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Synthesis of Lignin Models of β-5 Type

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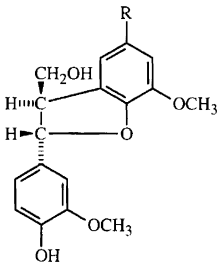
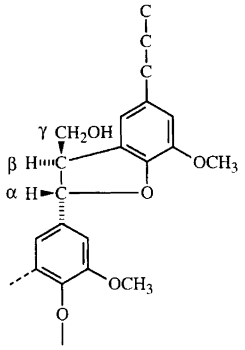
A β-5 lignin model of the phenylcoumaran type, *trans*-2-(3,4-dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[*b*]furan, was prepared by acid-catalysed cyclization of 1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol. The cyclization was accomplished by treatment with 0.2 M HCl in dioxane–water (1:1) at 50 °C. The reaction was first order with respect to the substrate ($\tau_{1/2}$ 36 min). 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 β-5 type, was in turn obtained by synthesis starting from *o*-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-(tetrahydropyran-2-yloxy)phenyl]-2,3-epoxypropanone. 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.

Dehydrodiconiferyl alcohol (**1**) is obtained in moderate yield on oxidation of coniferyl alcohol.[1] Catalytic hydrogenation of **1** gives the dihydro derivative **2**. This compound has frequently been used as a model compound representative of β-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 Nakatsubo 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-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[*b*]furan (**12**). A stereoselective 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]

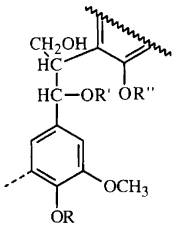


1 R= CH=CH-CH_2OH
2 R= $CH_2CH_2CH_2OH$



3

The synthesis of phenylcoumaran models reported by Nakatsubo and Higuchi,[3] as well as the one reported by Brunow and Lundquist,[4] proceeds via 1,2-diaryl-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-diaryl-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-diaryl-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**).



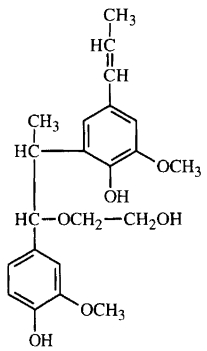
4a R=H, R'=H, R''=H

4b R=C, R'=H, R''=H

4c R=H, R'=H, R''=C

4d R=H, R'=C, R''=H

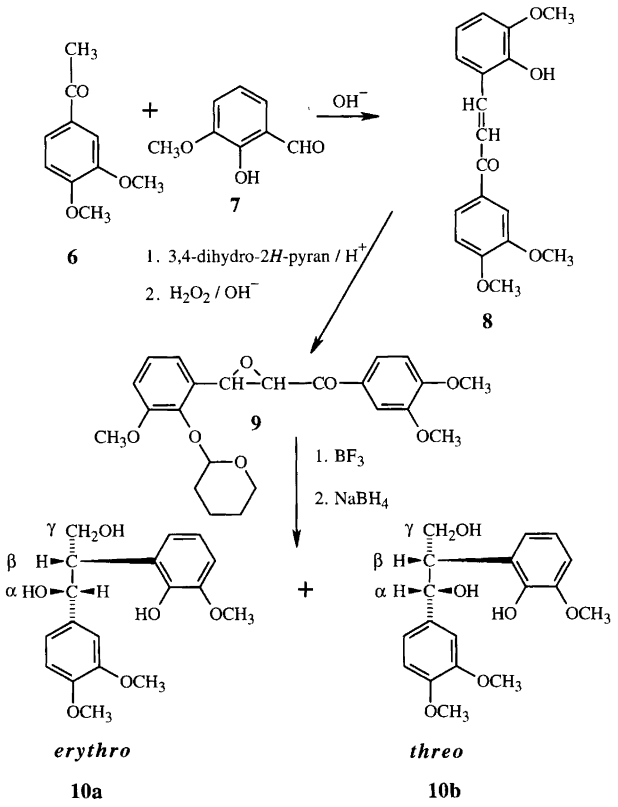
In connection with a study of the occurrence of lignin structures of phenylcoumaran type (**3**), we speculated on the possibility that non-cyclic β-5 structures of type **4** are present in lignins.[2] Experiments were carried out which showed that their number must be rather small. Unambiguous proof 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 isoeugenol 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.).



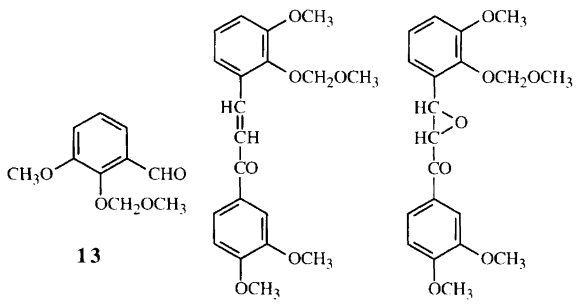
5

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 dimethoxymethane failed. A dimer of *o*-vanillin was obtained.[9] 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.



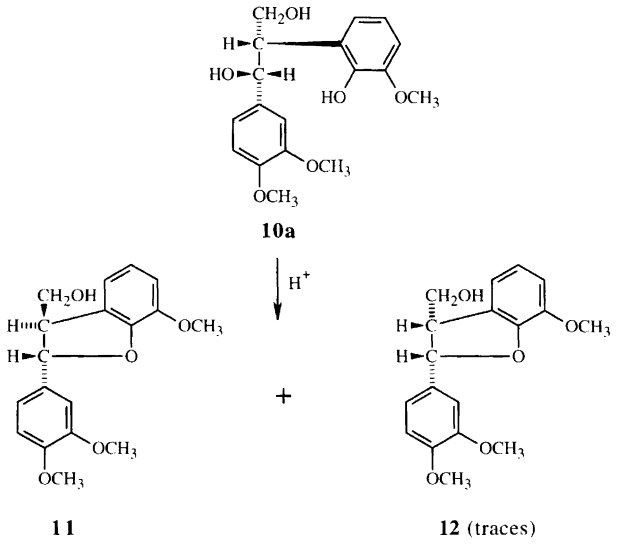
Scheme 1.



13 14 15

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-2*H*-pyran 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.[4,10] 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 BF_3 resulted in a rearrangement (cf. Refs. 4 and 11) and simultaneous removal of the protecting group. Reduction of the crude reaction 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 *erythro* (**10a**) and *threo* (**10b**) forms. The *erythro* 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[12] on an anion exchanger using borate solution as the eluent; the *erythro* 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). ^{1}H NMR and ^{13}C NMR spectral comparisons of **10a** and **10b** with analogous stereoisomers of lignin models of type **4c**[13] 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]furan (**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**



10a → (H$^+$) → **11** + **12** (traces)

Scheme 2.

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 ($\tau_{1/2}$ = 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. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100.6 MHz with a Varian XL-400 (VXR-5000) instrument. Measurement temperature was ca. 20 °C and deuteriochloroform was used as the solvent [internal reference, $(CH_3)_4Si$]. Thin layer chromatography (TLC) was performed on silica gel plates (Merck, Kieselgel 60 F_{254}) with toluene–dioxane–acetic acid (90:25:4) as the eluent. R_f 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–H_2SO_4 (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.[14] M.p. 54–55 °C (from benzene). ^{1}H NMR spectrum: δ 3.57 (3 H, s, CH_3O–C–O), 3.89 (3 H, s, OCH_3), 5.24 (2 H, s, O–CH_2–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′-dimethoxyacetophenone (**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.[15] M.p. 82–83 °C (from ethanol). ^{1}H NMR: δ 3.60 (3 H, s, CH_3O–C–O), 3.87 (3 H, s, OCH_3), 3.97 (6 H, s, OCH_3), 5.17 (2 H, s, O–CH_2–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)-2,3-epoxy-1-propanone (**15**) was prepared by epoxidation[4] of **14**. M.p. 108–109 °C (from ethanol). ^{1}H NMR: δ 3.30 (3 H, s, CH_3O–C–O), 3.87 (3 H, s, OCH_3), 3.95 (3 H, s, OCH_3), 3.96 (3 H, s, OCH_3), 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, δ_A=5.09, δ_B=5.08, J=6.2 Hz, O–CH_2–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′-dimethoxyacetophenone (**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** (^{1}H NMR). Recrystallization from ethanol did not raise the melting point. Somewhat higher yields (≈75%) were obtained on prolonged reaction time (3 days). ^{1}H NMR spectrum: δ 3.94 (3 H, s, OCH_3), 3.97 (3 H, s, OCH_3), 3.98 (3 H, s, OCH_3), 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-(tetrahydropyran-2-yloxy)phenyl]-2-propen-1-one. 3,4-Dihydro-2*H*-pyran (21 g, 250 mmol) and pyridinium toluene-*p*-sulfonate (1.25 g, 5 mmol) were added to a 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 Na_2SO_4. Removal of the solvents by film evaporation gave an oil weighing 14.1 g. The product consisted of the tetrahydropyran-2-yl ether of **8** contaminated with traces of other compounds (^{1}H NMR). Yield: 71%. ^{1}H NMR spectrum: δ 1.6–2.1 [6 H, m, C–$(CH_2)_3$–C], ≈3.58 (1 H, m, C–CH_2–O), 3.87 (3 H, s, OCH_3), 3.97 (6 H, s, OCH_3), ≈4.12 (1 H, m, C–CH_2–O), 5.43 (1 H, ≈t, 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-(tetrahydropyran-2-yloxy)phenyl]-2,3-epoxypropanone (**9**). The above described tetrahydropyran-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 diasteromeric forms, **9a** and **9b**) (^{1}H 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. ^{1}H NMR spectrum of **9a**: δ 1.1–1.9 [6 H, m, C–$(CH_2)_3$–C], 3.07 (1 H, m, C–CH_2–O), 3.50 (1 H, m, C–CH_2–O), 3.85 (3 H, s, OCH_3), 3.941 (3 H, s, OCH_3), 3.948 (3 H, s, OCH_3), 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, ≈t, J=3.6 Hz, O–CH–O), 6.85–6.93 (3 H, m, 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). ^{1}H NMR spectrum of **9b**: δ 1.3–1.9 [6 H, m, C–$(CH_2)_3$–C], 3.44 (1 H, m, C–CH_2–O), 3.86 (1 H, m, C–CH_2–O), 3.87 (3 H, s, OCH_3), 3.948 (3 H, s, OCH_3), 3.955 (3 H, s, OCH_3), 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–CH–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 Na_2SO_4. Evaporation of the solvents gave an oil weighing 9 g. The oily product was dissolved in dioxane–water (1:1) (200 ml) and $NaBH_4$ (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 (Na_2SO_4) 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 [SiO_2, 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 (^{1}H NMR). According to ^{1}H 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 separated from a mixture of the diastereomers by ion exchange chromatography[12] on an anion exchanger using borate as the eluent. ^{1}H NMR spectrum of the triacetate of **10a**: δ 1.92 (3 H, s, CH_3CO), 1.94 (3 H, s, CH_3CO), 2.36 (3 H, s, CH_3CO), 3.78 (3 H, s, OCH_3), ≈3.78 (1 H, m, Hβ), 3.82 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 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, Hγ), 6.01 (1 H, d, J=7.9 Hz, Hα), 6.65 (1 H, d, J=1.8 Hz, H–Ar), 6.78–6.90 (4 H, m, H–Ar), 7.14 (1 H, t, J=8.1 Hz, H–Ar). ^{13}C NMR spectrum of the triacetate of **10a**: δ 20.5 (CH_3CO), 20.8 (CH_3CO), 21.0 (CH_3CO), 42.4 (Cβ), 55.77 (OCH_3), 55.84 (OCH_3), 55.91 (OCH_3), 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). ^{1}H NMR spectrum of the triacetate of **10b**: δ 1.99 (3 H, s, CH_3CO), 2.09 (3 H, s, CH_3CO), 2.34 (3 H, s, CH_3CO), 3.76 (3 H, s, OCH_3), 3.77 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 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, Hγ), 6.06 (1 H, d, J=8.8 Hz, Hα), 6.6–6.8 (5 H, m, H-Ar), 7.04 (1 H, t, J=8.1 Hz, H–Ar). ^{13}C NMR spectrum of the triacetate of **10b**: δ 20.5 (CH_3CO), 20.9 (CH_3CO), 21.2 (CH_3CO), 42.6 (Cβ), 55.69 (OCH_3), 55.71 (OCH_3), 55.79 (OCH_3), 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).

trans-*2-(3,4-Dimethoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo*[b]*furan* (**11**). Compound **10** (1.0 g) was treated with 0.2 M HCl in dioxane–water (1:1) (100 ml) at 50 °C for 7 h. After cooling and addition of $NaHCO_3$ (1.51 g) (magnetic stirring), the reaction mixture was extracted with chloroform (100 + 3 × 30 ml). The extract was dried (Na_2SO_4) and solvents were removed by film evaporation. The residual product (0.94 g) consisted of **11** containing ≈2% of the *cis* isomer (**12**) (^{1}H NMR). Purification by column chromatography [40 g SiO_2; eluent, dichloromethane–ethyl acetate (10:1)] gave fractions of **11** weighing 0.13 g (contaminated with **12**, 8%), 0.71 g (contaminated with **12**, 1%) and 0.07 g (no *cis* isomer present). ^{13}C NMR of the acetate of **11**: δ 20.8 (CH_3CO), 50.4 (Cβ), 55.88 (OCH_3), 55.90 (OCH_3), 55.94 (OCH_3), 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]

Reaction rate of the acid-catalysed cyclization of erythro-*1-(3,4-dimethoxyphenyl)-2-(2-hydroxy-3-methoxyphenyl)-1,3-propanediol* (**10a**). Compound **10a** (267.5 mg, 0.8 mmol) was dissolved in 80 ml 0.2 M HCl in dioxane–water (1:1) at 50 ± 0.1 °C (thermostatted water-bath). After different periods of time (0.25, 0.5, 1, 1.5, 2, 3, 4 and 6 h) a 10 ml sample was taken from the reaction mixture and analysed for **10**. The acidity of the sample was reduced by addition of 0.4 M $NaHCO_3$ solution (4.5 ml). The resulting mixture was extracted with chloroform (10 ml + 3 × 5 ml). A solution of hexamethylbenzene (internal standard) in toluene (0.6 ml, 5.003 mg ml^{-1}) was injected into the extract and after drying (Na_2SO_4) the solvents were removed by film evaporation. The amount of **10** in the residue was determined by ^{1}H NMR spectrometry (cf. Ref. 16). The cyclization reaction was of the first order with respect to the substrate ($\tau_{1/2}$ 35.6 min, R^2=0.996). Traces of the *threo* form **10b** were present in the reaction mixtures showing that isomerization occurred to some extent.

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