Pergamon

Tetrahedron Letters 39 (1998) 3291–3294

TETRAHEDRON LETTERS

# Enantioselective Synthesis of a Benzofuranic Neolignan by Oxidative Coupling

Ezio Bolzacchini, Gosta Brunow[a], Simone Meinardi, Marco Orlandi*, Bruno Rindone, Petteri Rummakko[a], Harri Setala[a].

Department of Environmental Sciences, University of Milano, Via Emanueli 15, 20126 Milano, Italy.

[a]Department of Chemistry, P.O. Box55 FIN-00014 University of Helsinki, Finland

Received 15 January 1998; revised 20 February 1998; accepted 27 February 1998

***Abstract***: **The first stereoselective free radical coupling of a phenylpropenoidic phenolic compound is reported. The oxidation of a chiral ferulic acid amide to give dimeric benzofuranic neolignan is performed enzymatically using horseradish peroxidase as the catalyst. Enantiomeric excess in a biologically active compound with phenylcoumaran skeleton (β-5 dimer) is thus obtained.**



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 wall[4]. Moreover, the dilignol 3'-4-di-O-methylcedrusin is a wound healing agent and an inhibitor of thymidine incorporation in endothelial cells[5] and dehydrodiconiferyl alcohol has a role in plant physiology[6].

Unlike most biological oxidation, the bimolecular phenoxy radical coupling reaction is not under a strictly regio- and stereospecific control[7]. 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[8]. On the contrary, lignans are homochiral[2]. The biosynthetic pathway to enantiopure lignans has been proposed quite recently. A protein isolated from *Forsythia* species is suggested to be responsible for the formation of enantiomeric pure pinoresinol from coniferyl alcohol[9].

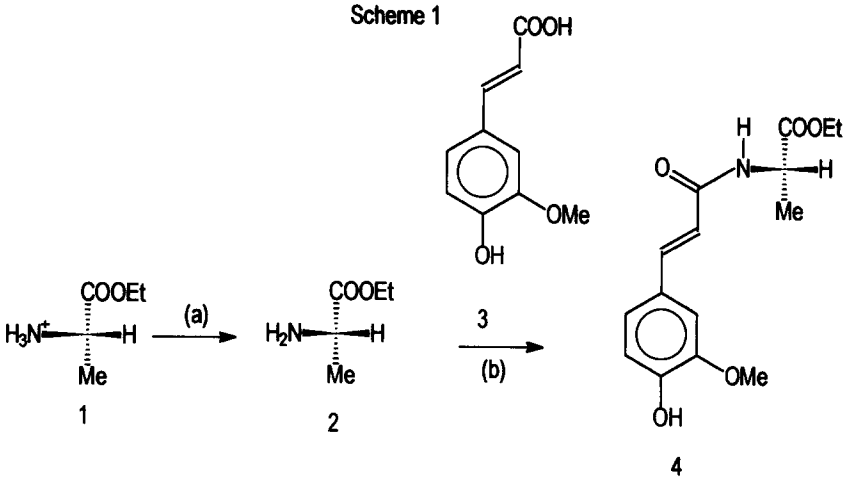
We recently reported that regio- and diastereoselectivity in the oxidative phenol coupling reaction may be obtained[10] using the horseradish peroxidase (HRP)-catalyzed oxidative coupling and hydrogen peroxide as the oxidant[11]. This reaction takes advantage from mild reaction conditions and fast reaction rates. It is possible to enhance the selectivity of this reaction by tuning the reaction pH and using the appropriate organic cosolvent, but stereoselection is not obtained under these conditions. The same negative result has been obtained using cyclodextrin as a chiral auxiliary[12].

Here we report the HRP-catalyzed enantioselective oxidative phenol coupling of a ferulic acid amide having the ethyl S-alaninate group as chiral auxiliary.

0040-4039/98/$19.00 
*PII:* S0040-4039(98)00473-0

The starting material was prepared as follows: ethyl-S-alaninate hydrocloride **1** was transformed to ethyl-S-alaninate **2** with triethylamine and reacted in situ with an equimolecular amount of ferulic acid **3** in tetrahydrofuran (THF) in the presence of dicyclohexylcarbodiimide (DCC) to give the amide **4** in 70% yield (Scheme 1).

Scheme 1

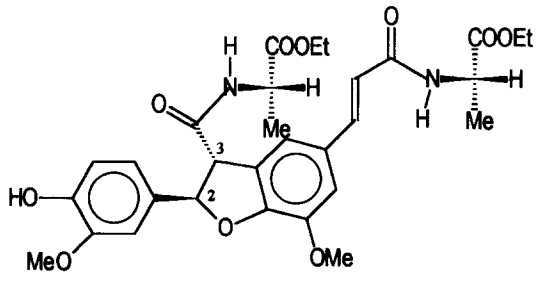



1 2 4

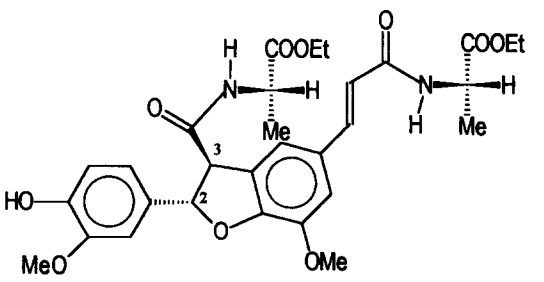
Reagents: a) $Et_3N$/THF rt 1h; b) DCC/THF rt 4h.

The HPR-catalyzed oxidative phenol coupling was performed in a dioxane-aqueous buffer pH 3. The mixture of the two diastereoisomers **5** and **6** was obtained in 70% yield.

Separation by silica gel flash chromatography, crystallisation and final purification by preparative RP-HPLC allowed to obtain the individual diastereoisomers which were characterised by $^{1}$H-NMR, $^{13}$C -NMR, UV, IR , MS[13]. The diastereoisomeric excess in the reaction was evaluated by RP-HPLC analysis of the crude reaction mixture[14] to be 65%.




**5**



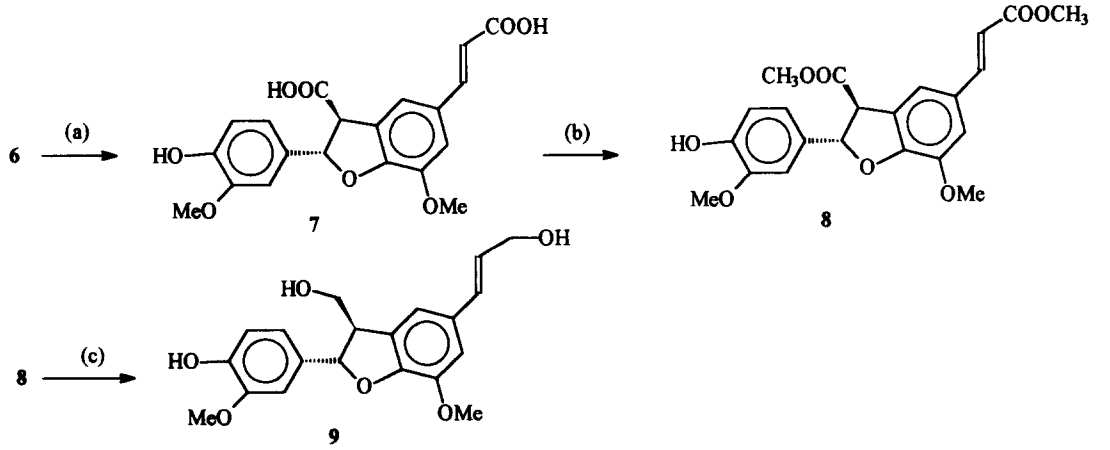

**6**

The absolute configuration of the two stereogenic carbons in the phenylcoumaran skeleton in the major diastereoisomer was attributed by hydrolysis with LiOOH in THF to give a crude mixture containing the

diacid **7** as the main product. Treatment of this mixture with diazomethane gave the diester **8** which was reduced with $LiBH_4$ to optically pure dehydrodiconiferyl alcohol **9**. Comparison of this product by chiral HPLC[15] with authentical specimens of both enantiomers of dehydrodiconiferyl alcohol[16] allowed to attribute the absolute configuration 2S,3R.

In summary, this is the first example of a bimolecular coupling reactions of phenoxy radicals to give phenylcoumarans with a significant enantiomeric excess. This result provides a whole new approach to the synthesis of valuable lignan structures. Studies are now in progress to obtain a higher enantiomeric excess.

Scheme 2




Reagents: a) $LiOH/H_2O_2$/THF rt 18h; b) $CH_2N_2$; c) $LiBH_4$/THF -78 °C

## REFERENCES AND NOTES

1. Higuchi, T.; Biosynthesis of Lignin, In *Biosynthesis and Biodegradation of Wood Components*; Higuchi, T. Ed.; Academic Press Inc., New York **1985**, pp 141-148.

2. Ayres, D. C.; Loike, J. D.; *Lignans. Chemical biological and clinical properties*; Cambridge University Press, Cambridge **1990**, pp 278-373.

3. Bernards, M. A.; Lopez, M. L.; Zajicek, J.; Lewis, N. G. *J. Biol. Chem.* **1995**, *270*, 7382-7387.

4. Ragan, M. A.; *Phytochemistry* **1984**, *23*, 2029-2032.

5. Pieters, L.; De Bruyne, T.; Claeys, M.; Vlietnick, A.; Calomme, M.; VandenBerghe, D.; *J. Nat. Prod.* **1993**, *56*, 899-906.

6. Binns, A. N.; Chen, R. H.; Wood, H. N.; Lynn, D. G.; *Proc. Nat. Acad, Sci. Usa* **1987**, *84*, 980-984.

7. Iqbal, I.; Bhatia, B.; Nayyar, N. K.; *Chem Rev.* **1994**, *94*, 519-564.

8. Aulin-Erdtman, G.; Tomita, Y.; *Acta Chem. Scand.* **1963**, *17*, 535-536; Nakatsubo, F.; Higuchi, T.; *Holzforschung* **1975**, *29*, 95-98.

9. Davin, L. B.; Wang, H.; Crowell, A. L.; Bedger, D. L.; Martin, D. M.; Sarkanen, S.; Lewis, N.G.; *Science* **1997**, *275*, 362-366.

10. Chioccara, F.; Poli, S.; Rindone, B.; Pilati, T.; Brunow, G.; Pietikainen, P.; Setala, H.; *Acta Chem. Scand.* **1993**, *47*, 610-616.

11. The HRP-catalysed phenol coupling oxidation is a well known reaction used amongst others by: Katayama, Y.; Fukuzumi, T.; *Mokuzay Gakkaishi*, **1978**, *24(9)*, 664-667; Donnelly, D. M. X.; Murphy, F. G.; Polonski, J.; Prangè, T.; *J. Chem. Soc. Perkin Trans 1* **1987**, 2719-2722; Krawczyk, A. R.; Lipowska, E.; Wrobel, J. T.; *Collect. Czech. Chem. Comm.* **1991**, *56(5)*, 1147-1150.

12. Ichihara, A.; Kawagishi, H.; Sakamura, S.; *24th Symposium on the chemistry of Natural Products*, Osaka, October **1981**, p. 490.

13. Data for **6**: white power m.p. = 205 °C; $^1$H-NMR (300 MHz, $CDCl_3$, ppm ): 7.58 (d, J=15 Hz, 1H), 6.35 (d, J=8 Hz, 1H), 6.31 (d, J=15 Hz, 1H), 6.12 (d, J=8 Hz, 1H), 5.95 (d, J=7 Hz, 1H), 5.60 (s, 1H), 4.71 (dq J=7-8 Hz, 1H), 4.60 (dq, J=7-8 Hz, 1H), 4.30 (q, J=8 Hz, 2H), 4.30 (q, J=8 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H) 1.45 (d, J=7 Hz, 3H), 1.40, (d, J=7 Hz, 3H), 1.25 (t, J=8 Hz, 3H),1.20 (t, J=8 Hz, 3H); m/z = 584 ($M^+$), 495, 481, 467; $\nu_{max}$(nujol): = 3200, 1462 $cm^{-1}$ ; $\alpha^{20}_D$ = + 48.3° (ethyl acetate).

Data for **5**: white power mp = 208 °C; $^1$H NMR (300 MHz, $CDCl_3$, ppm ): 7.40 (d, J=15 Hz, 1H), 6.65 (d, J=8 Hz, 1H), 6.22 (d, J=15 Hz, 1H), 6.55 (d, J=8 Hz, 1H), 5.93 (d, J=7 Hz, 1H), 6.10 (s, 1H), 4.65 (dq J=7-8 Hz, 1H), 4.60 (dq, J=7-8 Hz, 1H), 4.30 (q, J=8 Hz, 2H), 4.30 (q, J=8 Hz, 2H), 3.95 (s, 3H), 3.90 (s, 3H) 1.40 (d, J=7 Hz, 3H), 1.38, (d, J=7 Hz, 3H), 1.25 (t, J=8 Hz, 3H), 1.20 (t, J=8 Hz, 3H); m/z = 584 ($M^+$), 495, 467; IR (nujol):$\nu_{max}$ (nujol) = 3200, 1655 $cm^{-1}$; $\alpha^{20}_D$ = + 14° (ethyl acetate).

14. The analysis was performed using a Supelco RP C-18 column (5 μm, 100 A*4mm) eluting with a isocratic gradient 50% $CH_3CN$-50% $H_2O$. The instrument is equipped with a Diode Array detector.

15. The analysis was performed using a Chiralcel OF (4.6 i.d. x 250 mm) column eluting with an isocratic gradient 50% n-exane-50% 2-propanol. The HPLC is equipped with a Diode Array detector.

16. Hiray, N.; Okamoto, M.; Udagawa, H.; Yamamuro, M.; Kato, M.; Koshimizu, K.; *Biosci. Biotech. Biochem.* **1994**, *58*, 1678-1684.