Asymmetric Biomimetic Oxidations of Phenols: Enantioselective Synthesis of (+)- and (-)-Dehydrodiconiferyl Alcohol

Petteri Rummakko,[a,b*] Gösta Brunow,[a] Marco Orlandi,[c] and Bruno Rindone[c]

[a] Department of Chemistry, P.O.Box 55 FIN-00014 University of Helsinki, Finland

[b] Current address, Department of Pharmacy, P.O.Box 5B, FIN-00014 University of Helsinki, Finland

Fax (+358) 9 708 59556, E-mail: Petteri.Rummakko@Helsinki.fi

[c] Department of Environmental Sciences, University of Milan, Via Emanuell 15, 20126 Milan, Italy

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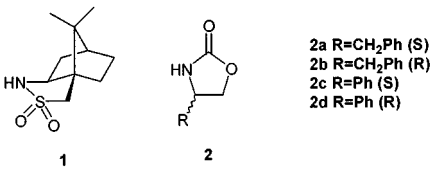
Abstract: Stereoselective bimolecular radical coupling reactions of phenylpropenoid phenols are described. Oppolzer's camphor sultam **1** and Evans's 2-oxazolidinone **2a-d** derivatives of ferulic acid were prepared and oxidized to give dimeric benzofuran neolignan structures **11** in 40-50% overall yields. The chiral phenols were oxidized either enzymatically with hydrogen peroxide and horseradish peroxidase (HRP) or by silver oxide. The observed enantioselectivity after reductive cleavage of chiral auxiliaries gave the neolignan dehydrodiconiferyl alcohol **12** in 18-84% e.e.

Key words: asymmetric synthesis, radical, phenol coupling, chiral auxiliary

We have recently reported a stereocontrolled enzymatic oxidative coupling of phenylpropenoid phenols.[1] In that work ferulic acid **3** covalently bound to a homochiral amino acid by an amide bond was oxidized with horseradish peroxidase (HRP) in 65% enantioselectivity. Also, Charlton *et al.* have reported that chiral sinapate esters can be coupled with $FeCl_3$ to aryltetralin lignan structures with moderate stereoselectivity.[2] The effects of cyclodextrins on the coupling of coniferyl alcohol was studied by Hirai *et al.*[3] but the observed e.e. values for oxidations performed in β-cyclodextrin were less than 10%.

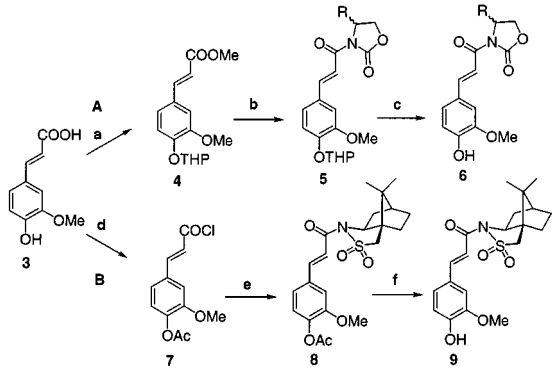
The biosynthetic pathway to (+)-pinoresinol has been elucidated quite recently. A protein has been isolated from *Forsythia suspensa* and found to be responsible for the formation of enantiomerically pure (+)-pinoresinol from *E*-coniferyl alcohol.[4] The importance of free radical reactions in organic synthesis has been increasing[5] and methods to control stereochemistry in free radical reactions have been found in recent years.[6] Our interest has been to extend the scope of asymmetric radical reactions into oxidative coupling reactions of phenols.

The problems of controlling regio- and stereoselectivity in phenol oxidations have limited the use of these reactions in organic synthesis. By careful selection of the reaction conditions the regioselectivity can be improved.[7] Lignan total syntheses are often known to involve multistep procedures with low overall yields.[8] Biomimetic oxidative coupling reactions of cinnamyl alcohols and acids provide a straightforward and cheap method for the preparation of various lignan and neolignan structures. We performed the oxidative coupling reaction of phenols using chiral auxiliaries to produce benzofuran neolignans **11** with chemical yields of 40-50% and enantiomeric excesses of **12** up to 84%. Two chiral auxiliaries, Oppolzer's (+)-2,10-camphor sultam **1** and Evans's 2-oxazolidinones **2a-d**, were used to induce asymmetry in phenol oxidations.



1 **2**

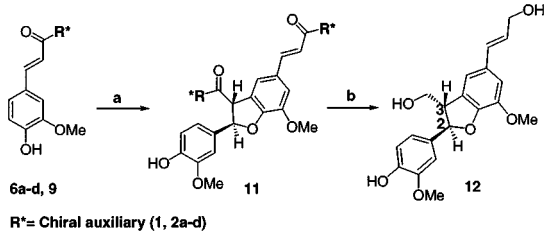
The *N*-acyloxazolidinone derivatives **5a-d** of THP protected[9] ferulic acid **4** were prepared by using the mixed anhydride *N*-lithiated oxazolidinone procedure (Scheme 1, Route A).[10,11] The deprotection of THP-ethers **5a-d** was performed conveniently by using ion-exchange resin (Amberlyst® IR-120) in methanol. The corresponding camphor sultam derivative **9** was prepared from protected ferulic acid chloride **7** under standard conditions (Route B).[12] Deprotection of the acetylated hydroxyl group of **8**, to obtain phenol **9**, was performed according to the method reported previously.[14]



Route A, **a**: i) MeOH, H^+, ii) CH_2Cl_2, DHP, PPTS, 92% **b**: i) KOH/EtOH, H_3O^+, 90%, ii) Pivaloyl chloride, Et_3N, THF, -78 °C and BuLi, 2-oxazolidinone **2a-d**, THF, -78 °C, 70-80% **c**: MeOH, Amberlyst® IR-120, 40 °C, 95%. **Route B, d**: i) Pyridine, Acetic anhydride, 90%, ii) $SOCl_2$, reflux **e**: Camphor sultam **1**, NaH, Toluene, ca.70% **f**: MeONa, MeOH, 95%.

Scheme 1

Oxazolidinones **6a-d** and camphor sultam **9**[13] were oxidized either enzymatically with HRP/H_2O_2 or chemically with silver oxide (Scheme 2).[7,15] Enzymatic oxidations were performed in aqueous buffer containing acetone or dioxane as the co-solvent.[16] Silver oxide oxidations were performed in dry dichloromethane. After the dimerization step the camphor sultam auxiliaries were removed by reduction with $LiAlH_4$/THF[12] and the oxazolidinones were removed by reduction with $LiBH_4$/THF.[17] Table 1 gives the results for the oxidations of chiral phenols **6a-d** and **9**.



Key a: Oxidation with Ag_2O/CH_2Cl_2 in Argon or enzymatically with HRP/H_2O_2, acetone or dioxane/buffer pH 3.5 **b**: Reduction with $LiAlH_4$ /THF, -20 °C or $LiBH_4$/ THF, -20 °C, (1 equiv. H_2O).

Scheme 2

Table 1. Oxidations of the chiral phenols.

Phenol	Oxidant	Solvent [a]	Temp. [°C]	% e.e. of 12 [b]	Abs. config.[c]
6a	HRP/H_2O_2	Dioxane/Buffer	25	21	2R,3S-(-)
6a	Ag_2O	CH_2Cl_2	25	18	2R,3S-(-)
6b	HRP/H_2O_2	Dioxane/Buffer	25	21	2S,3R-(+)
6b	Ag_2O	CH_2Cl_2	-20	20	2S,3R-(+)
6c	HRP/H_2O_2	Acetone/Buffer	-20	62	2R,3S-(-)
6c	HRP/H_2O_2	Acetone/Buffer	0	62	2R,3S-(-)
6c	Ag_2O	CH_2Cl_2	-20	53	2R,3S-(-)
6d	HRP/H_2O_2	Acetone/Buffer	0	59	2S,3R-(+)
9	HRP/H_2O_2	Acetone/Buffer	0	81	2S,3R-(+)
9	Ag_2O	CH_2Cl_2	-20	80	2S,3R-(+)
9	Ag_2O	CH_2Cl_2	25	84	2S,3R-(+)

[a] 0.02 M $NaHPO_4$/citric acid buffer, pH 3.5, organic solvent/buffer ratio was 3/1. [b] Ratios of diastereomeric pairs of **11** were determined by ^1H NMR (300 MHz) from the reaction mixture and compared with the chiral HPLC (Chiralcel OF) results obtained after reduction to **12**. [c] The absolute configurations of the dehydrodiconiferyl alcohols **12** were determined by chiral HPLC according to previously published results.[3]

The results show that among the auxiliaries used in oxidations the camphor sultam **1** gives better results that the corresponding oxazolidinones **2a-d**. The reason for this is probably the better rotational control of the camphor sultam compared to 2-oxazolidinones.[6] The temperature and solvent had only minor effects on the observed stereoselectivity. Among the oxazolidinone auxiliaries the sterically smaller phenyl oxazolidinone gave considerably higher selectivities (e.e. 62%) compared to the corresponding benzyl oxazolidinone (e.e. 21%). This observation is opposite to the results of Evans in Diels-Alder and alkylation reactions[11] and to the results of Sibi *et al.* in radical allylation reactions with the same type of auxiliaries.[18]

Attempts to use Lewis acid additives in phenol oxidations to restrict the rotational freedom of *N*-acyl oxazolidinones via chelative interactions failed. Addition of $MgBr_2$ or Zn-triflate to the oxidation with Ag_2O of **6a** 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.

In conclusion, these preliminary results demonstrate that chiral auxiliaries provide significant levels of diastereoselection in bimolecular coupling reactions of phenoxyl radicals and it is expected that this methodology could be extended to various lignan structures thus providing a new approach to the synthesis of valuable lignans.

Acknowledgement

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(13) Experimental data for phenol **6c** and **9**. Compound **6c** ^1H NMR (200 MHz, $CDCl_3$) δ: 3.93 (s, 1H), 4.31 (dd, J=4.0, 8.8 Hz, 1H), 4.74 (t, J=8.8 Hz, 1H), 5.57 (dd, J=4.0, 8.8 Hz, 1H), 5.97 (s, 1H), 6.90 (d, J=8.1 Hz, 1H), 7.10 (s, 1H), 7.12 (d, J=7.8 Hz, 1H), 7.32-7.39 (m, 5H), 7.71 (d, J=15.8 Hz, 1H), 7.80 (d, J=15.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 56.0, 57.9, 69.9, 109.5, 114.0, 114.6, 124.1, 125.9, 127.1, 128.6, 129.1, 139.1, 146.7, 146.9, 148.4, 153.8, 164.8. HREIMS cal-

culated for $C_{19}H_{17}O_5N$ 339.1107, found 339.1098. MS m/z (%) = 339 $[M]^+$ (100), 177 (90), 145 (20), $[\alpha]_D^{25}$ **6c** (c = 0.91, $CHCl_3$) = -32.1. Compound **9** ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (s, 3H), 1.21 (s, 3H), 1.25-1.45 (m, 3H), 1.85-1.96 (m, 3H), 2.15-2.20 (m, 2H), 3.51 (d, J=3.8 Hz, 2H), 3.92 (s, 3H), 3.99 (dd, J=5.5, 7.0 Hz, 1H), 5.89 (s 1H), 6.88-7.19 (m, 4H), 7.73 (d, J=15.3 Hz, 1H). ^{13}CNMR (75 MHz, $CDCl_3$) δ: 20.2, 21.1, 26.8, 33.1, 38.8, 45.0, 48.1, 48.7, 53.5, 56.3, 65.6, 110,1, 115.0, 124.2, 127.2, 146.1, 147.0, 148.7, 164.8. HREIMS of **8** (the acetate of **9**) calculated for $C_{22}H_{27}O_6NS$ 433.1559, found 433.1573. MS m/z (%) = 433 $[M]^+$ (10), 391 (65), 177 (100). $[\alpha]_D^{23}$ **9** (c = 0.43, $CHCl_3$) = +63.1.

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(16) **Typical experimental procedure for the enzymatic phenol coupling**. A solution of the phenol **6c** (1.03 mmol) in acetone (14 ml) and the 0.02 M phosphate/citric acid buffer (4 ml, pH 3.5) was cooled to 0 °C. Horseradish peroxidase (0.93 ml, 900 U/ml, 837 U) in water and 0.86 M H_2O_2 (0.60 ml, 0.52 mmol) were alternately added to the reaction vessel in small portions during 15 min. After addition the reaction mixture turned cloudy and slightly yellow color appeared. The reaction was stirred at 0 °C and after 4 hours saturated NaCl-solution (20 ml) was added to the reaction mixture. The acetone was removed by evaporation and the products were extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried with Na_2SO_4 and evaporated. The remainig yellowish foam (350 mg) was partially purified (250 mg) with column chromatography (silica gel, ethyl acetate / toluene). The purification gave (110 mg) benzofuran diastereoisomers in 4/1 ratio. The major diastereoisomer white powder **11c** (R* = **2c**). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.81 (s, 3H), 3.90 (s, 3H), 4.30 (dd, J=3.5, 8.8 Hz, 2H), 4.74 (t, J=8.8 Hz, 1H), 4.85 (t, J=8.8 Hz, 1H), 5.50 (dd, J=3.5, 8.6 Hz, 1H), 5.56 (dd, J=3.6, 8.6 Hz, 1H), 5.69 (s, 1H), 5.83 (d, J=7.6 Hz, 1H), 6.00 (d, J=7.6 Hz, 1H), 6.71 (d, J=8.0 Hz, 1H), 6.82 (d, J=8.0 Hz, 1H), 6.85 (s, 1H), 7.07 (s, 2H), 7.32-7.43 (m, 10H), 7.70 (d, J=15.6 Hz, 1H), 7.77 (d J=15.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 54.0, 55.1, 55.6, 57.7, 57.9, 69.5, 69.9, 88,2, 108.4, 112.1, 113.9, 114.1, 117.9, 119.3, 125.5, 126.3, 128.4, 128.5, 128.8, 130.1, 138.1, 145.7, 146.2, 150.4, 153.1, 153.5, 164.3, 170.1. FAB MS *m/z* 677 (M^+ +1).

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