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Regioselectivity in oxidative cross-coupling of phenols. Application to the synthesis of dimeric neolignans

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Abstract—The problems of regioselectivity in oxidative coupling of phenols are outlined, and recent research on the application to the synthesis of lignans and neolignans is reviewed. Lignans and neolignans are dimers that are typically formed by oxidative coupling of propenyl phenols. The coupling of structurally different phenols (cross-coupling) is an extension of this synthesis. Recent results show that cross-coupling can be achieved if the phenols have compatible reactivities. The regioselectivity is often quite different in cross-coupling compared to dimerization. Coupling of phenols with widely different rates of oxidation is difficult but can be achieved if the concentration of the more reactive phenol can be kept low enough during the reaction, for instance by diffusion through a dialysis membrane. © 2000 Elsevier Science Ltd. All rights reserved.

Oxidative coupling is an important pathway in the biosynthesis of lignans and lignins and it is also extensively used for syntheses in vitro. Oxidation of phenols often yields phenoxy radicals which couple with little selectivity. Both C–C and C–O bonds are formed, mainly in *ortho*- and *para*-positions to the phenolic hydroxyl. Synthetically useful reactions are obtained only when the reactivity is blocked by substituents. For instance from 2,6- or 2,4-substituted phenols, C–C bonded biphenyls can be obtained in good yields. In other cases coupling can be directed by carrying out the reaction intramolecularly, ring closure being an effective way of inducing regioselectivity.[1] In the case of lignan synthesis the starting materials for coupling are propenyl substituted phenols. The radicals formed on oxidation are very reactive, especially at the β position. This is reflected in the product composition; for instance, the dimers that have been isolated from oxidation of **1**–**3** are all coupled in the β position; some important products are shown in Scheme 1. When both *ortho*-positions are occupied β–β-coupled lignans (**7**–**9**) are formed.[1,2] With one *ortho*-substituent, the yields of β–β-coupled product is lower but can be synthetically useful in certain solvent systems.[3] Biosynthethic formation of pinoresinol (**6**) with high enantioselectivity has been observed recently.[4] For propenyl phenols with one *ortho*-substituent, β-5-coupling is dominant. The β-5-coupling of propenyl phenols is a useful synthetic procedure, and a number of oxidants can be used for this reaction.[3,5] In most cases only one diastereomer is formed, where the stereochemistry of the five-membered ring is *trans*. It is also possible to synthesize phenylcoumarans (**5**) with a high degree of enantioselectivity with the aid of chiral auxiliaries.[6,7,8] The formation of β-*O*-4-coupled products by dimerization has been successfully carried out with propenyl phenols using oxidants such as silver oxide,[3,9] and peroxidase-H_2O_2.[10] The formation of β-*O*-4-dimers differs from the other two dimers in that it requires the addition of water to an intermediate quinone methide; this is an acid catalyzed reaction which is very slow at neutral pH.[11,12]

An important extension of oxidative coupling for synthesis is to obtain coupling between two structurally different phenols. This type of reaction is also supposed to play an important role in lignin biosynthesis.[13] The formation of mixtures of oligomers in oxidative reactions have recently been reported.[14] Oxidation of a mixture of two phenols can lead to a mixture of dimers of the individual phenols and cross-coupling products between the different phenols. When one phenol reacts much faster than the other, for instance if it has a lower oxidation potential, it tends to dimerize without formation of significant amounts of cross-coupling products.[13] In connection with studies on the biosynthesis of lignin we have studied the factors contributing to efficient cross-coupling between two different phenols. We have found that cross-coupling yielding oligomeric neolignans in yields up to 40% can be obtained when the phenols have similar rates of oxidation.[13] The effect of oxidation potentials of the phenols on the extent of cross-coupling was reported in a previous article.[15]

The coupling of phenols with widely different rates of oxidation is more problematic. One approach is to start with the less reactive phenol in large excess, and continually add the more reactive phenol (and the oxidant) at a rate

Keywords: cross-coupling; dimeric neolignans; dialysis membrane.

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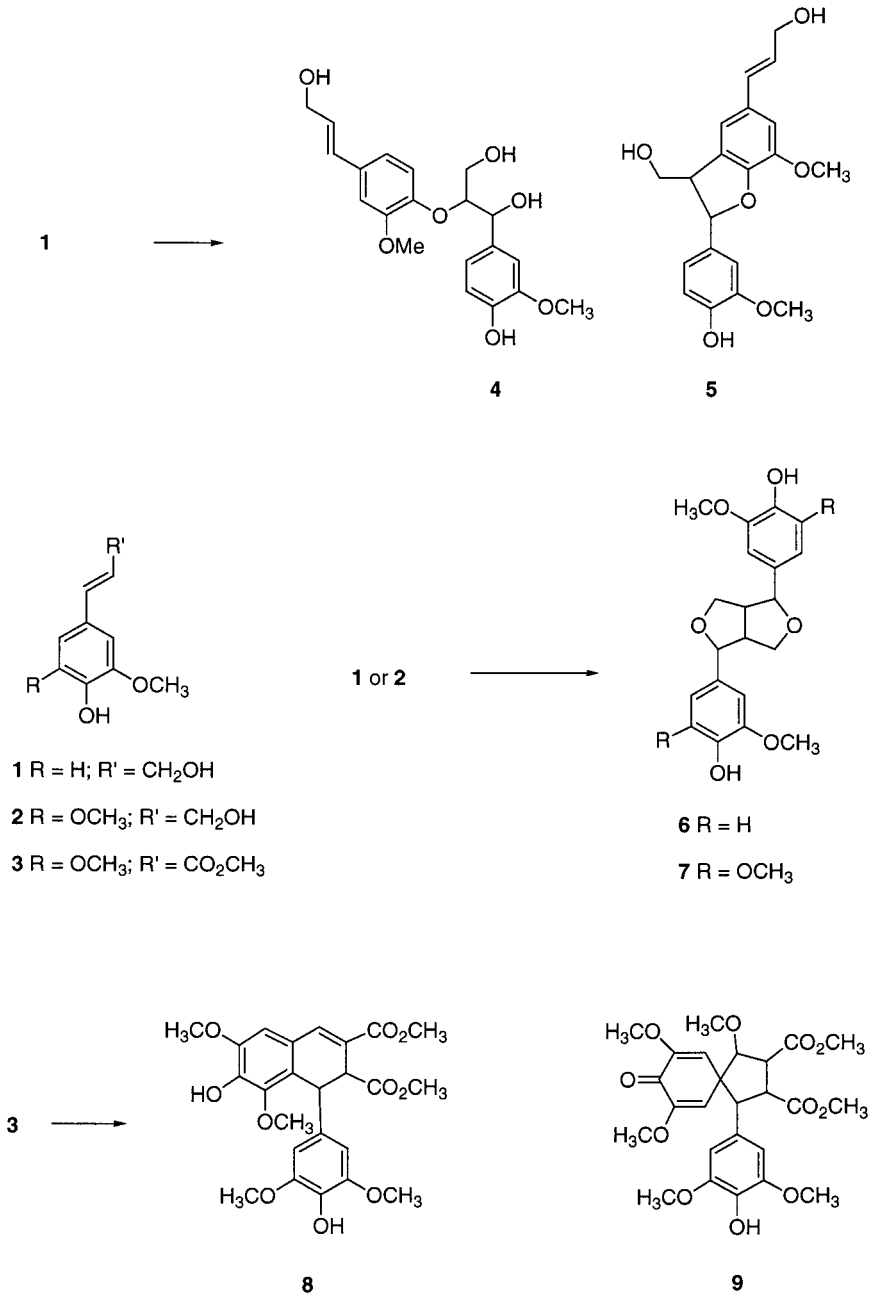
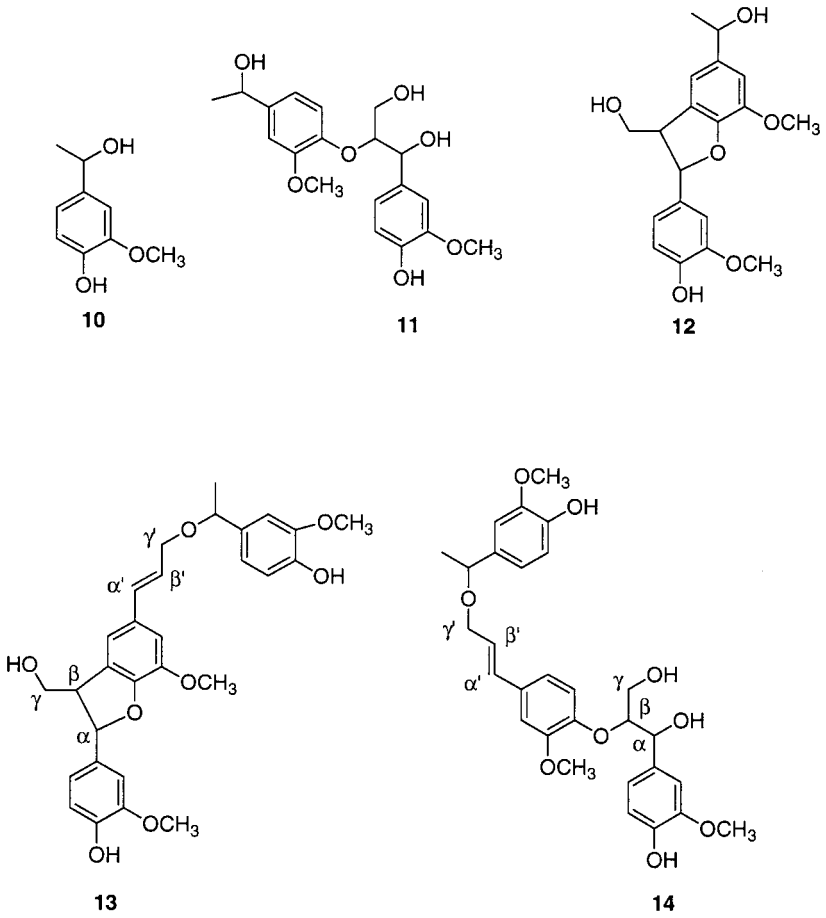


Scheme 1.

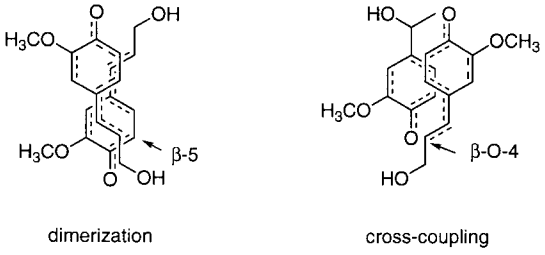
which is slow enough to keep its concentration too low for significant dimerization. This approach has been reported to work in the case of so-called 'Zutropf' oxidation in the preparation of synthetic lignin. In a typical preparation, coniferyl alcohol and hydrogen peroxide are added simultaneously over a period of several days to a dilute solution of peroxidase.[16] The method is cumbersome, leading to large reaction volumes, and is difficult to reproduce.

We have explored the use of the Zutropf method for the synthesis of cross-coupling products, using more convenient concentrations of reactants in order to avoid excessively large volumes of dilute reaction mixtures. We have studied oxidative cross-coupling using coniferyl alcohol (**1**) and apocynol, 2-methoxy-4-(1-hydroxyethyl)-phenol (**10**), as substrates.[17] We found that adding coniferyl alcohol, the more reactive of the two phenols, with a syringe pump at a slow rate, yielded mostly dimers **4**–**6** and very small amounts of cross-coupling products **11** and **12**. This indicates that the rate of dilution of the coniferyl alcohol is insufficient to suppress dimerization. Analysis of the dimer mixture does, however reveal striking differences in regioselectivity between dimerization and cross-coupling. For instance when coniferyl alcohol (**1**) forms dimers, the β-5- and β-*O*-4-dimers **4** and **5** are formed in roughly equal amounts. When coupling with phenol (apocynol) that lacks the conjugated bond in the side chain, the ratio of β-*O*-4- to β-5-products is about 10 to 1. This remarkable change in regioselectivity may be due to different configurations of intermediate π-complexes. The lack of a conjugated double



Scheme 2.

bond in one phenol may lead to a π-complex with a configuration favoring β-*O*-4-coupling over β-5-coupling (Formula 1).

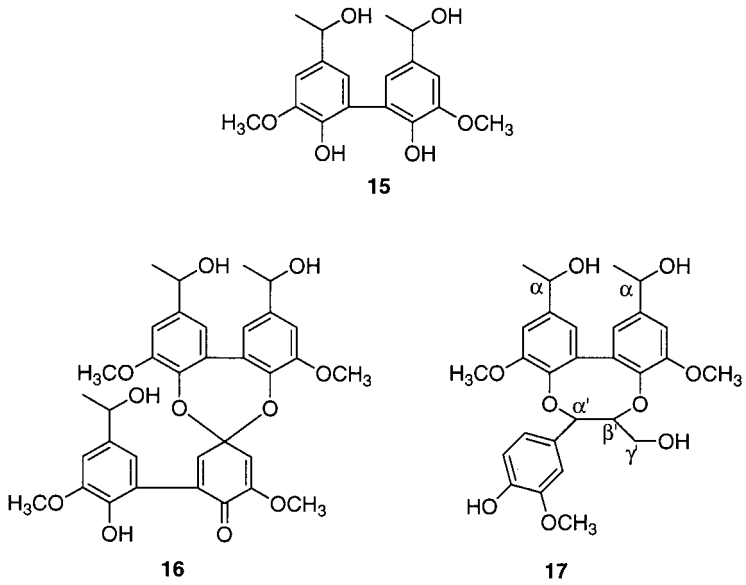


In an effort to increase the yield of cross-coupling products at the expense of dimerization products, slower modes of addition were tested. In experiments with carbohydrate gels (Carrageenan), the more reactive phenol (coniferyl alcohol) and oxidant (H_2O_2) were added on top of a 0.25% gel containing the excess of the less reactive phenol (apocynol) and the catalyst (horseradish peroxidase). The rate of diffusion still proved to be too high. Analysis of the contents of the gel showed that coniferyl alcohol had formed the normal dimerization products. Two novel products were isolated. Their mass spectra showed them to be dimers of coniferyl alcohol plus one mole of apocynol. The ^{1}H NMR spectra (δ_H for **13**: 2.09, aliph. $OCOCH_3$; 2.34, 2.36, arom. $OCOCH_3$; 4.54, C*H*CH_3; 5.57, Hα in phenylcoumarane unit and 6.53, Hα′ in coniferyl alcohol side chain and δ_H for **14** *erythro*: 2.05, 2.13, aliph. $OCOCH_3$; 2.34, 2.36, arom. $OCOCH_3$; 4.53, C*H*CH_3 and 6.51, Hα′ in coniferyl alcohol side chain) proved that a β-5-dimer and a β-O-4-dimer had become etherified with apocynol in the γ-position (Scheme 2). Both *erythro*- and *threo*-isomers of **14** were identified. A possible explanation for the occurrence of these compounds is that the acidic groups in the gel have caused an acid-catalyzed substitution reaction.

A rate of addition that was sufficiently slow to suppress dimerization was finally achieved by letting the coniferyl alcohol diffuse through a dialysis membrane, an approach pioneered by Tanahashi and Higuchi.[18]

1. Dialysis experiment

We performed dialysis experiments with a dialysis tube with a pore size (18 Å) chosen to allow molecules smaller than the enzyme to pass through the membrane. Apocynol and enzyme (horseradish peroxidase) in buffer (pH=3.5) were placed inside the tube, and a solution of coniferyl alcohol and hydrogen peroxide in the same buffer were added outside the tube.[17] The apocynol concentration was ten times that of coniferyl alcohol. Both the content of the tube and the outer layer were agitated. Both mixtures were analysed after 17 h reaction at room temperature. The products inside the tube comprised 38% of the total added materials. The outer solution contained 62% and was a mixture of equal amounts of apocynol and coniferyl



Scheme 3.

alcohol. This shows that some diffusion of apocynol out of the tube had taken place. No dimers were found outside the tube. Inside the tube the main products were dehydrodiapocynol **15** (ca. 15% of the products inside), cross β-*O*-4-dimer **11** (ca. 10%) and dioxepin **16**[19] (ca. 15%) and a small amount of dibenzodioxocin **17** (1–2%) (Scheme 3). About 30% was polymeric (on the basis of chromatographic behaviour and NMR spectra) and the rest was unreacted apocynol (25%) and unidentified minor products. The polymer was different from normal dehydrogenation polymers in that it contained mainly β-*O*-4-structural units and no β-5-bonds. Also a lot of apocynol moieties were included. The dialysis experiment was repeated at pH 6.5. The main products inside the tube, which contained 38% of the added material, were **11**, **15**, **16** and **17** as at pH 3.5; only some quantitative differences were observed. More compound **17** (ca 5% of the products) and less **16** (<10%) was detected, the polymeric fraction was smaller (only 10%) and more apocynol remained unreacted. In the outer solution there was unreacted apocynol and coniferyl alcohol and also some dimer **5** present. Compound **5** has apparently diffused through the membrane because in the reference reaction no reaction of coniferyl alcohol with hydrogen peroxide at pH 6.5 was observed.

2. Conclusions

Selective cross-coupling of propenyl substituted phenols is a viable method for the synthesis of lignans and neolignans. The regioselectivity of cross-coupling differs significantly from that of dimerization; the mechanistic reasons for this have not yet been elucidated. Cross-coupling between phenols with different rates of oxidation can be promoted at the expense of dimerization by regulating the addition of reactants to the reaction mixture. A method described here, involving the use of diffusion through a dialysis membrane, shows promise in this respect.

3. Experimental

3.1. General

The buffered aqueous solution was obtained using citric acid (0.01 M)–phosphate (0.02 M) buffer pH=3.5, 6.0 and 6.5. Horseradish peroxidase (E 1.11.1.7) was from Serva, activity 529 U mg^{-1}. A 30% aqueous hydrogen peroxide (Merck) was diluted to give a 3% solution (ca. 0.8 M) before use. Silica gel for column chromatography used Merck Kieselgel 60 (230–400 mesh). Thin layer chromatography was performed on silica gel plates (Merck Kieselgel 60 F_{254}). Spots were made visible with UV light. In the dialysis experiment regenerated cellulose tubular membrane (Cellu Sep, T2 23mm, pore size 18 Å, nominal MWCO 6,000–8,000) was used. ^{1}H NMR and ^{13}C NMR spectra were recorded at 200 and 300 MHz on Varian Gemini instruments. Deuteriochloroform was used as a solvent. Mass spectra were recorded on a JEOL JMS-SX102 instrument. The HPLC was performed using Waters 600 pump, LiChrospher Si 60 (5 μm) column (4×250 mm and 10×250 mm) and Waters 996 UV spectrophotometric detector with detection at 280 nm. Hexane–ethyl acetate was used as an eluent. The injection volume was 20 μl or 500 μl. Evaporations were conducted under reduced pressure at a temperature less than 40°C. Products were acetylated with dry acetic anhydride and pyridine (1:1) overnight at room temperature.[20]

3.2. Synthesis of model compound 1, 10, 11 and 16

Coniferyl alcohol (**1**) was prepared from vanillin (commercial grade, Fluka). A Knoevenagel reaction with vanillin and malonic acid[21] and then esterification with ethanol–sulfuric acid gave ethyl ferulate. Reduction of ethyl ferulate to coniferyl alcohol was made with DIBAL-H as described by Quideau and Ralph.[22] Apocynol (**10**) was prepared from acetovanillone (commercial grade, Aldrich) as

described by Bailey and Dence.[23] Synthesis and NMR for compounds **11** and **16** see Ref. 17.

3.3. Synthesis of dibenzodioxocin compound 17

3.3.1. Dehydrodiacetovanillone. Acetovanillone (20 g; 120 mmol) and horseradish peroxidase (40 mg) were dissolved in ethanol (200 ml)–water (200 ml). Hydrogen peroxide (8.8 ml; 8 M; 70 mmol) diluted to 60 ml ethanol–water was added slowly to the solution with syringe pump during 6 h 20 min. The mixture was then stirred for an additional 10 h. The precipitate was filtered and washed with water and acetone. The yield of dehydrodiacetovanillone was 55% (10.78 g; 32.7 mmol).

3.3.2. Dehydrodiapocynol (15). Dehydrodiacetovanillone (2 g; 6.1 mmol) was added to the ethanol (30 ml)–water (30 ml) solution. The starting material dissolved after $NaBH_4$ (0.45 g; 12 mmol) was added. The mixture was stirred at room temperature for 6 days and then neutralized with 1N HCl. Water was then added and the whole mixture was extracted with ethyl acetate, dried with $NaSO_4$ and the solvent was evaporated. The crude yield of compound **15** was 1.8 g (88%). The synthesis made according to earlier published method[24] gave poor yield but by using ethanol–water as a solvent instead of 1N sodium hydroxide, the yield was raised and the product was pure according to NMR-spectra. Reaction time was not optimized, a shorter time is probably sufficient.

Compound **15**: δ_H (200 MHz; $CDCl_3$): 1.49 (6H, d, J=6.4 Hz, CH_3), 3.89 (6H, s, OCH_3), 4.83 (2H, q, J=6.4 Hz, C*H*CH_3), 6.35 (arom. OH), 6.89 (2H, d, J=2.2 Hz, arom.), 6.95 (2H, d, J=2.2 Hz, arom.). δ_C (200 MHz; $CDCl_3$): 25.6 (CH_3), 56.7 (OCH_3), 70.8 (CH), 108.2,121.0, 124.8, 138.5, 142.5, 148.0 (arom. C).

3.3.3. Dibenzodioxocin compound (17). Dehydrodiapocynol (0.33 g; 1 mmol) and horseradish peroxidase (20 mg; 529 U/mg) were dissolved in acetone (1 ml)—buffer (4 ml; pH=6). Coniferyl alcohol (0.36 g, 2 mmol) dissolved in acetone (8 ml)—buffer (12 ml; pH=6) and hydrogen peroxide (1.25 ml; 1 mmol) dissolved in 20 ml of buffer (pH=6) were added slowly with the aid of syringe pump to the mixture of HRP and dehydrodiapocynol over 6 h. During the first 10 min the addition was faster and 3 ml of both coniferyl alcohol and hydrogen peroxide were added during that time. The mixture was stirred at room temperature for additional 14 h and then extracted with ethyl acetate, dried with $NaSO_4$ and the solvent evaporated. The whole product was acetylated for purification and analysis. Dibenzodioxocin tetra-acetate was separated by flash chromatography (eluent: ethyl acetate/hexane 9:11) and the yield of *trans*-isomer was 0.13 g (25%). The *cis*-isomer was not detected. For HRMS and NMR analysis further purification was done by preparative HPLC (same eluent as in flash chromatography).

Tetra-acetate of compound **17**: *m/z* 680 (M^+, 6%), 620 (8), 560 (70), 500 (53), 458 (65), 341 (14), 296 (100). (Found: M^+, 680.2451. $C_{36}H_{40}O_{13}$ requires M, 680.2469). δ_H (300 MHz; $CDCl_3$): 1.63 (6H, t, J=6.9 Hz, CH_3), 1.99 (3H, d, J=2.7 Hz, $OCOCH_3$), 2.11–2.17 (6H, m, $OCOCH_3$), 2.34 (3H, s $OCOCH_3$), 3.79 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 4.05–4.21 (2H, m, Hγ'), 4.54, (1H, dd, J=11.9 and 3.5 Hz, Hβ') 4.90 (1H, d, J=9.6 Hz, Hα'), 5.89–6.04 (2H, m, Hα), 6.91–7.09 (7H, arom.). δ_C (300 MHz; $CDCl_3$): 21.4, 21.5, 22.1, 22.6, 23.2 (CH_3, OCO*C*H_3), 56.7 (OCH_3), 64.5 (γ'), 72.8 (α), 73.0 (α), 83.3 (β'), 85.0 (α'), 110.4, 111.1, 111.9, 119.3, 119.8, 120.1, 120.5, 123.3, 133.1, 133.6, 137.6, 138.9, 140.5, 146.8, 147.2, 151.9, 153.1 (arom. C), 169.5, 171.0, 171.4 (C=O). The assignments were done with the aid of HSQC-TOCSY spectra.

3.4. Carbohydrate gel experiment

Carrageenan (0.13 g, Type 1, Commercial Grade, [9000-07-1], Sigma) was added to the buffer (48 ml, pH=3.5) and the mixture was stirred at 50°C untill clear homogeneous 0.25% gel was formed. The solution was cooled to 30°C and apocynol (0.17 g; 1 mmol) in acetone (2 ml) and horse radish peroxidase (10 mg) in buffer (1 ml; pH=3.5) were added. The gel was allowed to cool. Coniferyl alcohol (0.18 g; 1 mmol) and hydrogen peroxide (0.65 ml; 0.5 mmol) in acetone (1 ml)–buffer (19 ml) were added on top of the gel. The gel was quite soft and added solution started to immediately diffuse into the gel. The gel was left in room temperature for 20 h. The whole mixture was extracted with ethyl acetate, the organic layer dried with $NaSO_4$, evaporated and acetylated. The main products were β-*O*-4-, β-5- and β-β-dimers (**4**–**6**) from coniferyl alcohol and two unexpected cross products (**13** and **14**) from coniferyl alcohol and apocynol. Some β-O-4-cross-coupling product **11** was also detected. Both *erythro*- and *threo*-isomers of **14** were formed. Yields were not reproducible, but more compound **13** than compound **14** was formed each time. The yields of the dimers of coniferyl alcohol were similar to those observed in homogeneous solutions.[17]

Triacetate of trimer **13**: *m/z* 634 (M^+, 14%), 472 (2), 440 (13), 424 (13), 338 (33), 324 (20), 168 (37), 150 (100), 135 (32). (Found: M^+, 634.2404. $C_{35}H_{38}O_{11}$ requires M, 634.2414). δ_H (300 MHz; $CDCl_3$): 1.51 (3H, d, J=6.5 Hz, CH_3), 2.09 (3H, s, $OCOCH_3$), 2.34 (3H, s, arom. $OCOCH_3$), 2.36 (3H, s, arom. $OCOCH_3$), 3.78–3.91 (1H, m, Hβ), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 3.99 (1H, ddd, J=1.2, 6.6 and 12.4 Hz, Hγ'_1), 4.11 (1H, ddd, J=1.3, 5.7 and 12.3 Hz, Hγ'_2), 4.33 (1H, dd, J=7.8 and 11.2 Hz, Hγ_1) 4.49 (1H, dd, J=5.4 and 11.2 Hz, Hγ_2), 4.54 (1H, q, J=6.4 Hz, C*H*CH_3), 5.57 (1H, d, J=6.8 Hz, Hα), 6.18 (1H, dt, J=5.6 and 15.9 Hz, Hβ'), 6.53 (1H, d, J=15.9 Hz, Hα'), 6.78–7.11 (8H, arom.). δ_C (300 MHz; $CDCl_3$): 21.4 (OCO*C*H_3), 25.0 (CH_3), 51.2 (β), 56.6 (OCH_3), 66.1 (γ), 69.9 (γ'), 88.7 (α), 125.0 (α'), 132.8 (β'), 110.5–151.8 (arom. C), 169.5, 171.4 (C=O). The assignments were done with the aid of HSQC-TOCSY spectra.

Tetra-acetate of *erythro*-isomer of compound **14**: *m/z* 694 (M^+, 1%), 662 (1), 323 (3), 221 (6), 192 (10), 150 (100), 135 (36). (Found: M^+, 694.2615. $C_{37}H_{42}O_{13}$ requires M, 694.2625). δ_H (200 MHz; $CDCl_3$): 1.51 (3H, d, J=6.4 Hz, CH_3), 2.05 (3H, s, $OCOCH_3$), 2.13 (3H, s, $OCOCH_3$), 2.34 (3H, s, arom. $OCOCH_3$), 2.36 (3H, s, arom. $OCOCH_3$), 3.83

(3H, s, OCH_3), 3.85 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.93–4.16 (2H, m, Hγ′), 4.28 (1H, dd, J=12.1 and 4.1 Hz, $H\gamma_1$) 4.48 (1H, dd, J=12.1 and 5.9 Hz, $H\gamma_2$), 4.53 (1H, q, J=6.4 Hz, C*H*CH_3), 4.64–4.73 (1H, m, Hβ), 6.11 (1H, d, J=5.4 Hz, Hα), 6.20 (1H, dt, J=6.1 and 16.0 Hz, Hβ′) 6.51 (1H, d, J=16.0 Hz, Hα′), 6.77–7.11 (9H, arom.).

Tetra-acetate of *threo*-isomer of compound **14**: *m/z* 694 (M^+, 1%), 647 (1), 323 (2), 252 (5), 192 (10), 150 (100), 135 (37). (Found: M^+, 694.2640. $C_{37}H_{42}O_{13}$ requires M, 694.2625). δ_H (200 MHz; $CDCl_3$): 1.51 (3H, d, J=6.4 Hz, CH_3), 2.04 (3H, s, $OCOCH_3$), 2.09 (3H, s, $OCOCH_3$), 2.34 (3H, s, arom. $OCOCH_3$), 2.36 (3H, s, arom. $OCOCH_3$), 3.85 (6H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90–4.16 (3H, m, Hγ′ and $H\gamma_1$) 4.34 (1H, dd, J=11.8 and 4.2 Hz, $H\gamma_2$), 4.54 (1H, q, J=6.4 Hz, C*H*CH_3), 4.60–4.70 (1H, m, Hβ), 6.15 (1H, d, J=6.2 Hz, Hα), 6.21 (1H, dt, J=6.0 and 16.2 Hz, Hβ′) 6.52 (1H, d, J=16.2 Hz, Hα′), 6.88–7.08 (9H, arom.).

3.5. Dialysis experiment[17,18]

Apocynol (0.17 g; 1 mmol) and horseradish peroxidase (20 mg; 529 U/mg) in acetone (1 ml)–buffer (20 ml; pH=3.5) were placed into the dialysis tube. The tube was placed to the solution of coniferyl alcohol (0.18 g; 1 mmol) and hydrogen peroxide (0.65 ml; 0.5 mmol) in buffer (250 ml; pH=3.5)–acetone (2 ml). The outer solution was stirred by magnetic stirrer and the content of the dialysis tube was mixed using peristaltic pump. The stirring was continued for 17 h at the room temperature. The content of the dialysis tube and the outer solution were extracted separately with ethyl acetate. The extracts were dried with $NaSO_4$, the solvent evaporated and the products were acetylated. Rough quantitation was made. The products were separated by flash chromatography, fractions were weighed and compounds identified by normal phase HPLC and NMR.[17] The outer solution contained 62% of the material and there were only unreacted starting materials, equal amounts of coniferyl alcohol and apocynol. In the dialysis tube there was 200 mg (38%) of the mixture and the main products were dehydrodiapocynol **15** (ca. 15% from the products of the dialysis tube), dioxepin **16** (ca 15%), β-*O*-4-cross-coupling product **11** (ca. 10%); a small amount of dibenzodioxocin **17** (1–2%) was also observed. Some apocynol remained unreacted (25%) and ca. 30% of the content was polymeric material. The polymer fraction was characterized by NMR and it contained mainly β-*O*-4-structural units; no β-5-units were found. Apocynol moieties were also included in the polymer. Dialysis experiment was also done in pH 6.5. In the dialysis tube there was 200 mg (38%) of the material and the main products were dehydrodiapocynol **15** (ca. 10% from the content of dialysis tube), dioxepin **16** (5–10%), β-*O*-4-cross-coupling product **11** (<5%) and dibenzodioxocin **17** (ca 5%). Approximately 10% of the products were polymeric material and ca. 55% was unreacted apocynol. Outside of the tube there were equal amounts of coniferyl alcohol and apocynol and some β-5-dimer from coniferyl alcohol.

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