

Synthesis of Lignin Model Compounds of the Arylglycerol β -Syringyl Ether Type

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Lignin model compounds of the arylglycerol β -syringyl ether type have been prepared by the reaction of aromatic aldehydes with the α -lithiated carboxylate of (2,6-dimethoxyphenoxy)acetic acid and subsequent reduction of the 3-aryl-2-(2,6-dimethoxyphenoxy)-3-hydroxypropanoic acids formed.

Syntheses of lignin model compounds of the arylglycerol β -aryl ether type involving α -lithiated carboxylic acid intermediates have been published.^{1,2} This paper describes further developments of this synthetic method and its application for the preparation of some lignin model compounds of the arylglycerol β -syringyl ether type, namely the *erythro* and *threo* forms of **5a**, **5b** and **5c**.

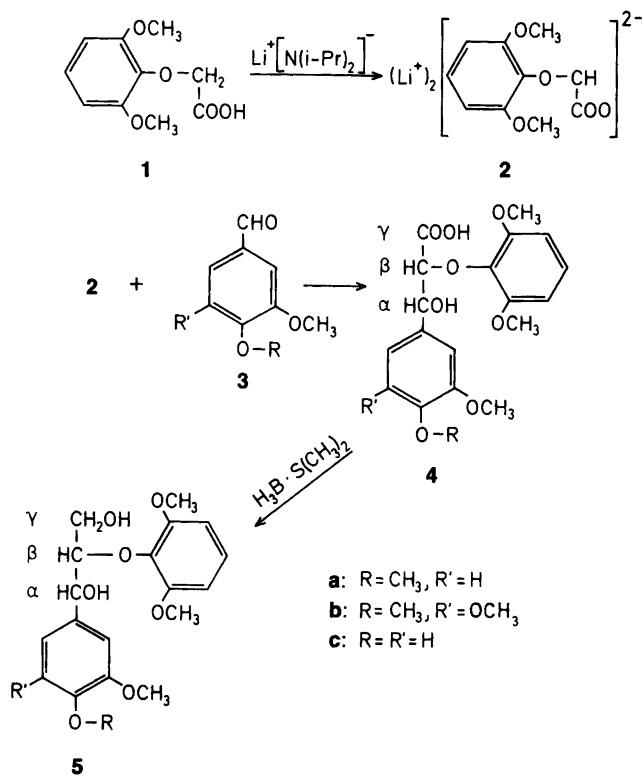
The structure and stereochemistry of the diastereomers of **5a** have been elucidated in a previous study.³ We have prepared these compounds on a preparative scale; the synthetic route shown in Scheme 1 was followed. In the first step the α -lithiated carboxylic acid **2** was prepared (Scheme 1). This intermediate was reacted with veratraldehyde (**3a**) yielding a product consisting primarily of a mixture of about equal amounts of the diastereomers of **4a** (yield, 54%), Acid **4a** was converted to **5a** by reduction with borane–dimethyl sulfide complex. Purification was accomplished by flash chromatography on silica gel. The *erythro* and *threo* forms were separated by ion exchange chromatography on an anion exchanger, using a borate solution as eluent. The *threo* isomer crystallized (m.p. 110–112 °C from ethyl acetate) while the *erythro* isomer was obtained as an oil.

It was possible to separate the diastereomers of the intermediate acid **4a** by column chromatography; the *threo* form was obtained in crystalline

form (m.p. 141–143 °C) and its crystal structure was determined.³ This, together with the determination of the crystal structure of a second synthetic intermediate,³ provided a basis for the unambiguous assignment of the *erythro* and *threo* forms of **5a**.

The synthetic method described above was also used for the preparation of the *threo* and *erythro* forms of **5b**. The stereochemical assignments for these compounds could be made on the basis of ¹H NMR spectral comparisons with the diastereomers of **5a** and *erythro*-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-hydroxy-methyl-2,6-dimethoxyphenoxy)-1,3-propanediol⁴ (¹H NMR data for the acetate derivatives of these compounds are given in Ref. 3); the crystal structure of the latter compound has recently been determined (Fig. 1 and Ref. 5).

In earlier syntheses of arylglycerol β -aryl ethers via α -lithiated carboxylic acid intermediates the procedure described by Moersch and Burkett⁶ was adapted. In this work we have used milder conditions during the lithiation step (30 min, 35 °C; cf. Creger⁷), which resulted in somewhat higher yields and also in reduction of the amount of a contaminant invariably found in the reaction product. The contaminant could be isolated from the crude product of **4a** and was identified as acid **6**. Evidently, a partial demethylation occurred during the lithiation and the demethylated/ α -lithiated product reacted in the



Scheme 1.

following step with veratraldehyde to give **6**. Syntheses of phenolic β -ethers via α -lithiated intermediates using a benzyl protective group have been performed.² We have now shown that protective groups are not required in such syntheses (cf. also the reaction route suggested above for the formation of the contaminant **6**). Thus, reaction of the lithium salt of vanillin (**3c**) with **2** gave a mixture of similar amounts of the diastereomers of acid **4c**; the yield (30%) was lower than that obtained in analogous syntheses with protective group. The *threo* form could be obtained in crystalline form (m.p. 163–166 °C). Reduction of the diastereomers of **4c** gave the *erythro* and *threo* forms of **5c**. Only one report which describes the synthesis of phenolic arylglycerol β -aryl ethers without the use of protective groups has been published previously.⁸

To summarize, our studies show that arylglycerol β -guaiacyl ethers^{1,2} as well as arylglycerol β -syringyl ethers can be synthesized via α -lithiated intermediates. This suggests that the current synthetic route has general applicability for the syn-

thesis of lignin model compounds of the β -aryl ether type.

Experimental

Tetrahydrofuran (THF) was freshly distilled over sodium. Silica gel for flash chromatography was Merck Kieselgel 60 (230–400 mesh).

Mass spectra were recorded on a VG Analytical ZAB/HF instrument.

NMR spectra. ¹H NMR spectra were recorded at 270 MHz with a Bruker WH270 instrument (temperature ca. 300 K), unless otherwise specified. ¹³C NMR spectra were recorded at 100.6 MHz with a Varian XL-400 instrument. Deuteriochloroform was used as solvent (internal reference: TMS).

Thin layer chromatography (TLC) was performed on silica gel plates (Merck, Kieselgel 60 F₂₅₄) with toluene/dioxane/acetic acid (90:25:4) as

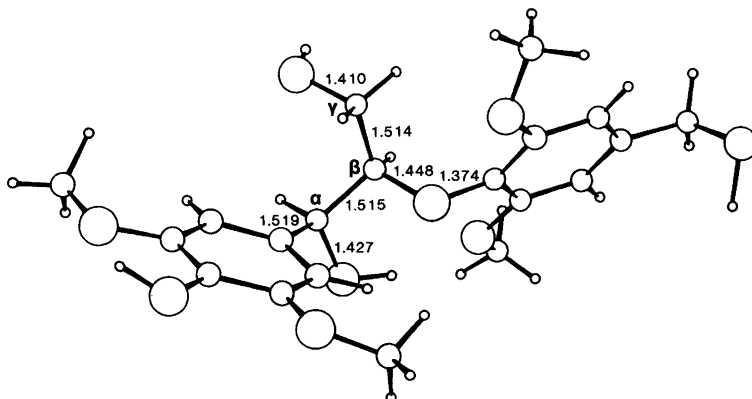


Fig. 1. Perspective drawing of the molecule *erythro*-3-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4-hydroxymethyl-2,6-dimethoxyphenoxy)-1,3-propanediol. The torsion angle $H\alpha-C-C-H\beta$ is -50° (large circles represent oxygen atoms, medium circles carbon atoms and small circles hydrogen atoms).

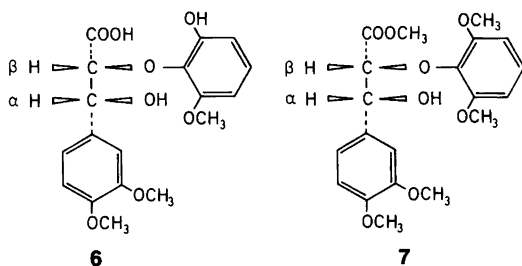
eluent. Spots were made visible with UV light and by spraying with formalin/ H_2SO_4 (1:9) with subsequent heating.

R_f values: **4c**(*threo*), 0.07; **6**, 0.08; **4c**(*erythro*), 0.08; **4a**(*threo*), 0.09; **4a**(*erythro*), 0.10; **1**, 0.16; **5c**(*erythro*), 0.22; **5c**(*threo*), 0.23; **5a**(*erythro*), 0.24; **5b**(*erythro*), 0.26; **5a**(*threo*), 0.27; **5b**(*threo*), 0.28.

(2,6-Dimethoxyphenoxyacetic) acid (**1**). 2,6-Dimethoxyphenol (7.7 g, 50 mmol), chloroacetic acid (4.7 g, 50 mmol), NaOH (4.0 g, 100 mmol) and 30 ml of water were heated under reflux for 7 h. Chloroacetic acid (2.35 g) and NaOH (2.0 g) dissolved in a small amount of water were added to the reaction mixture, and reflux was continued for a further 7 h period. The reaction mixture was acidified (pH 2) with hydrochloric acid and extracted with ether. The combined ether layers were extracted with 8% aqueous $NaHCO_3$. The

extract was acidified and extracted with ether. The ether extract was dried over Na_2SO_4 and the solvent removed by film evaporation. Crystallization of the residue from water gave 8.8 g of product melting at $79-80^\circ C$ (yield, 83%). 1H NMR: δ 3.91 (6H, s; OCH_3), 4.61 (2H, s; CH_2), 6.62 (2H, d, $J = 8.5$ Hz) and 7.07 (1H, t, $J = 8.5$ Hz) (aromatic protons).

Preparation of 2-(2,6-Dimethoxyphenoxy)-3-(3,4-dimethoxyphenyl)-3-hydroxypropanoic acid (**4a**), using an α -lithiated carboxylic acid intermediate. Butyllithium in hexane (4.0 ml of 10.4 M solution, 42 mmol; similar results were obtained with 1.6 M solution) was injected with a syringe into a solution of diisopropylamine (4.0 g, 40 mmol) in 60 ml of THF at $0^\circ C$ (argon atmosphere). The mixture was stirred magnetically at $0^\circ C$ for 10 min, whereupon (2,6-dimethoxyphenoxy)acetic acid (4.24 g, 20 mmol) in THF (15 ml) was added. To achieve α -lithiation of the carboxylic acid, the mixture was kept at $35^\circ C$ for 30 min (magnetic stirring). After cooling to $0^\circ C$ (ice-bath), veratraldehyde (3.32 g, 20 mmol) in THF (10 ml) was added. The mixture was stirred at $0^\circ C$ for 2 h and was then set aside overnight (room temperature). After cooling to $0^\circ C$ the reaction mixture was acidified (pH 2) with 3 M hydrochloric acid. The organic layer was separated and the aqueous layer extracted with ether (3×200 ml). The combined organic layers were extracted with 0.2 M NaOH (3×75 ml) and



the extract acidified with 3 M hydrochloric acid. Exhaustive extraction with ether (4×200 ml) followed by drying of the ether extract (Na₂SO₄) and removal of the solvent (film evaporation) gave a residual oil weighing 6.30 g. One half of the crude product (3.15 g) was chromatographed on a silica gel column [150 g SiO₂; eluents, dichloromethane–ethyl acetate (9:1) and (5:1)] which gave 2.03 g of an essentially pure mixture of the diastereomers of **4a** (yield, 54%). The *threo/erythro* ratio was approximately 1:1 (¹H NMR). The product was contaminated with a small amount of the *erythro* form of acid **6**; this compound was isolated and identified in a separate experiment (see below). The other half of the crude product was subjected to reduction with borane–dimethyl sulfide complex (see below).

Chromatographic separation of the diastereomers of acid 4a. Crude product from a synthesis of **4a** (1.2 g), obtained according to the above described procedure, was chromatographed on silica gel (50 g SiO₂, Mallinckrodt) with ethyl acetate/dichloromethane (1:9) as eluent. Fractions of 20 ml were collected and examined by TLC. The *erythro* form (0.21 g) was obtained from fractions 50–72 and the *threo* form (0.18 g) from fractions 88–120. Fractions 73–87 contained a mixture of the diastereomers (0.14 g). The *threo* form was obtained in a crystalline state and was recrystallized from ethyl acetate (m.p. 141–143°C). The *erythro* form was obtained as an oil. Reduction of the *threo* form of acid **4a** gave the *threo* form of **5a**.³ Analogously, reduction of the *erythro* form gave the *erythro* isomer of **5a**.

The ¹H NMR spectra of the isomeric acids were recorded after treatment with D₂O to exchange hydroxyl protons. ¹H NMR (*threo*): δ 3.83 (6H, s; OCH₃), 3.86 (3H, s; OCH₃), 3.86 (3H, s; OCH₃), 4.58 (1H, d, *J* = 5.6 Hz; Hβ), 5.23 (1H, d, *J* = 5.6 Hz; Hα), 6.5–7.1 (6H, m; aromatic protons). ¹H NMR (*erythro*): δ 3.87 (3H, s; OCH₃), 3.88 (3H, s; OCH₃), 3.90 (6H, s; OCH₃), 4.80 (1H, d, *J* = 3.3 Hz; Hβ), 5.21 (1H, d, *J* = 3.3 Hz; Hα), 6.6–7.2 (6H, m; aromatic protons). ¹³C NMR (*threo*): δ 55.9 and 56.0 (OCH₃), 74.5 (Cα), 86.7 (Cβ), 105–153 (aromatic C), 172.8 (COOH). ¹³C NMR (*erythro*): δ 55.9 and 56.3 (OCH₃), 74.1 (Cα), 86.9 (Cβ), 105–152 (aromatic C), 169.9 (COOH).

Exact mass measurements of the molecular ion

of the *threo* form gave: *m/z* 378.133. Calc. for C₁₉H₂₂O₈: *m/z* 378.131. The crystal structure of the *threo* form has been determined.³

erythro-3-(3,4-Dimethoxyphenyl)-3-hydroxy-2-(2-hydroxy-6-methoxyphenoxy)propanoic acid (6). Crude product of acid **4a** (1.24 g), obtained according to the procedure described above with the exception that the α-lithiated carboxylic acid intermediate was prepared by heating for 5 h at 40°C instead of 30 min at 35°C, was chromatographed on a silica gel column (50 g SiO₂, Mallinckrodt) using ethyl acetate/dichloromethane (1:7) as eluent. The fractions in which acid **6** was present (TLC) were collected and the solvent evaporated. The residue (0.30 g), consisting of acids **4a** and **6**, was chromatographed on cross-linked polyvinylpyrrolidone (10 g; Polyclar AT, BDH) using acetone/water (1:2) as eluent. Acid **6** moved slower than acid **4a**, and a fraction of **6** contaminated with small amounts of materials from the column could be isolated. The contaminants were removed by filtration through a small silica gel column [solvent, ethyl acetate/dichloromethane (1:7)]. Evaporation of the solvent gave an oil (40 mg) consisting of chromatographically pure acid **6**. Exact mass measurements of the molecular ion gave: *m/z* 364.116. Calc. for C₁₈H₂₂O₈: *m/z* 364.116. ¹H NMR of acid **6**: δ 3.86 (6H, s; OCH₃), 3.87 (3H, s; OCH₃), 4.78 (1H, d, *J* = 3.3 Hz; Hβ), 5.43 (1H, d, *J* = 3.3 Hz; Hα), 6.4–7.1 (6H, m; aromatic protons). ¹³C NMR of **6**: δ 55.8 (OCH₃), 55.9 (OCH₃), 56.1 (OCH₃), 74.2 (Cα), 86.1 (Cβ), 103–152 (aromatic C), 171.6 (COOH).

Proof of the stereochemistry of acid **6** was obtained by its conversion to the *erythro* form of acid **4a**. This was accomplished by preparation of the methylated derivative **7** and subsequent saponification (treatment with NaOH in ethanol at room temperature overnight); the product was identified as the *erythro* form of **4a** by TLC and ¹H NMR. Methylation of **6** using phase-transfer catalysis (cf. Ref. 3) gave the methyl ester, and further methylation (CH₃I/K₂CO₃/acetone) gave **7**. ¹H NMR of **7** (400 MHz, 293 K): δ 3.61 (3H, s; COOCH₃), 3.86 (6H, s; OCH₃), 3.87 (3H, s; OCH₃), 3.89 (3H, s; OCH₃), 4.59 (1H, d, *J* = 7.6 Hz; OH), 4.74 (1H, d, *J* = 4.0 Hz; Hβ), 4.96 (1H dd, *J* = 4.0 Hz and 7.6 Hz; Hα), 6.6–7.1 (6H, m; aromatic protons).

Preparation of the erythro and threo forms of 2-(2,6-dimethoxyphenoxy)-1-(3,4-dimethoxyphenyl)-1,3-propanediol (5a). Crude product of acid **4a** (3.15 g), obtained according to the procedure described above, was dissolved in 40 ml of THF and borane-dimethyl sulfide complex (30 ml 2.0 M in THF, 60 mmol) was injected into the solution at 0°C (argon atmosphere). The reaction mixture was stirred for two days at room temperature. Methanol (40 ml) was added slowly at 0°C to decompose excess borane, after which the solvents were removed by film evaporation. To ensure complete removal of boric acid a second portion of methanol was added and subsequently removed by film evaporation. Compound **5a** (diastereomeric mixture) was obtained from the reaction product in an essentially pure state by flash chromatography (35 g SiO₂) using ethyl acetate/dichloromethane (1:4) as eluent. The separation of the diastereomers of **5a** and removal of minor amounts of contaminants was accomplished by ion exchange chromatography; this was carried out on an anion exchange column (30 g QAE-Sephadex A-25, Pharmacia) using 0.06 M K₂B₄O₇ in acetone/water (1:4) as eluent.

The eluate was collected in fractions of 15 ml; the *threo* form was found in fractions 5–8, and fractions 9–15 contained the *erythro* form. Extraction with chloroform, drying (Na₂SO₄) and removal of solvents gave the *erythro* form (0.90 g) and the *threo* form (0.90 g) of **5a**. The *threo* form crystallized on standing, and recrystallization from ethyl acetate gave 0.57 g of product melting at 110–112°C. ¹H NMR spectral data for the acetate derivatives of the *erythro* and *threo* forms of **5a** are given in Ref. 3.

2-(2,6-Dimethoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)-1,3-propanediol (5b). The *erythro* and *threo* forms of **5b** were prepared via acid **4b** by a procedure analogous to the one used for the preparation of the corresponding isomers of **5a** (see above), i.e. the syntheses differed only in the respect that veratraldehyde was replaced by 3,4,5-trimethoxybenzaldehyde. Similar amounts of the *erythro* and *threo* forms of **5b** were obtained; the total yield was about 30%.

¹H NMR of the diacetate of the *erythro* form of **5b**: δ 1.97 (3H, s; COCH₃), 2.14 (3H, s; COCH₃), 3.76 (6H, s; OCH₃), 3.82 (3H, s; OCH₃), 3.83 (6H, s; OCH₃), 4.26 (1H, dd, *J* = 3.6 Hz and 11.9 Hz; H_γ), 4.48 (1H, dd, *J* = 5.8

Hz and 11.9 Hz; H_γ), 4.67 (1H, m; H_β), 6.04 (1H, d, *J* = 4.8 Hz; H_α), 6.54 (2H, d, *J* = 8.4 Hz; aromatic protons), 6.62 (2H, s; aromatic protons), 6.97 (1H, t, *J* = 8.4 Hz; aromatic proton). ¹H NMR of the diacetate of the *threo* form of **5b**: 1.97 (3H, s; COCH₃), 2.01 (3H, s; COCH₃), 3.79 (6H, s; OCH₃), 3.83 (3H, s; OCH₃), 3.84 (6H, s; OCH₃), 3.93 (1H, dd, *J* = 4.7 Hz and 11.9 Hz; H_γ), 4.35 (1H, dd, *J* = 4.1 Hz and 11.9 Hz; H_γ), 4.56 (1H, m; H_β), 6.10 (1H, d, *J* = 6.9 Hz; H_α), 6.56 (2H, d, *J* = 8.4 Hz; aromatic protons), 6.65 (2H, s; aromatic protons), 6.98 (1H, t, *J* = 8.4 Hz; aromatic proton).

2-(2,6-Dimethoxyphenoxy)-3-hydroxy-3-(4-hydroxy-3-methoxyphenyl) propanoic acid (4c). Butyllithium (10.0 ml 1.6 M in hexane, 16 mmol) was injected into an ice-chilled solution of diisopropylamine (1.50 g, 15 mmol) in 20 ml of THF (argon atmosphere). The mixture was stirred magnetically for 10 min and (2,6-dimethoxyphenoxy)acetic acid (1.05 g, 5.0 mmol) dissolved in 5 ml of THF was added. The stirring was continued for 30 min at 35°C and vanillin (0.76 g, 5.0 mmol) dissolved in 5 ml of THF was added at 0°C. This temperature was maintained for 2 h, after which the mixture was stirred at room temperature overnight, then cooled to 0°C and acidified with 3 M HCl. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×200 ml). The combined organic layers were extracted with aqueous 8% NaHCO₃ (3×75 ml). The extract was acidified with 3 M HCl and then extracted with dichloromethane (3×200 ml). The extract was dried (Na₂SO₄) and solvents removed by film evaporation. The residue (1.3 g) consisted primarily of similar amounts of the two diastereomers of acid **4c**. The crude product was chromatographed on a silica gel column (45 g SiO₂, Mallinckrodt) using ethyl acetate/dichloromethane (1:8) as eluent. The *erythro* form of acid **4c** moved faster on the column than the *threo* form and could be obtained in a pure state (0.21 g). The other fraction contained the *threo* form contaminated with small amounts of the *erythro* form (¹H NMR). Removal of solvents gave an oil (0.34 g). The total yield of the diastereomers of acid **4c** was 0.55 g (30%). The *threo* isomer crystallized on standing. Recrystallization from dichloromethane/ether yielded 0.21 g of crystals (white needles, m.p. 163–166°C).

¹H NMR of the *erythro* form of acid **4c**: δ 3.87 (3H, s; OCH₃), 3.90 (6H, s; OCH₃), 4.79 (1H, d, *J* = 3.3 Hz; Hβ), 5.19 (1H, d, *J* = 3.3 Hz; Hα), 6.6–7.2 (6H, m; aromatic protons). ¹H NMR of the *threo* form of acid **4c**: δ 3.81 (6H, s; OCH₃), 3.85 (3H, s; OCH₃), 4.46 (1H, d, *J* = 6.3 Hz; Hβ), 5.16 (1H, d, *J* = 6.3 Hz; Hα), 6.5–7.1 (6H, m; aromatic protons). The *erythro* and *threo* forms of compound **5c** were prepared by reduction of the corresponding diastereomers of acid **4c** with borane-dimethyl sulfide complex according to above-described procedures. ¹H NMR data for the triacetates of the diastereomers of **5c** are given in Ref. 3.

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