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Synthesis of *erythro* and *threo* Forms of Lignin Models of the Arylglycerol β-Guaiacyl Ether Type

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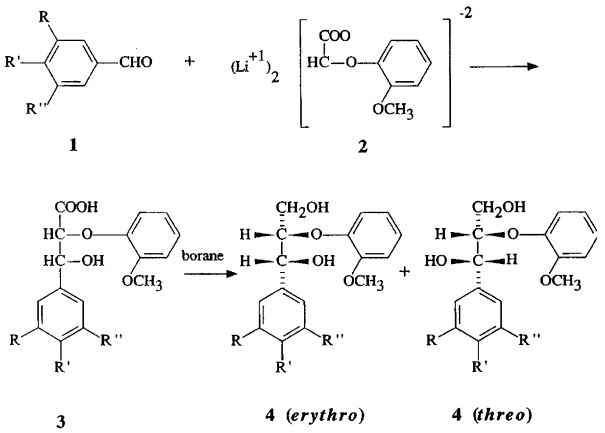
Lignin-related arylglycerol β-guaiacyl ethers [2-(2-methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)-1,3-propanediol, 2-(2-methoxyphenoxy)-1-(4-methoxyphenyl)-1,3-propanediol, 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol and 1-(3,4-dimethoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol] have been prepared by reacting α-lithiated (2-methoxyphenoxy)acetic acid with aromatic aldehydes and subsequent reduction of the 3-hydroxypropionic acids formed with borane–dimethyl sulfide complex. Isolation of the *erythro* and *threo* forms from the product mixtures was accomplished by ion-exchange chromatography. The tetrabutylammonium salt of vanillin was used as a reactant in the synthesis of 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol.

Arylglycerol β-aryl ethers are the most important types of structural element in lignins and some 40% of the lignin units are arylglycerols that are attached to adjacent units by such ether linkages (see, e.g., Refs. 1 and 2). This paper describes the synthesis of a series of lignin model compounds of the arylglycerol β-guaiacyl ether type using a synthetic method involving a reaction of an aromatic aldehyde (**1**) with α-lithiated (2-methoxyphenoxy)ethanoic acid (**2**) (Scheme 1). This synthetic approach has previously been used for the synthesis of a variety of arylglycerol β-aryl ethers.[3–6] The particular procedure employed in the syntheses reported in this paper is based on previous work but modifications and improvements have been introduced.



a. R=R'=R''= OCH_3

b. R= H, R'=R''= OCH_3

c. R= H, R'= OCH_3, R''= H

d. R= H, R'= OH, R''= OCH_3

Scheme 1.

The crude mixtures of 3-hydroxypropionic acids (**3**) from reactions of aromatic aldehydes with α-lithiated 2-(2-methoxyphenoxy)ethanoic acid were reduced with the borane–dimethyl sulfide complex. The bulk of the contaminants in the reduction products were removed by flash chromatography. Examinations of acetylated samples of the products by ^{1}H NMR spectroscopy showed that the *threo* and *erythro* forms of the arylglycerol β-guaiacyl ethers were present in about equal amounts. Further purification and separation of the *threo* and *erythro* forms was accomplished by ion-exchange chromatography (IEC) on an anion exchanger using a borate solution as the eluent.[5,7] In all cases the *erythro* form gave the stronger borate complex and was eluted after the *threo* form. This is expected from a conformational analysis of the borate complexes: in the borate complex of the *threo* forms, the bulky aryl substituents are *cis* orientated and energetically unfavorable interactions between these groups cannot be avoided.[8]

The total yield of the *erythro* and *threo* forms of **4a** was 60%. Until now this compound has not been synthesized on a preparative scale. Small samples have previously been prepared by methylation/reduction of 3-hydroxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)-1-propanone[9] in connection with ^{1}H NMR spectroscopic studies.[10] Compound **4b** has previously been synthesized by a method closely resembling the one applied in this

work.[3,7] However, the particular procedure described in this paper gave a higher yield of the pure diastereomers (total yield, ≈60%). A somewhat lower yield (45%) was obtained in the synthesis of the hitherto unknown **4c**.

The phenolic model **4d** was synthesized by reacting the tetrabutylammonium salt of vanillin with α-lithiated (2-methoxyphenoxy)ethanoic acid and subsequent reduction of the crude product; no protective group was used. In spite of the presence of phenolic groups, efficient separation of the diastereomers was achieved by IEC. The elution volumes are comparatively large and satisfactory separation of the isomers is obtained with small ion-exchange columns. Since the synthesis comprises few steps we think it is competitive, although the yield is moderate (27%). Compound **4d** is frequently synthesized via an 1-aryl-3-hydroxy-2-(2-methoxyphenoxy)-1-propanone intermediate;[11,12] the phenol group in the aryl substituent is usually protected by benzylation. Reduction of this intermediate results in a mixture of *erythro* and *threo* forms of arylglycerol β-guaiacyl ethers[4,13] and subsequent removal of the protective group gives the corresponding mixture of diastereomers of **4d**. According to one report[14] the use of protective groups can be avoided provided the synthesis is properly modified.

Experimental

Tetrahydrofuran (THF) was purified by distillation over Na. Merck Kieselgel 60 (230–400 mesh) was used for flash chromatography.

^1H NMR spectroscopy. The spectra were recorded at 400 MHz with a Varian VXR-5000 instrument (temperature, 300 K).

Deuteriochloroform was used as the solvent [internal reference, $(CH_3)_4Si$]. ^1H NMR data for the acetate derivatives of **4a**, **4b**, and **4d** are reported in Ref. 10. Some peak positions reported for **4a** are erroneous; corrected spectral data are given below.

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: **4d** (*erythro*), 0.17; **4d** (*threo*), 0.18; **4a** (*erythro*), 0.20; **4a** (*threo*), 0.20; **4b** (*erythro*), 0.20; **4b** (*threo*), 0.21; **4c** (*erythro*), 0.28; **4c** (*threo*), 0.29]. Spots were made visible by UV light and by spraying with formalin–H_2SO_4 (1:9) and subsequent heating.

Ion exchange chromatography (IEC). Separation of the *erythro* and *threo* forms of the arylglycerol β-aryl ethers was accomplished by ion-exchange chromatography; this was carried out on an anion-exchange column (100 g QAE-Sephadex A-25, Pharmacia; column dimensions: 4.2 × 42 cm) using 0.06 M $K_2B_4O_7$ in acetone–water (1:4) as the eluent. The samples (1–2 g) were dissolved in the eluent and applied to the column; the samples were dissolved in a small amount of acetone to facilitate the dissolution in the eluent. The effluent was collected in 25 ml fractions. The effluent fractions were pooled on the basis of examinations by TLC. The pooled fractions (volume, V ml) were extracted with chloroform (0.75V ml + 2 × 0.25V ml). The extract was dried over Na_2SO_4 and solvents were removed by film evaporation. The residue was dried *in vacuo* over KOH and P_2O_5. Elution volumes (ml) from a QAE-Sephadex A-25 (33 g) column: **4a** (*erythro*), 260; **4a** (*threo*), 200; **4b** (*erythro*), 270; **4b** (*threo*), 200; **4c** (*erythro*), 300; **4c** (*threo*), 200; **4d** (*erythro*), 630; **4d** (*threo*), 380.

(2-Methoxyphenoxy)ethanoic acid was prepared according to a procedure previously described for the synthesis of (2,6-dimethoxyphenoxy)ethanoic acid.[5] M.p. 121–122°C (from ethanol), lit.[15] 121–121.4°C.

The tetrabutylammonium salt of vanillin. Tetrabutylammonium hydrogen sulfate (8.2 g) was dissolved in water (110 ml). Vanillin (**3d**) (3.04 g, 20 mmol) and 1 M NaOH (54 ml) were added. The mixture was extracted with chloroform (150 ml + 2 × 100 ml). The extract was washed with a small amount of water and dried over Na_2SO_4 and the solvents were removed by film evaporation. The product was carefully dried *in vacuo* over KOH and P_2O_5. The product weighed 6.33 g.

*General procedure for the synthesis of arylglycerol β-guaiacyl ethers using α-lithiated (2-methoxyphenoxy)ethanoic acid (**2**) as reactant*

*(a) Reaction of α-lithiated (2-methoxyphenoxy)ethanoic acid (**2**) with aromatic aldehydes.* A 250 ml three-necked flask was used in the experiments. The flask was equipped with an inlet and an outlet for argon, a septum for injection of reagents, and a thermometer. A slow stream of argon was allowed to pass through the reaction vessel (the flow rate was registered by means of a silicone oil seal). Butyllithium in hexane (43 ml 1.6 M solution) was injected with a syringe into a solution of diisopropylamine (4.0 g, 40 mmol) in THF (50 ml). The mixture was stirred magnetically for about 0.5 h. A solution of (2-methoxyphenoxy)ethanoic acid (3.65 g, 20 mmol) in THF (ca. 15 ml) was slowly injected into the flask. The mixture was kept at 35–40°C for ca. 0.5 h (magnetic stirring). After cooling to 0°C (ice-bath) a solution of the aromatic aldehyde (20 mmol) in THF (17–50 ml) was slowly added to the reaction mixture. Stirring at 0°C was continued for 1 h whereupon the reaction mixture was set aside overnight (argon atmosphere). The cooled (0°C) reaction mixture was acidified by injection of 3 M hydrochloric acid (38 ml) and transferred to a separatory funnel by means of ether (100 ml) and 3 M hydrochloric acid (10 ml). The layers were separated and the aqueous layer extracted with ether (200 ml + 3 × 100 ml). The combined organic layers were extracted with 0.2 M NaOH (3 × 75 ml). The extract was acidified with 3 M hydrochloric acid (21 ml)

and extracted with ether (250 ml + 3 × 100 ml). The ethereal solution was dried (Na_2SO_4) and the solvent removed by film evaporation. The residue was dried *in vacuo* over KOH and P_2O_5.

(b) Reduction with borane–dimethyl sulfide complex. The crude product was dissolved in THF (30–50 ml) in a 250 ml flask and 2 M borane–dimethyl sulfide complex in THF (40–50 ml) was injected into the flask with a syringe (argon atmosphere, magnetic stirring). After 48 h the reaction was quenched by the slow addition of methanol (ca. 10 ml) and solvents were then removed by film evaporation. To ensure complete removal of boric acid the residue was dissolved in methanol (40 ml) and the solvent removed by film evaporation. The residue was dried *in vacuo* over KOH and P_2O_5.

2-(2-Methoxyphenoxy)-1-(3,4,5-trimethoxyphenyl)-1,3-propanediol (**4a**). Application of the general procedure for the synthesis of arylglycerol β-guaiacyl ethers with 3,4,5-trimethoxybenzaldehyde (**1a**) as starting material gave a crude product weighing 6.7 g. Purification by flash chromatography (120 g SiO_2; eluent: methylene chloride–ethyl acetate mixtures in the range 10:1 to 1:3) gave 4.9 g slightly contaminated **4a**. Further purification and separation of the *threo* and *erythro* forms was achieved by IEC which gave a total of 4.35 g product [2.05 g **4a** (*threo*), 2.30 g **4a** (*erythro*)]. Yield: 60%. The first fraction from the silica gel column (0.2 g) consisted of the *threo* form admixed with contaminants. ^{1}H NMR of the acetate of **4a** (*erythro*): δ 2.04 (3 H, s, CH_3CO), 2.09 (3 H, s, CH_3CO), 3.79 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.84 (6 H, s, OCH_3), 4.27 (1 H, dd, J = 3.7 and 12 Hz, H_γ), 4.45 (1 H, dd, J = 5.9 and 12 Hz, H_γ), 4.69 (1 H, m, H_β), 6.00 (1 H, d, J = 5.6 Hz, H_α), 6.66 (2 H, s) and ca. 6.9 (4 H, m) (aromatic protons). ^{1}H NMR of the acetate of **4a** (*threo*): δ 2.02 (3 H, s, CH_3CO), 2.06 (3 H, s, CH_3CO), 3.82 (6 H, s, OCH_3), 3.83 (6 H, s, OCH_3), 4.05 (1 H, dd, J = 5.8 and 12 Hz, H_γ), 4.31 (1 H, dd, J = 4.1 and 12 Hz, H_γ), 4.63 (1 H, m, H_β), 6.06 (1 H, d, J = 6.6 Hz, H_α), 6.63 (2 H, s) and ca. 6.9 (4 H, m) (aromatic protons).

2-(2-Methoxyphenoxy)-1-(4-methoxyphenyl)-1,3-propanediol (**4c**). The general synthetic procedure was adopted and anisaldehyde (**1c**) was used as the reactant. The crude product weighed 5.4 g. Purification by flash chromatography (120 g SiO_2; eluent: methylene chloride–ethyl acetate mixtures in the range 20:1 to 1:1) gave 4.0 g of **4c** contaminated with substantial amounts of 2-(2-methoxyphenoxy)-1-ethanol. Further purification and separation of the diastereomers was achieved by IEC giving a total of 2.71 g product [1.31 g of **4c** (*threo*) and 1.40 g of **4c** (*erythro*)]. Yield: 45%. The first fraction from the silica gel column (0.28 g) was impure and gave 0.1 g of the *threo* form on IEC. ^{1}H NMR of the acetate of **4c** (*erythro*): δ 2.01 (3 H, s, CH_3CO), 2.07 (3 H, s, CH_3CO), 3.79 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.22 (1 H, dd, J = 4.0 and 11.7 Hz, H_γ), 4.43 (1 H, dd, J = 6.1 and 11.7 Hz, H_γ), 4.66 (1 H, m, H_β), 6.04 (1 H, d, J = 5.2 Hz, H_α), ca. 7 (8 H, m, aromatic protons). ^{1}H NMR of the acetate of **4c** (*threo*): δ 1.99 (3 H, s, CH_3CO), 2.00 (3 H, s, CH_3CO), 3.79 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 3.98 (1 H, dd, J = 5.6 and 12 Hz, H_γ), 4.26 (1 H, dd, J = 3.8 and 12 Hz, H_γ), 4.64 (1 H, m, H_β), 6.10 (1 H, d, J = 7.1 Hz, H_α), ca. 7 (8 H, m, aromatic protons).

1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol (**4d**). The general procedure was followed using vanillin (as its tetrabutylammonium salt) as the reactant but, instead of 3 M hydrochloric acid, the equivalent amounts of 2 M H_2SO_4 were used for acidification. The crude product weighed 5.7 g. The major part of the contaminants were removed by flash chromatography using mixtures of methylene chloride and ethyl acetate as eluents. The product (2.7 g) was subjected to further purification by flash chromatography (80 g SiO_2; eluent: methylene chloride–ethyl acetate mixtures in the range 10:1 to 1:2) giving an essentially pure fraction of the diastereomers of **4d** weighing 1.47 g. A fraction eluted before this fraction (0.18 g) gave, on purification by IEC, 0.11 g of **4d** (*threo*). A fraction eluted after the main fraction (0.13 g) gave, on IEC, a total of 0.08 g of the *threo* and *erythro* forms. Yield: 1.7 g (27%).

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