Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3289–3292

TETRAHEDRON LETTERS

The reaction of methyl isoferulate with $FeCl_3$ or Ag_2O—hypothesis on the biosynthesis of lithospermic acids and related nor and neolignans

Philippe Cotelle* and Hervé Vezin

Laboratoire de Chimie Organique et Macromoléculaire, UMR CNRS 8009, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France

Received 25 February 2003; revised 27 February 2003; accepted 1 March 2003

Abstract—Methyl isoferulate reacts with $FeCl_3$ to give (2-6) dimer **3** (6-6) dimer **4** and (6-O-3) dimer **5** in low yields, whereas it reacts with Ag_2O leading to (2-O-3) dimer **6** and (6-O-3, 2-O-3) trimer **7**. By comparison with literature data, we suggest that the biosynthesis of lithospermic acids and related nor and neolignans that possess a β-2 bond may be due to the cross dimerisation of ferulate radical on isoferulate.

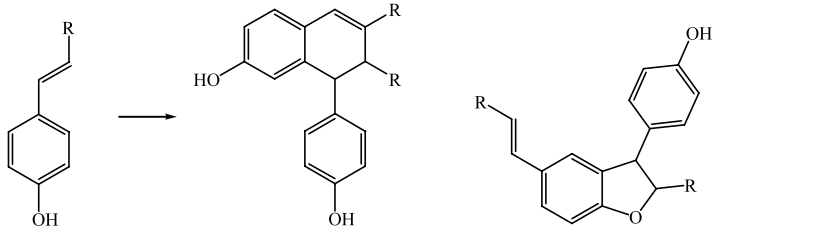
Lignans and neolignans have attracted much interest over the years on account on their widespread occurrence in vegetal kingdom and their broad range of biological activity including antitumoral, anti-inflammatory and antiviral activities. Of possibly even greater importance is the isolation of lignans from animals including human beings, which has led to the suggestion that such compounds may be examples of a new type of hormone controlling cell growth.[1]

Lignans and neolignans are formed in nature by the oxidative dimerisation of coniferyl alcohol[2] and can be prepared from various C6C3 phenols **1** either by enzymatic oxidation or by using conventional oxidising agents.

The most popular enzymatic system, i.e. horseradish peroxidase/H_2O_2,[3] led to the obtention of neolignans as main products, whereas the oxidative dimerisation of ferulic alcohol with chloroperoxidase/H_2O_2[4] or the oxidation of caffeic acid by catechol oxidase[5] led to an almost equimolar mixture of lignans and neolignans.

Chemically, the oxidative dimerisation of C6C3 phenols **1** may lead mainly to either lignans ($FeCl_3$,[6] cathodic reduction[7] or hepatic metabolism[8]) or neolignans (Ag_2O,[9] K_3FeCN_6,[10], tri-*t*-butylphenoxyl radical,[11] proflavin,[12] anodic oxidation[13] or sodium periodate[14]) or to a mixture of lignans and neolignans (alkaline autoxidation[15]) (Scheme 1).

However, a new class of 'neolignans' has appeared (lithospermic[16], salvianolic,[17] przewalskinic[18] acids) which cannot be biogenetically regarded as a product of oxidative dimerisation of **1**, since the C6C3 units are linked by a β-2 bond.



1 Example of β–β bond: lignans Example of β–O-4 bond: neolignans

Scheme 1.

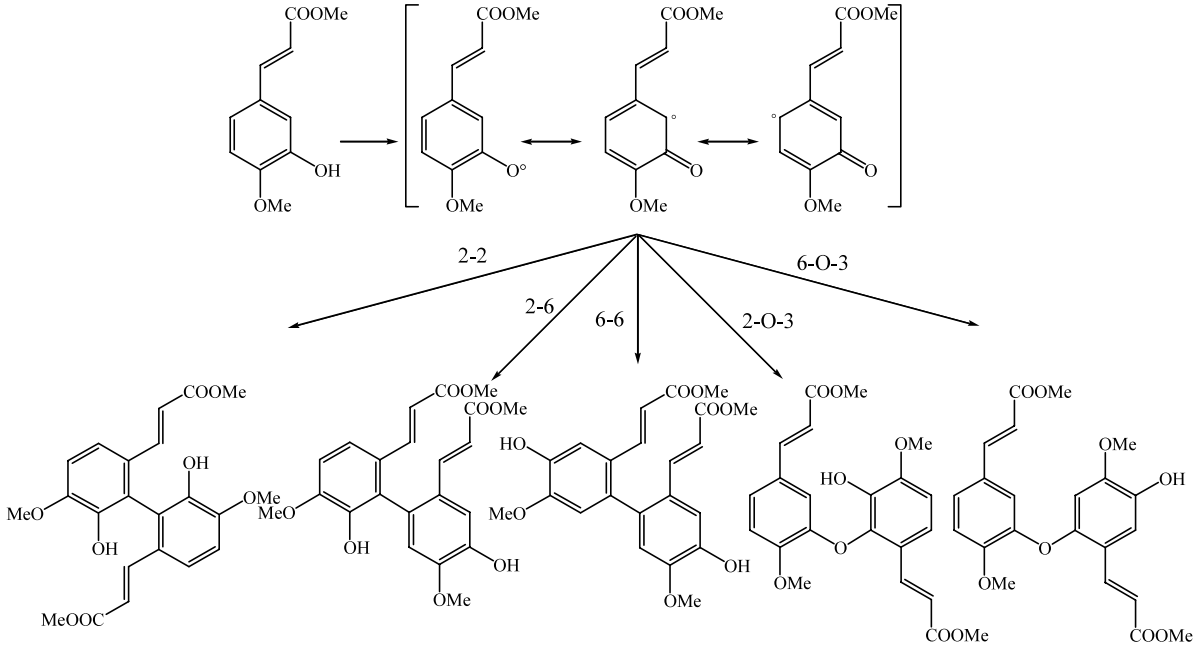
* Corresponding author. Tel.: 333 20 33 72 31; fax: 333 20 33 69 09; e-mail: philippe.cotelle@univ-lille1.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00584-7

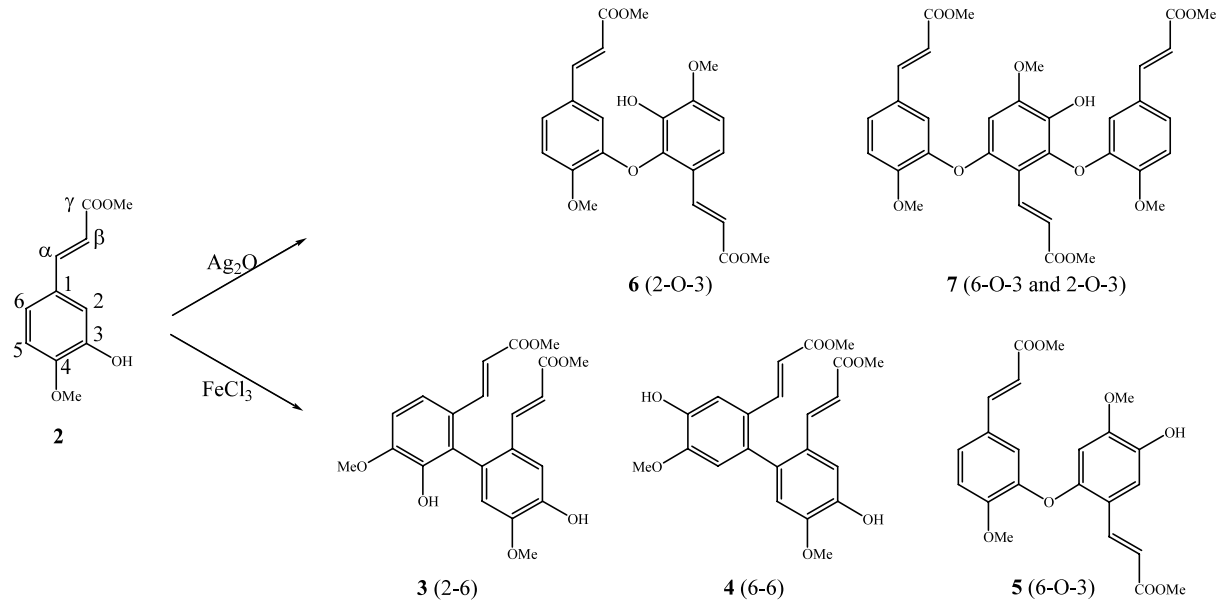
In addition to our efforts devoted to the synthesis of salvianolic acids,[19,20] we studied the oxidation of methyl isoferulate **2** since isoferulic acid has been isolated from *Salvia miltiorrhiza* beside salvianolic acids A–E.[21] Of the mesomeric forms of the phenoxy radical formed from methyl isoferulate, only three may be reactive leading to only five possible new bonds (2-O-3, 2-2, 2-6, 6-O-3, 6-6) (Scheme 2). Moreover, accordingly to the different antioxidant properties of ferulic and isoferulic acids, we may anticipated a lower reactivity of methyl isoferulate to the oxidation than methyl ferulate. Effectively, a previous work[22] using Co(II)(salen) catalyst has shown that both methyl ferulate and methyl isoferulate can be oxidised with the formation of an intermediate phenoxy species detected by ESR spectroscopy. The intensity of the signal of the phenoxy species is three times lower and decreases more rapidly indicating a lowest capability for methyl isoferulate than for methyl ferulate to generate a phenoxy radical and therefore a lowest reactivity to oxidation. Furthermore, the reactivities of ferulic and isoferulic acids towards DPPH (diphenylpycrylhydrazyl radical, a well-known stable radical used to evaluate the antioxidant properties) show that ferulic acid is a better scavenger of DPPH radical than isoferulic acid.[23] This paper deals with the reactivity of methyl isoferulate with $FeCl_3$ or Ag_2O.

As expected, the reaction of methyl isoferulate with $FeCl_3$[24] led to the isolation of **3** (6% yield), **4** (2% yield) and **5** (3% yield) (65% of unreacted methyl isoferulate was recovered) whereas methyl isoferulate and Ag_2O[25] gave 3% of a dimer **6** and 3% of a trimer **7** (42% of unreacted methyl isoferulate was recovered) (Scheme 3). Compared to methyl ferulate, methyl isoferulate showed a very modest reactivity to the oxidation whatever the oxidant used. Under the same reaction conditions, methyl ferulate reacts with $FeCl_3$ to give **8** in 36% yield and **9** in 31% yield[26] and with Ag_2O to give **9** in 38–50% yield[27] (Scheme 4). These results also showed the different reactivities of methyl isoferulate to $FeCl_3$ and Ag_2O. The structure of the products obtained by oxidation of methyl isoferulate resulted from the reaction of a radical centred at positions 2,6 or O-3. Theoretical calculations on methyl ferulate and isoferulate radicals at the DFT B3LYP levels using EPR-II basis set[28] afford the atomic spin densities (Table 1). The spin densities give the most reactive positions: O-4>C-β>C-5 for methyl ferulate radical and O-3>C-6>C-2 for methyl isoferulate radical. These results are in accordance with the experimental data. Nevertheless, we cannot explain the differences in the set of products obtained from $FeCl_3$ and Ag_2O. The same observations may be made from the literature data. In the case of the oxidative dimerisation of methyl ferulate β-4 bond was obtained with Ag_2O whereas β–β bond was also formed with $FeCl_3$. Similarly 2-O bond was also mainly observed with Ag_2O whereas C-C bond was the principal feature with $FeCl_3$ in the case of methyl isoferulate. This may be rationalised by the HSAB theory: hard acid (Fe^{3+}) reacts with hard base (phenolate) whereas soft acid (Ag^+) does not interact with phenolate and then the oxygen may be engaged in a new bond when Ag_2O was used as oxidant but not with $FeCl_3$. In order to confirm the role of the ferric complex, methyl isoferulate was reacted with K_3FeCN_6. As expected, **6** and **7** were obtained. In the absence of free Fe(III) ions in solution, no ferric complex was formed and C–C bonds were not observed.

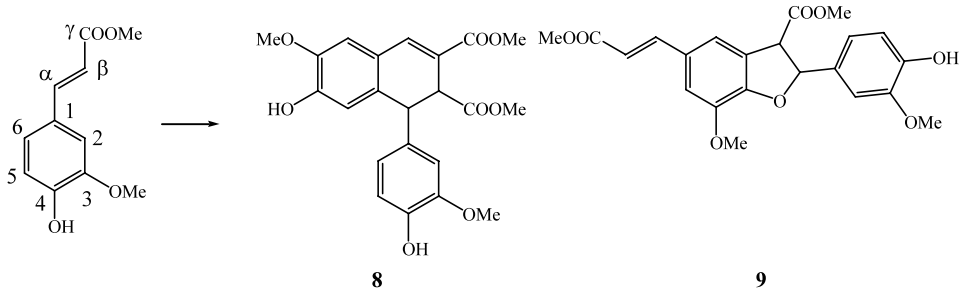
Enzymatically, the iron atom in horseradish peroxidase which is complexed in an hemic structure with a fifth strong ligand (N of histidine) cannot interact with the phenolic oxygen of **1** leading to neolignan whereas the



Scheme 2.



Scheme 3.



Scheme 4.

iron atom in chloroperoxidase which is complexed in an hemic structure with a less stronger ligand (S of cysteine) may interact with the phenolic oxygen of **1** leading to lignan. Enzyme with a metal in a high spin state seems to be needed for C–C bond whereas enzyme with a metal in a low spin state afforded more likely C–O bond.

Table 1. Total atomic spin densities of methyl ferulate and isoferulate radicals

Position[a]	Methyl ferulate radical	Methyl isoferulate radical
1	0.259	−0.070
2	−0.128	0.229
3	0.256	−0.046
4	−0.017	0.226
5	0.143	−0.128
6	−0.064	0.337
α	−0.113	0.022
β	0.215	−0.030
γ	−0.013	0.002
O-3	0.099	0.364
O-4	0.316	0.079

[a] Numbering of methyl ferulate and methyl isoferulate are given on Schemes 4 and 3, respectively.

As it may be anticipated from the spin densities of the isoferulate radical, the oxidation of methyl isoferulate does not lead to the formation of β-2 bond since the total atomic spin density at the β position is very low. Nevertheless, the reactivity of methyl isoferulate at the 2 position may suggest that β-2 type neolignans may be regarded as cross-condensation dimers of ferulate radical (where the β position is the most reactive) on isoferulate (mainly on position 2 as shown in this paper).

References

1. Axelson, M.; Sjovall, J.; Gustafsson, B. E.; Setchell, K. D. R. *Nature* **1982**, *290*, 659–660.
2. Davin, L. B.; Wang, H. B.; Crowell, A. L.; Bedgar, D. L.; Martin, D. M.; Sarkanen, S.; Lewis, N. G. *Science* **1997**, *275*, 362–366.
3. Sarkanen, K. V.; Wallis, A. F. A. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1869–1878.
4. Sih, C. J.; Ravikumar, P. R.; Huang, F. C.; Buckner, C.; Whitlock, H. *J. Amer. Chem. Soc.* **1976**, *98*, 197–199.
5. Rompel, A.; Fischer, H.; Meiwes, D.; Büldt-Karentzopoulos, K.; Magrini, A.; Eicken, C.; Gerdemann, C.; Krebs, B. *FEBS Lett.* **1999**, *445*, 103–110.

6. Ahmed, R.; Lehrer, M.; Stevenson, R. *Tetrahedron* **1973**, *29*, 3753–3759.
7. Utley, J. H. P.; Gullu, M.; Motevalli, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1961–1970.
8. Grumbinger, H. G.; Vahlensieck, U.; Winterhoff, H. *Planta Med.* **1993**, *59*, 491–493.
9. Pieters, L.; VanDyck, S.; Gao, M.; Bai, R.; Hamel, E.; Vlietinck, A.; Lemière, G. *J. Med. Chem.* **1999**, *42*, 5475–5481.
10. Wasserman, H. H.; Brunner, R. K.; Buynak, J. D.; Carter, C. G.; Oku, T.; Robinson, R. P. *J. Am. Chem. Soc.* **1985**, *107*, 519–521.
11. Miller, I. J. *Tetrahedron Lett.* **1972**, 4955–4958.
12. Eskins, K.; Glass, C.; Rohwedder, W.; Kleiman, R.; Sloneker, J. *Tetrahedron Lett.* **1972**, 861–864.
13. (a) Iguchi, M.; Nishiyama, A.; Hara, M.; Terada, Y.; Yamamura, S. *Chem. Lett.* **1978**, 1015–1018; (b) Iguchi, M.; Nishiyama, A.; Eto, H.; Terada, Y.; Yamamura, S. *Chem. Lett.* **1979**, 1397–1400.
14. Fulcrand, H.; Cheminat, A.; Brouillard, R.; Cheynier, V. *Phytochemistry* **1994**, *35*, 499–505.
15. Cilliers, J. J. L.; Singleton, V. L. *J. Agric. Food Chem.* **1991**, *39*, 1298–1303.
16. (a) Kelley, C. J.; Mahajan, J. R.; Brooks, L. C.; Neubert, L. A.; Breneman, W. R.; Carmack, M. *J. Org. Chem.* **1975**, *40*, 1804–1815; (b) Wagner, H.; Wittman, D.; Schaffer, W. *Tetrahedron Lett.* **1975**, 547–550.
17. Li, L.; Tan, R.; Chen, W. *Planta Med.* **1984**, *50*, 227–228.
18. Lu, X. Z.; Xu, W. H.; Shen, J. X.; Naoki, H. *Chinese Chem. Lett.* **1991**, *2*, 301–302.
19. Dalla, V.; Cotelle, P. *Tetrahedron Lett.* **1998**, *39*, 8285–8286.
20. Dalla, V.; Cotelle, P. *Tetrahedron* **1999**, *55*, 6923–6930.
21. Ai, C. B.; Li, L. N. *Planta Med.* **1992**, *58*, 197–199.
22. Bolzacchini, E.; Canevali, C.; Morazzoni, F.; Orlandi, M.; Rindone, B.; Scotti, R. *J. Chem. Soc., Dalton Trans.* **1997**, 4695–4699.
23. Burdette, J. E.; Chen, S. N.; Lu, Z. Z.; Xu, H.; White, B. E. P.; Fabricant, D. S.; Liu, J.; Fong, H. H. S.; Farnsworth, N. R.; Constantinou, A. I.; Van Breemen, R. B.; Pezzuto, J. M.; Bolton, J. L. *J. Agric. Food Chem.* **2002**, *50*, 7022–7028.
24. Methyl isoferulate was reacted with $FeCl_3$ using the previously described procedure[26]. After chromatographic column four products can be isolated: methyl isoferulate (65%), **3** (6%), **4** (2%) and **5** (3%).

3: ^{1}H NMR ($CDCl_3$): 3.669 (s, 3H), 3.672 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 5.64 (brs, 1H), 5.83 (brs, 1H), 6.16 (d, 1H, $^3J=15.9$ Hz), 6.22 (d, 1H, $^3J=15.9$ Hz), 6.62 (s, 1H), 6.93 (d, 1H, $^3J=8.6$ Hz), 7.25 (d, 1H, $^3J=15.9$ Hz), 7.29 (d, 1H, $^3J=8.6$ Hz), 7.30 (d, 1H, $^3J=15.9$ Hz), 7.32 (s, 1H). FAB neg: 413.

4: ^{1}H NMR ($CDCl_3$): 3.68 (s, 6H), 3.87 (s, 6H), 5.80 (brs, 2H), 6.20 (d, 2H, $^3J=15.9$ Hz), 6.63 (s, 2H), 7.24 (d, 2H, $^3J=15.9$ Hz), 7.27 (s, 2H). FAB neg: 413.

5: ^{1}H NMR ($CDCl_3$): 3.73 (s, 3H), 3.75 (s, 3H), 3.78 (s, 3H), 3.93 (s, 3H), 5.63 (brs, 1H), 6.14 (d, 1H, $^3J=15.9$ Hz), 6.34 (d, 1H, $^3J=16.2$ Hz), 6.41 (s, 1H), 6.83 (d, 1H, $^4J=2.2$ Hz), 6.97 (d, 1H, $^3J=8.6$ Hz), 7.19 (s, 1H), 7.22 (dd, 1H, $^4J=2.2$ Hz, $^3J=8.6$ Hz), 7.51 (d, 1H, $^3J=16.2$ Hz), 7.85 (d, 1H, $^3J=15.9$ Hz). FAB neg: 413.

25. Methyl isoferulate was reacted with Ag_2O using the procedure described by Lemière et al.[27]. After chromatographic column three products can be isolated: methyl isoferulate (42%), **6** (3%) and **7** (3%). **6**: ^{1}H NMR ($CDCl_3$): 3.72 (s, 3H), 3.73 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H), 5.28 (brs, 1H), 6.07 (d, 1H, $^3J=15.9$ Hz), 6.42 (d, 1H, $^3J=16.1$ Hz), 6.65 (d, 1H, $^4J=1.9$ Hz), 6.82 (d, 1H, $^3J=8.6$ Hz), 6.98 (d, 1H, $^3J=8.6$ Hz), 7.17 (dd, 1H, $^4J=1.9$ Hz, $^3J=8.6$ Hz), 7.20 (d, 1H, $^3J=8.6$ Hz), 7.45 (d, 1H, $^3J=15.9$ Hz), 7.73 (d, 1H, $^3J=16.1$ Hz). FAB neg: 413.

7: ^{1}H NMR (CD_3COCD_3): 3.57 (s, 3H), 3.66 (s, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 6.08 (d, 1H, $^3J=16.2$ Hz), 6.26 (d, 1H, $^3J=15.9$ Hz), 6.41 (s, 1H), 6.74 (d, 1H, $^3J=16.5$ Hz), 6.75 (d, 1H, $^4J=2.0$ Hz), 7.04 (d, 1H, $^3J=8.4$ Hz), 7.09 (d, 1H, $^3J=8.7$ Hz), 7.19 (d, 1H, $^4J=2.0$ Hz), 7.21 (dd, 1H, $^4J=2.0$ Hz, $^3J=8.4$ Hz), 7.36 (dd, 1H, $^4J=2.0$ Hz, $^3J=8.7$ Hz), 7.43 (d, 1H, $^3J=15.9$ Hz), 7.53 (d, 1H, $^3J=15.9$ Hz), 7.79 (d, 1H, $^3J=16.5$ Hz). FAB neg: 619

26. Kuo, Y. H.; Kuo, P. C.; Lin, S. T. *Proc. Natl. Sci. Counc.* **1983**, *7*, 28–34.
27. (a) Antus, S.; Gottsegen, A.; Kolonits, P.; Wagner, H. *Justus Liebigs Ann. Chem.* **1989**, 593–594; (b) Maeda, S.; Masuda, H.; Tokoroyama, T. *Chem. Pharm. Bull.* **1994**, *42*, 2500–2505; (c) Lemière, G.; Gao, M.; DeGroot, A.; Dommisse, R.; Lepoivre, J.; Buss, V. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1775–1779.
28. Cossi, M.; Barone, V.; Cammi, R.; Tomasi, J. *Chem. Phys. Lett.* **1996**, *255*, 327–335.