Synthesis of Lignin Models of \( \beta \)-5 Type

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A \( \beta \)-5 lignin model of the phenylcoumaran type, trans-2-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan, was prepared by acid-catalysed cyclization of 1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol. The cyclization was accomplished by treatment with 0.2 M HCl in dioxane–water (1:1) at 50 °C. The reaction was first order with respect to the substrate \( \left( t_{1/2} \approx 36 \text{ min} \right) \). 1-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol, which is a model compound representative of a second type of lignin structure of \( \beta \)-5 type, was in turn obtained by synthesis starting from \( \alpha \)-vanillin and 3,4-dimethoxyacetophenone. In the first step equimolar amounts of these compounds were treated with alkali to give 1-(3,4-dimethoxyphenyl)-3-(2-hydroxy-3-methoxyphenyl)-2-propen-1-one. Conversion of this compound into its tetrahydropyran-2-yl ether and subsequent epoxidation gave 1-(3,4-dimethoxyphenyl)-3-[3-methoxy-2-(tetrahydro-2-yloxy)phenyl]-2,3-epoxypropane. Acid-catalysed (boron trifluoride) rearrangement of this compound (the tetrahydropyran-2-yl group was removed simultaneously), reduction of the resulting product with sodium borohydride and subsequent chromatographic purification gave a mixture of the erythro and threo forms of 1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol (yield, 57%). The erythro form predominated in the mixture and could be isolated by fractional crystallization. Separation of the diastereomers could be accomplished by ion exchange chromatography.

Dehydrodimethyl alcohol (1) is obtained in moderate yield on oxidation of coniferol alcohol.\(^1\) Catalytic hydrogenation of 1 gives the dihydro derivative 2. This compound has frequently been used as a model compound representative of \( \beta \)-5 structures of the phenylcoumaran type (3) in lignins. Compound 2 can be prepared according to the method described by Freudenberg and Hübner\(^1\) or modifications thereof (see, e.g., Ref. 2). An alternative method for the synthesis of lignin models of this type has been developed by Nakatsuho and Higuchi.\(^3\) The key step in their synthesis is a Claisen reaction. A third synthetic route to models for lignin structures of type 3 proceeds via an acid-catalysed rearrangement of a chalcone epoxide.\(^4\) A modification of this synthetic method involving the use of tetrahydropyran-2-yl as a protective group is described in this paper. The modified method has been applied to the synthesis of the model compound trans-2-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan (11) (Schemes 1 and 2). The crude product was contaminated with traces of cis-2-(3,4-dimethoxyphenyl)-3-hydroxy-methyl-7-methoxy-2,3-dihydrobenzo[b]furan (12). A stero-selective synthesis of this diastereomer is described in Ref. 5. Compound 11 has previously been prepared by methylation of trans-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan.\(^5,6\)
The synthesis of phenylcoumaran models reported by Nakatsubo and Higuchi,\(^1\) as well as the one reported by Brunow and Lundquist,\(^2\) proceeds via 1,2-diaeryl-1,3-propanediols of type 4a. Intermediates of this type are labile and prone to undergo ring-closure. However, it is possible to trap them as acetate derivatives.\(^4\) The 1,2-diaeryl-1,3-propanediol 10 is an intermediate in the synthesis of 11 described in this paper. Compound 10 was found to be comparatively stable and it was possible to isolate both the erythro and threo forms in a pure state. The stability of 10 is probably related to the fact that it belongs to a second type of 1,2-diaeryl-1,3-propanediol, namely 4b. The p-hydroxybenzyl alcohol group in 4a has been replaced by a p-alkoxybenzyl alcohol group in 4b. This might be expected to lower the reactivity. The cyclization reaction of 4a and 4b leading to phenylcoumarans can be blocked by etherification (see, e.g., formulas 4c and 4d).

Besides being an intermediate in the above-mentioned synthesis of 11, compound 10 is an appropriate model compound for lignin structures of type 4. Knowledge of the properties of 10 gained in this work is expected to be useful in studies of the occurrence of structures of type 4 in lignins.

**Synthesis of the erythro (10a) and threo (10b) forms of 1-[(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol.** The synthetic route applied for the synthesis of 10 is shown in Scheme 1. In the first step a chalcone (8) is prepared by alkali-catalysed condensation of 3,4′-dimethoxyacetophenone (6) with o-vanillin (7). In preliminary experiments 10 was prepared using chalcone 14 as an intermediate. This compound was obtained by condensation of 6 with the methoxymethyl ether of o-vanillin (13). Attempts to prepare 13 from o-vanillin by acid-catalysed reaction with dimethoxy methane failed. A dimer of o-vanillin was obtained.\(^5\) The methoxymethyl derivative of o-vanillin (13) was obtained by reaction of 7 with chloromethyl methyl ether in an alkaline medium. Epoxidation of 14 gave 15. BF\(_3\)-catalysed rearrangement of 15 and subsequent reduction of the reaction product with borohydride (cf. Scheme 1) gave 10. However, the yield was rather low owing to formation of rather large amounts of by-products (including acetals of formaldehyde) and the synthetic route to 10 via 14 was abandoned.

In connection with a study of the occurrence of lignin structures of phenylcoumaran type (3), we speculated on the possibility that non-cyclic β-5 structures of type 4 are present in lignins.\(^6\) Experiments were carried out which showed that their number must be rather small. Unambiguous proof of the existence of lignin structures of type 4 has not been achieved so far. It is noteworthy that 5 is formed on oxidation of isoegenol in the presence of glycol.\(^7\) Analogous formation of lignin structures of type 4d during the biosynthesis of lignin from coniferyl alcohol is conceivable. It is also of interest in this context that structural elements of type 4a are present in a series of lignans isolated from *Arctium lappa* (see, e.g., Ref. 8.).
In the succeeding synthetic work methoxymethyl was exchanged for tetrahydropyran-2-yl as a protecting group. Protection of the phenolic group of o-vanillin is not required in the synthesis of chalcone 8 (Scheme 1). Attempts to prepare the tetrahydropyran-2-yl ether of o-vanillin by acid-catalysed reaction with 3,4-dihydro-2H-pyrane failed. Protection of the phenolic group is necessary in the epoxidation step. This was accomplished by converting chalcone 8 into its tetrahydropyran-2-yl ether. For the epoxidation step a method involving phase-transfer catalysis was used. The epoxide 9 was obtained in almost quantitative yield. The product consisted of about equal amounts of two diastereomeric forms of 9. Pure samples of the two isomers (m.p. 128 °C and m.p. 97–98 °C) could be obtained by fractional crystallization from ethanol. Treatment of the epoxide with BF3 resulted in a rearrangement (cf. Refs. 4 and 11) and simultaneous removal of the protecting group. Reduction of the crude product with sodium borohydride gave 10 together with substantial amounts of other compounds. Essentially pure 10 (yield 57%) could be separated from the reaction mixture by column chromatography. The product consisted of a mixture of the erthro (10a) and threo (10b) forms. The erthro form (10a) was the predominant constituent and could be obtained in crystalline form (m.p. 123–124 °C). The threo form (10b) could be isolated by ion exchange chromatography on an anion exchanger using borate solution as the eluent; the erthro form is eluted before the threo form. The steric assignments of the diastereomers of 10 are based on the elution order from the ion exchanger (cf. Ref. 12). 1H NMR and 13C NMR spectral comparisons of 10a and 10b with analogous stereoisomers of lignin models of type 4c as well as lignin models of β-1 type (see, e.g., Ref. 11) are also of interest in this context.

Conversion of 10 into trans-2-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2, 3-dihydrobenzo[b]furane (11). In preliminary experiments the reaction mixtures from borohydride reduction of the rearrangement product (Scheme 1) were not subjected to work-up but acidified [composition of the reaction medium: 1 M HCl in dioxane–water (1:2)] and set aside overnight. Ring-closure of 10 with formation of 11 occurred (cf. Scheme 2) but it turned out to be difficult to isolate 11 in a completely pure state (in spite of chromatographic purification). Therefore 10 was separated from the borohydride-reduced product and subsequently treated with acid to accomplish the cyclization to 11 (Scheme 2). This procedure yielded 11 contaminated with the cis isomer (12) (≈2%). Purification by column chromatography gave 11 containing 1% of the cis isomer. Suitable conditions for the conversion of 10 into 11 were determined by studies of the kinetics of the cyclization reaction. In the cyclization studies 10a was treated with 0.2 M HCl in dioxane–water (1:1) at 50 °C. It was found that the reaction was first order with respect to the substrate (t1/2 = 36 min). In experiments on a preparative scale 10 was treated with the acid reagent at 50 °C for 7 h. Knowledge of the tendency of 10 to undergo cyclization is also of interest in connection with investigations of the occurrence of lignin structures of type 4 (see the introductory section of this paper).

**Experimental**

Silica gel (Grace, Matrex LC 60 Å/35–70 µm) was used for flash chromatography. Reagent grade dioxane was distilled over Na. 1H NMR spectra were recorded at 400 MHz and 13C NMR spectra at 100.6 MHz with a Varian XL-400 (VXR-500) instrument. Measurement temperature was ca. 20 °C and deuteriochloroform was used as the solvent [internal reference, (CH3)4Si]. Thin layer chromatography (TLC) was performed on silica gel plates (Merck, Kieselgel 60 F254) with toluene–dioxane–acetic acid (90:25:4) as the eluent. Rf values: 10a, 0.14; 10b, 0.14; 11, 0.31; 12, 0.34. Spots were made visible with UV light and by spraying with formalin–H2SO4 (1:9) and subsequent heating.

3-Methoxy-2-methoxymethoxybenzaldehyde (13) was prepared from o-vanillin and chloromethyl methyl ether according to a method used for the preparation of
the methoxymethyl ether of vanillin. M.p. 54–55 °C (from benzene). 1H NMR spectrum: δ 3.57 (3 H, s, CH3-O-C=O), 3.89 (3 H, s, OCH3), 5.24 (2 H, s, O-CH2-O), 7.1–7.5 (3 H, m, H-Ar), 10.48 (1 H, s, CHO).

1-(3,4-Dimethoxyphenyl)-3-(3-methoxy-2-methoxymethoxyphenyl)-2-propen-1-one (14) was prepared from 3',4'-dimethylocacetophenone (6) and 3-methoxy-2-methoxymethoxybenzaldehyde (13) following a procedure used for the preparation of 1,3-bis(3,4-dimethoxyphenyl)-2-propen-1-one. M.p. 82–83 °C (from ethanol). 1H NMR: δ 3.60 (3 H, s, CH3-O-C=O), 3.87 (3 H, s, OCH3), 3.97 (6 H, s, OCH3), 5.17 (2 H, s, O-CH2-O), 7.60 (1 H, d, J=15.6 Hz, vinyl H), 8.21 (1 H, d, J=15.6 Hz, vinyl H), 6.9–7.8 (6 H, m, H-Ar).

1-(3,4-Dimethoxyphenyl)-3-(3-methoxy-2-methoxymethoxyphenyl)-2-propen-1-one (15) was prepared by epoxidation of 14. M.p. 108–109 °C (from ethanol). 1H NMR: δ 3.30 (3 H, s, CH3-O-C=O), 3.87 (3 H, s, OCH3), 3.95 (3 H, s, OCH3), 3.96 (3 H, s, OCH3), 4.21 (1 H, d, J=2.0 Hz, >CH-O), 4.49 (1 H, d, J=2.0 Hz, >CH-O), 5.08 (2 H, AB spectrum, δa=5.09, δb=5.08, J=6.2 Hz, O-CH2-O), 6.8–7.8 (6 H, m, H-Ar).

1-(3,4-Dimethoxyphenyl)-3-(2-hydroxy-3-methoxyphenyl)-2-propen-1-one (8). Solutions of 3',4'-dimethylocacetophenone (6) (10.9 g, 60 mmol) in ethanol (240 ml) and KOH (120 g) in water (120 ml) were combined. A solution of o-vanillin (9.13 g, 60 mmol) in ethanol (240 ml) was slowly added to the mixture (magnetic stirring). The reaction mixture was stored at room temperature for 24 h and then acidified with 4 M hydrochloric acid. The yellow precipitate that formed was filtered off and washed with water. The dried product weighed 11.8 g (m.p. 139–140 °C) and consisted of pure 8 (1H NMR). Recrystallization from ethanol did not raise the melting point. Somewhat higher yields (≈75%) were obtained on prolonged reaction time (3 days). 1H NMR spectrum: δ 3.94 (3 H, s, OCH3), 3.97 (3 H, s, OCH3), 3.98 (3 H, s, OCH3), 6.28 (1 H, s, OH), 7.77 (1 H, d, J=15.7 Hz, vinyl H), 8.02 (1 H, d, J=15.7 Hz, vinyl H), 6.80–7.73 (6 H, m, H-Ar).

1-(3,4-Dimethoxyphenyl)-3-[3-methoxy-2-(tetrahydropryan-2-yl)oxyphenyl]-2-propen-1-one (3). 3,4-Dihydro-2H-pyranyl (21 g, 250 mmol) and pyridinium toluene-p-sulfonate (1.25 g, 5 mmol) were added to the solution of 1-(3,4-dimethoxyphenyl)-3-(2-hydroxy-3-methoxyphenyl)-2-propen-1-one (8) (15.7 g, 50 mmol) in dry dichloromethane (50 ml). After 20 h the reaction mixture was diluted with ether (250 ml) and washed with 0.1 M NaOH (5 × 100 ml) and 0.05 M NaOH (3 × 100 ml). Drying of the solution was accomplished by extraction with brine and storage over Na2SO4. Removal of the solvents by film evaporation gave an oil weighing 14.1 g. The product consisted of the tetrahydropryan-2-yl ether of 8 contaminated with traces of other compounds (1H NMR). Yield: 71%. 1H NMR spectrum: δ 1.6–2.1 [6 H, m, C-(CH3)2-C], 3.58 (1 H, m, C-CH2-O), 3.87 (3 H, s, OCH3), 3.97 (6 H, s, OCH3), 4.12 (1 H, m, C-CH2-O), 5.43 (1 H, s, J=3.0 Hz, O-CH-O), 7.54 (1 H, d, J=16.0 Hz, vinyl H), 8.32 (1 H, d, J=16.0 Hz, vinyl H), 6.9–7.8 (6 H, m, H-Ar).

1-(3,4-Dimethoxyphenyl)-3-[3-methoxy-2-(tetracydropyranyl-2-yloxy)phenyl]-2,3-epoxypropanone (9). The above described tetrahydropryan-2-yl derivative (14.0 g) was converted into the chalcone epoxide 9 by oxidation with hydrogen peroxide according to a method involving phase-transfer catalysis.4,10 The crude product (14.0 g) consisted of essentially pure 9 (a mixture of nearly equal amounts of two diastereomeric forms, 9a and 9b) (1H NMR). In separate experiments the two diastereomeric forms were isolated by fractional crystallization. A fraction consisting of 9a contaminated with a small amount of 9b was obtained from ethanol. Recrystallization gave pure 9a (m.p. 128 °C). A second crop of crystals was obtained from the first mother liquor; it consisted of 9b contaminated with 9a. Repeated recrystallizations (ethanol) gave 9b of m.p. 97–98 °C. 1H NMR spectrum of 9a: δ 1.1–1.9 [6 H, m, C-(CH3)2-C], 3.07 (1 H, m, C-CH2-O), 3.50 (1 H, m, C-CH2-O), 3.85 (3 H, s, OCH3), 3.941 (3 H, s, OCH3), 3.948 (3 H, s, OCH3), 4.20 (1 H, d, J=1.8 Hz, >CH-O), 4.59 (1 H, d, J=1.8 Hz, >CH-O), 5.18 (1 H, s, J=3.6 Hz, O-CH2-O), 5.97 (1 H, s, H-Ar), 7.11 (1 H, t, J=8.1 Hz, H-Ar), 7.59 (1 H, d, J=2.0 Hz, H-Ar), 7.69 (1 H, dd, J=2.0 and 8.4 Hz, H-Ar). 1H NMR spectrum of 9b: δ 1.3–1.9 [6 H, m, C-(CH3)2-C], 3.44 (1 H, m, C-CH2-O), 3.86 (1 H, m, C-CH2-O), 3.87 (3 H, s, OCH3), 3.948 (3 H, s, OCH3), 3.955 (3 H, s, OCH3), 4.13 (1 H, d, J=2.0 Hz, >CH-O), 4.58 (1 H, d, J=2.0 Hz, >CH-O), 5.23 (1 H, dd, J=2.8 and 4.4 Hz, O-CH2-O), 6.88–6.95 (3 H, m, H-Ar), 7.11 (1 H, t, J=8.0 Hz, H-Ar), 7.60 (1 H, d, J=2.0 Hz, H-Ar), 7.73 (1 H, dd, J=2.0 and 8.4 Hz, H-Ar).

1-(3,4-Dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol (10). Epoxide 9 (8.29 g, 20 mmol) was dissolved in anhydrous ether (500 ml) and boron trifluoride diethyl ether (28.4 g, 200 mmol) was added to the solution. After 25 min at room temperature (magnetic stirring) the reaction mixture was washed with water (200+3×50 ml) and dried over Na2SO4. Evaporation of the solvents gave an oil weighing 9 g. The oily product was dissolved in dioxane-water (1:1) (200 ml) and NaBH4 (3.02 g, 80 mmol) was added in portions (magnetic stirring). After 24 h the reaction mixture was acidified (1 M HCl) and extracted with chloroform (100+2×50 ml). The extract was dried (Na2SO4) and solvents were removed by film evaporation. The residual light yellow oil weighed 8.4 g. Purification of the crude reaction product by column chromatography [SiO2, 150 g; eluents, dichloromethane-ethyl acetate (10:1, 5:1, 2:1 and 1:1)] gave 3.85 g of an oil consisting of essentially pure 10 (yield, 57%). Both diastereomeric
forms were present in the product (1H NMR). According to 1H NMR examinations the erythro form (10a)/threo form (10b) ratio was 4:1. Crystallization from chloroform–ether gave a fraction consisting of the erythro form (3.1 g) contaminated with minor amounts of the threo form (ca. 5%). Recrystallization lowered the amount of the threo form and 2.7 g crystals of m.p. 122–123 °C were obtained. A final recrystallization from chloroform gave the pure erythro form (m.p. 123–124 °C). The threo form (liquid) could be recovered from a mixture of the diasteromers by ion exchange chromatography 12 on an anion exchanger using borate as the eluent. 1H NMR spectrum of the triacetate of 10a: δ 1.92 (3 H, s, CH3CO), 1.94 (3 H, s, CH2CO), 2.36 (3 H, s, CH3CO), 3.78 (3 H, s, OCH3), 3.79 (3 H, s, OCH3), 3.80 (3 H, s, OCH3), 4.04 (1 H, dd, J = 7.5 and 11.2 Hz, Hγ), 4.28 (1 H, dd, J = 5.7 and 11.2 Hz, Hδ), 6.01 (1 H, d, J = 7.9 Hz, Hβ), 6.65 (1 H, d, J = 1.8 Hz, Hδ), 6.78–6.90 (4 H, m, H-Ar), 7.14 (1 H, t, J = 8.1 Hz, H-Ar). 13C NMR spectrum of the triacetate of 10a: δ 20.5 (CH3CO), 20.8 (CH3CO), 21.0 (CH3CO), 42.4 (Cβ), 55.77 (OCH3), 55.84 (OCH3), 55.91 (OCH3), 63.8 (Cγ), 75.0 (Cα), 110–152 [110.4, 110.8 (2 C), 119.5, 119.8, 126.0, 130.2, 131.3, 139.0, 148.6, 148.9, 151.1, aromatic C], 168.5 (CO), 169.8 (CO), 170.8 (CO). 1H NMR spectrum of the triacetate of 10b: δ 1.99 (3 H, s, CH3CO), 2.09 (3 H, s, CH3CO), 2.34 (3 H, s, CH3CO), 3.76 (3 H, s, OCH3), 3.77 (3 H, s, OCH3), 3.81 (3 H, s, OCH3), 3.81 (1 H, m, Hβ), 4.35 (1 H, dd, J = 5.6 and 11.2 Hz, Hγ), 4.38 (1 H, dd, J = 7.0 and 11.2 Hz, Hδ), 6.06 (1 H, d, J = 8.8 Hz, Hβ), 6.6–6.8 (5 H, m, H-Ar), 7.04 (1 H, t, J = 8.1 Hz, H-Ar). 13C NMR spectrum of the triacetate of 10b: δ 20.5 (CH3CO), 20.9 (CH3CO), 21.2 (CH3CO), 42.6 (Cβ), 55.69 (OCH3), 55.71 (OCH3), 55.79 (OCH3), 64.4 (Cγ), 75.4 (Cα), 110–152 [110.4, 110.5, 110.8, 119.9, 120.5, 126.0, 130.2, 131.2, 138.6, 148.4, 148.7, 151.1, aromatic C], 168.2 (CO), 170.0 (CO), 170.9 (CO).

Reaction rate of the acid-catalysed cyclization of erythro-1-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzofuran (11) is 10-fold greater than that of the threo form. 11a The rate-determining step is the isomerization of the threo form to the erythro form. 11b The isomerization is a fast equilibrium process.

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References


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trans-2-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzofuran (11) was obtained by treating 0.2 M HCl in dioxane–water (1:1) (100 ml) at 50 °C for 7 h. After cooling and addition of NaHCO3 (1.51 g) (magnetic stirring), the reaction mixture was extracted with chloroform (100 + 3 × 30 ml). The extract was dried (Na2SO4) and solvents were removed by film evaporation. The residual product (0.94 g) consisted of 11a as a mixture of the cis isomer (12a) (1H NMR). Purification by column chromatography [40 g SiO2; eluent, dichloromethane–ethanol (10:1) ] gave fractions of 11a weighing 0.13 g (contaminated with 12a, 8%), 0.71 g (contaminated with 12a, 1%) and 0.07 g (no cis isomer present). 13C NMR of the acetate of 11: δ 20.8 (CH3CO), 50.4 (Cβ), 55.88 (OCH3), 55.90 (OCH3), 55.94 (OCH3), 65.4 (Cγ), 88.2 (Cα), 109–150 [109.2, 110.9, 112.1, 116.5, 118.8, 121.5, 127.4, 133.0, 144.5, 147.9, 149.04, 149.09, aromatic C], 170.7 (CO). Additional NMR spectral data for 11 and NMR spectral data for 12 are reported elsewhere. 5