated quite recently. In fact, a protein has been isolated from *Forsythia suspensa* and found to be responsible for the formation of enantiomerically pure (+)-pinoresinol from *E*-coniferyl alcohol.[10]

In a more recent approach,[2] stereoselective bimolecular radical coupling of enantiopure phenylpropenoidic phenols starting from enantiopure ferulic acid amides with Oppolzer camphor sultam gave the enantioselective phenol coupling with enantiomeric excess 80–84%. The conformational analysis of the quinomethide intermediates showed the reasons of the diastereoselectivity in the formation of reaction products.

EXPERIMENTAL

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were recorded with a FT-IR Jasco spectrophotometer. Mass spectra were measured by the direct injections system mode with positive electron impact with a VG 7070 EQ instrument. ^{1}H NMR spectra were taken with a Bruker AMX 300 instrument (in $CDCl_3$ solutions). Chemical shifts are given as ppm from tetramethylsilane and *J* values are given in Hz. Optical rotations were recorded on a Perkin Elmer 241 polarimeter at the sodium D line at 25 °C.

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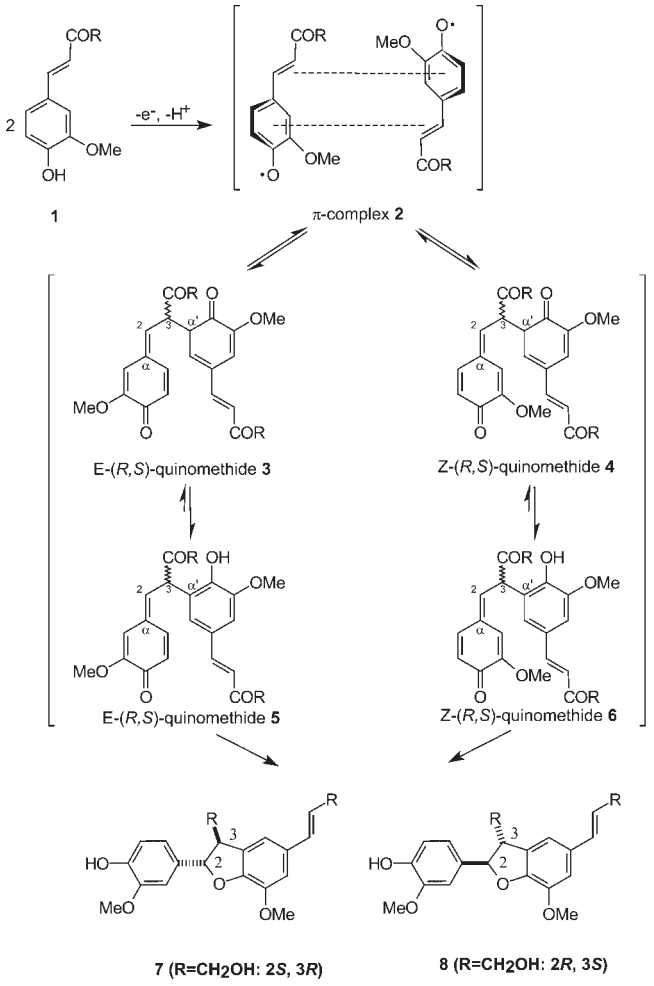


Scheme 1

HPLC analysis were performed on a WATERS 600 E instrument by using an HP 1040 Diode Array Detector.

Preparation of compound 10(a–d)

A mixture of ferulic acid **9** (427 mg, 2.2 mmol) , 2-chloro-1-methylpyridine iodide (670 mg, 2.6 mmol), and the appropriate chiral oxazolidinone (2.4 mmol) were dissolved in 6 mL of dry CH_2Cl_2 under nitrogen atmosphere. A solution of triethylamine (0.3 mL 5.6 mmol), dissolved in 2 mL of dry CH_2Cl_2, was added dropwise for 15 min. The mixture was stirred at 80 °C for 120 h, then 10 mL of a saturated aqueous NaCl solution were added. The organic phase was separated, then washed with a pH 4 solution of aqueous HCl (10 mL), with a 10% aqueous $NaHCO_3$ solution (10 mL), with water (10 mL), and finally dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash chromatography, (eluent CH_2Cl_2-acetone 7:3). Yields >40%.

Compounds **10a–b** showed: ^{1}H NMR: 7.58 (d, $J = 15.0$, 1H), 7.18–7.10 (m, 16H), 6.57–6.60 (m, 3H), 6.31 (d, $J = 15.0$, 1H), 4.67 (m, 1H), 4.35, (dd, $J = 9,9$ Hz, 1H), 4.20 (dd, $J = 9,9$ Hz, 1H), 3.95 (s, 3H), 2.77 (m-2H); IR (nujol): 3200, 1462 cm^{-1}; compounds **10c–d** showed: ^{1}H NMR: 7.55 (d, $J = 15.0$, 1H), 7.18–7.10 (m, 16H), 6.57–6.60 (m, 3H), 6.31 (d, $J = 15.0$, 1H), 4.97 (m, $J = 9,9$ Hz ,1H), 4.73, (dd, $J = 9,9$ Hz, 1H), 4.30 (dd, $J = 9,9$ Hz, 1H), 3.95 (s, 3H), IR (nujol): 3200, 1462 cm^{-1}.

Oxidative phenol coupling of compound 10(a–d) catalyzed by horseradish peroxidase (HRP)

A solution of **10(a–d)** (1.0 mmol) in the appropriate solvent (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 min. The mixture was then stirred at 0 °C. After 4 h, a saturated aqueous NaCl solution (20 mL) was added. The organic solvent was then removed under reduced pressure, and the resulting solution was extracted with AcOEt (4 × 20 mL). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ (25 mL), then with water (25 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was purified by silica gel flash cromatography (eluent toluene-AcOEt, gradient mode, from 4:1 to 1:1) yielding a mixture of phenylcoumarans **11(a–d)** and **12(a–d)**.

Ag_2O-promoted oxidative phenol coupling of compound 10(a–d)

Silver(I)oxide (0.18 g, 0.8 mmol) was added to a solution of **11(a–d)** (0.5 mmol) in dry CH_2Cl_2 (5.0 mL) under argon atmosphere at room temperature. After stirring for 24 h, the mixture was filtered through celite and evaporated under reduced pressure. The residue was purified by silica gel flash chromatography (eluent toluene-AcOEt, gradient mode, from 4:1 to 1:1) yielding a mixture of phenylcoumarans **11(a–d)** and **12(a–d)**. The two diastereomers were then separated by preparative HPLC (isocratic mode, CH_3CN—H_2O 1:1). A 40% yield was obtained.

Compound **12c** showed ^{1}H NMR: 7.58 (d, $J = 15.0$, 1H), 7,28–7.20 (m, 10H), 6.55–6.60 (m, 5H), 6.31 (d, $J = 15.0$, 1H), 6.12 (d, $J = 8.0$, 1H), 5.90 (dd, $J = 9,9$, 1H), 5.70 (dd, J 9,9, 1H), 4.97 (dd, $J = 9,9$ Hz, 1H), 4.80 (dd, $J = 9,9$ Hz, 1H), 4.73 (dd, $J = 9,9$ Hz, 1H), 4.60 (dd, $J = 9,9$ Hz, 1H), 4.30 12 (d, $J = 8.0$, 1H), 3.95 (s, 3H), 3.90 (s, 3H), IR (nujol): 3200, 1462 cm^{-1}; HREIMS of

12c calculated for $C_{22}H_{44}O_8N_2$: 433.1559; found 433.1573.

Reductions of phenylcoumarans 12(a–d) or 13(a–d) to dehydrodiconiferyl alcohol 7–8 (R = CH_2OH)

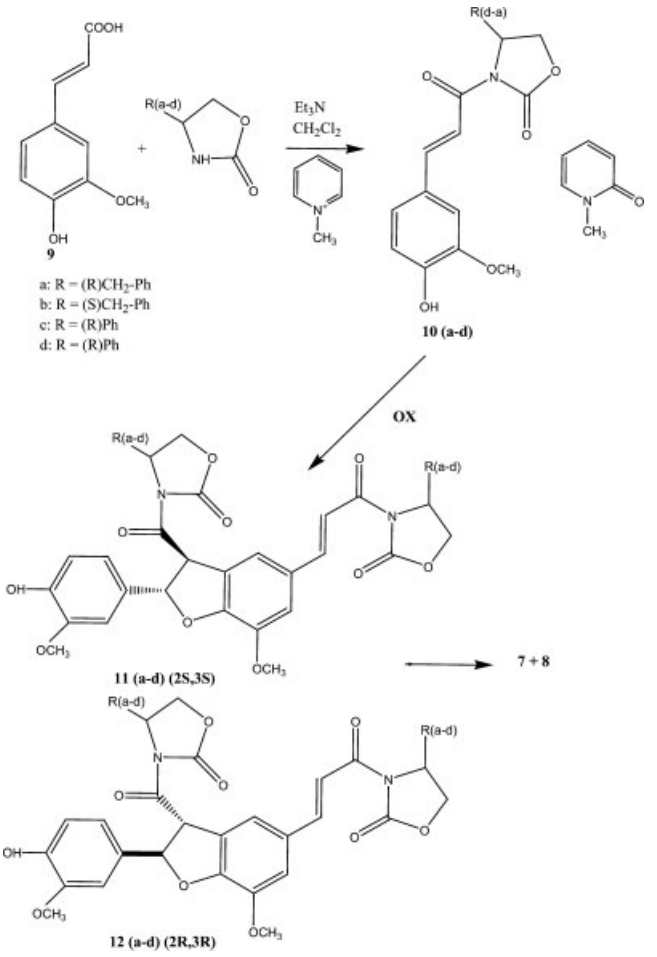
Phenylcoumarans **12(a–d)** or **13(a–d)** (0.024 mmol) were dissolved in dry THF (5 mL) under argon at −78 °C. $LiBH_4$ (1 mg, 0.054 mmol) was suspended in dry THF (1.0 mL) and added to the reaction mixture, which was further stirred for 2 h at −78 °C. After diluting with aqueous THF (10 mL), aqueous 0.1 M ammonium chloride (5 mL) was added. The mixture was extracted with AcOEt (2 × 10 mL), and the combined organic extracts were washed with water (10 mL), then dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was analysed by HPLC with a chiral column (Chiralcell OF; isocratic mode, eluent hexane-isopropanol 1:1). The absolute configurations of dehydrodiconiferyl alcohols **7–8** (R = CH_2OH) were determined by comparison with literature data.[11]

RESULTS AND DISCUSSION

Two chiral 2-oxazolidinones,[12] namely (*R*-) and (*S*-) 2-phenyl- and (*R*-) and (*S*-) 2-benzyloxazolidinine were used to induce asymmetry in these oxidative dimerizations.

Chiral compounds **10a–d** were prepared by using a ''one pot'' reaction from ferulic acid **9** and chiral 2-oxazolidinones in the presence of 2-chloro-1-methylpyridine iodide with a yield of 46% (Scheme 2). Compounds **10a–d** were thus oxidized using HRP/H_2O_2 or with silver oxide[6,13] to give the diastereoisomeric dehydrodimers **11–12a–d**. Enzymatic oxidations were performed in aqueous buffer systems and acetone or dioxane was used as a co-solvent. Silver oxide oxidations were performed in dry dichloromethane. After dimerization, oxazolidinone fragments were removed by reduction with $LiBH_4$/THF[14] to give the mixture of enantiomeric dehydrodiconiferyl alcohols **7–8** (R = CH_2OH).

Table 1 shows the results thus obtained. In these experiments, the sterically smaller chiral auxiliaries 2-phenyloxazolidinone gave considerably higher selectivities (e.e. 62%) compared to the corresponding 2-benzyl oxazolidinone chiral auxiliary (e.e. 21%). This observation is opposite to Evans results in Diels–Alder and alkylation reactions[15] and the results of Sibi *et al*. in radical allylation reactions with similar auxiliaries.[16] The attempts to use of Lewis acid additives in phenol oxidations to restrict the rotational freedom of *N*-acyloxazolidinones failed. In fact, addition of $MgBr_2$ or Zn-triflate to Ag_2O oxidation reaction mixture of **10a**



Scheme 2

prevented the reaction completely. It seems that the use of Lewis acids to control conformational rotamers via chelative interactions is not possible in phenol oxidations. The temperature and solvent system had only small effect to the observed stereoselectivity.

In our experiments, chiral auxiliaries with opposite chirality gave opposite chirality of the resulting *trans*-dehydrodimer **11–12a–d**, thus indicating that the observed diastereoselection was due to the influence of the stereogenic centers of the chiral auxiliaries. Hence, the nature of the product-determining step was investigated in order to understand the reasons of the observed diastereoselectivity in the formation of the diastereoisomeric dehydrodimers **11–12a–d**.

These quinomethides undergo nucleophilic attack of the phenolic oxygen to the quinomethide double bond to give cyclization to the final phenylcoumarans **11–12c–d** Two diastereofaces are involved in this reaction. Hence, chiral induction from the intermediate quinomethide may result in diastereoselectivity in the cyclization reaction and the stereochemistry of the product phenylcoumarans **11–12c–d** may be predicted if the energy of activation of

Table 1. Oxidations of chiral phenols

Chiral auxiliary	Oxidant	Solvent	T/ °C	Absolute configuration of the major enantiomer **7–8**	e.e %
(*R*)-benzyl (**10a**)	HRP/H_2O_2	Dioxane/buffer pH 3.5 8/2	25	*2R,3S*-(−)	21
(*R*)-benzyl (**10a**)	Ag_2O	CH_2Cl_2	25	*2R,3S*-(−)	18
(*S*)-benzyl (**10b**)	HRP/H_2O_2	Dioxane/buffer pH 3.5 8/2	25	*2S,3R*-(+)	21
(*S*)-benzyl (**10b**)	Ag_2O	CH_2Cl_2	−20	*2S,3R*-(+)	20
(*R*)-phenyl (**10c**)	HRP/H_2O_2	Acetone/Buffer pH 3.5 8/2	−20	*2R,3S*-(−)	62
(*R*)-phenyl (**10c**)	HRP/H_2O_2	Acetone/buffer pH 3.5 8/2	0	*2R,3S*-(−)	62
(*R*)-phenyl (**10c**)	Ag_2O	CH_2Cl_2	−20	*2R,3S*-(−)	53
(*S*)-phenyl (**10d**)	HRP/H_2O_2	Acetone/buffer pH 3.5 8/2	0	*2S,3R*-(+)	59

the cyclization reaction is nearly the same for all the cyclization reactions leading to *trans*-phenylcoumarans.

The conformational analysis on rotating the C2–C3 and Cα'–C3 bond in the intermediate quinomethides **3–6** was performed using the semiempirical PM3 Hamiltonian. This analysis allowed to predict the amount of each isomeric quinomethide at the equilibrium. The potential energy surfaces for the most stable intermediates are shown in Figs. 1 and 2. Here, using (*R*)-2-phenyloxazolidinone as the chiral auxiliary, the isomer having chirality (*R*) at C3, *Z*-arrangement of the double bond and two (*R*)-2-phenyloxazolidinone fragments (the *3-SERR* isomer) resulted about 2 kcal mol^{-1} more stable than the *3-RERR* isomer).

The phenolic oxygen of several minimum energy conformers of the most stable *3-SERR* isomer is suitably located to attack the (*re*) face of the double bond of the quinomethide to give the (*2R–3R*) phenylcoumaran **12c**. The subsequent reduction with $LiBH_4$ will then afford the (*2R,3S*) dehydrodiconiferyl alcohol **8** (R = CH_2OH). This prediction is in line with the observation that (*2R,3S*) reaction product was the major isomer experimentally found with e.e. 52–63%.

In the same way, the phenolic oxygen of few lower energy conformers of the less stable *3-RERR* quinomethide isomer will attack the (*si*) face of the quinomethide double bond and this predicts for the formation of (*2S,3R*) dehydrodiconiferyl alcohol **7** (R = CH_2OH), which was in fact formed in minor amounts.

As expected, opposite results were obtained using (*S*)-2-phenyloxazolidinone as the chiral auxiliary. Here, the *3-SESS* isomer of the intermediate quinomethide **3–6** was more than 1 kcal mol^{-1} less stable than the *3-RZSS* isomer.

The *3-RZSS* isomer may be predicted to attack the (*si*) face of the quinomethide double bond to give the (*2S–3S*) phenylcoumaran **11d**. The subsequent reduction with $LiBH_4$ will then afford the (*2S,3R*) dehydrodiconiferyl

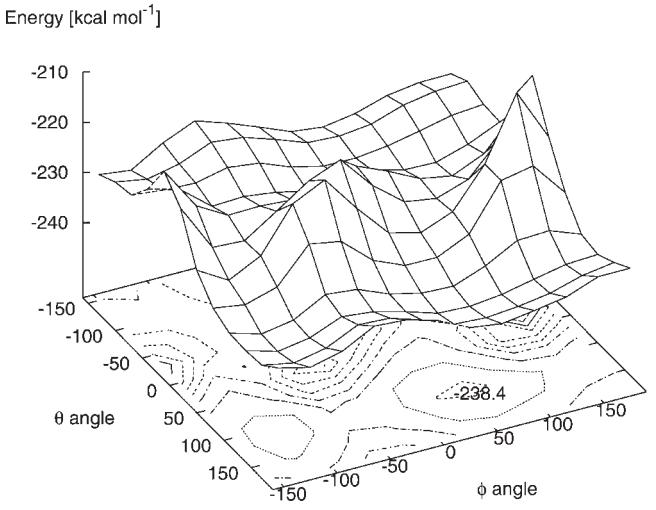


Figure 1. Potential energy surface for quinomethide 3-*SERR* for R = (*R*)-2-phenyloxazolidinone. Angle φ is Cα'-C3; angle θ is C2–C3

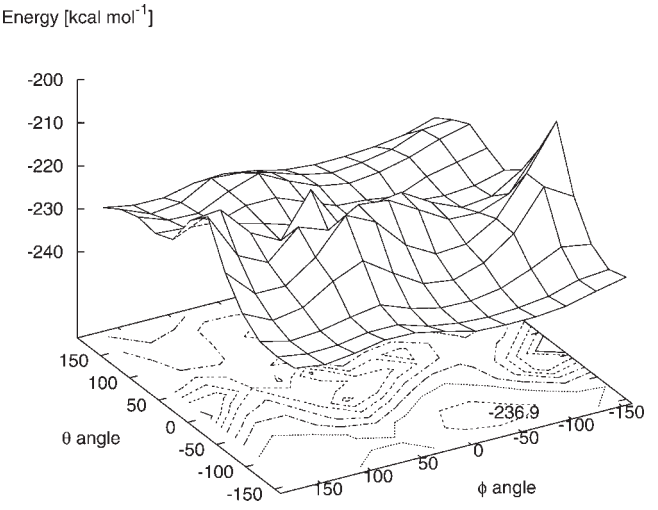


Figure 2. Potential energy surface for quinomethide *3-RERR* for R = (*R*)-2-phenyloxazolidinone. Angle φ is Cα'-C3; angle θ is C2–C3

alcohol **7** ($R = CH_2OH$). This is in line with the observation that (*2S,3R*)-(−) reaction product was the major isomer experimentally found with e.e. 59%.

The *3-SESS* isomer may be predicted to attack the (*re*) face of the quinomethide double bond to form, after reduction, (*2R,3S*)-(+) dehydrodiconiferyl alcohol **8** ($R = CH_2OH$), which was in fact formed in minor amounts.

These predictions require that *trans*-cyclization reactions have similar activation energy. The activation energy for the transformation of both 3-*SERR* and *3-RERR* phenolate anions to the corresponding dimers was calculated by PM3 to be 8.32 and 6.67 kcal mol^{-1}, respectively.

Moreover, the fact that *cis*-cyclization was never observed in spite of the fact that the quinomethide conformations undergoing this reaction are sometimes relatively stable implies that *cis*-cyclization involves higher activation energy than the *trans*-cyclization.

This was clear observing the results from (*R*)-2-benzyloxazolidinone as the chiral auxiliary. Many conformations of the most stable isomers predict for the *cis*-cyclization, which was never observed. Hence, in the case of the more flexibile benzyloxazolidinone moiety, quinomethide stability is unable to predict the enantioselectivity of the reaction.

In conclusion, these results show that chiral auxiliaries provide significant levels of diastereoselection in bimolecular coupling reactions of phenoxyl radicals, and this results in enantioselection in the final product. Evaluation of the stability of the intermediate quinomethides allows to predict the degree of enantioselection. It is expected that this methodology could be extended to various lignan structures thus providing a new approach to the synthesis of valuable lignans.

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