Synthesis of the *erythro* and *threo* Forms of 1,2-Bis(4-hydroxy-3-methoxyphenyl)-1,3-propanediol

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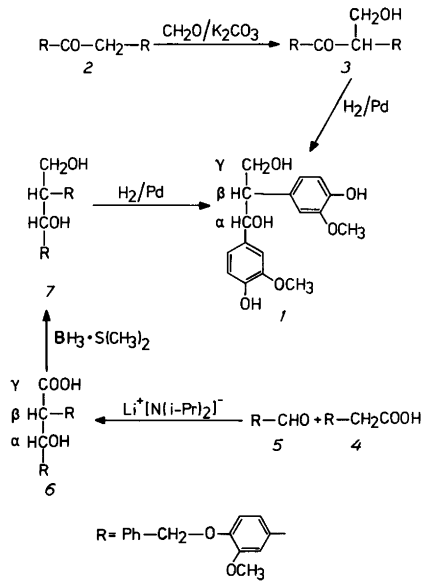
The synthesis of lignin model compound *1* starting from desoxybenzoin *2* has been described in a previous paper.[1] Ketol *3* is an intermediate in this synthesis (Scheme 1).Desoxybenzoin *2* was prepared by a benzoin condensation of benzylvanillin[2,1] followed by reduction.[1] Alternatively, compound *2* can be prepared by benzylation of 1,2-bis(4-hydroxy-3-methoxyphenyl)-1-ethanone (see Experimental).

Preparation of *1* by the previously described method gave a mixture of the two possible diastereomers.[1,3] One of the stereoisomers dominated strongly and was obtained in a crystalline state from ethyl acetate – hexane (m.p. 158 – 159 °C).[3] On the basis of ^{1}H NMR spectral comparisons with 1,2-diaryl-1,3-propanediols of known configuration[4,5] it could be concluded that the crystalline isomer has the *erythro* configuration. By the same method, the material in the mother liquor



Scheme 1.

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was found to consist of a mixture of the *erythro* and *threo* forms of compound *1*.

A new synthetic method offered a possibility of obtaining the *threo* isomer in a sterically pure state. In the first step, acid *6* was prepared from compounds *4* and *5*, using a method[6] involving an α-lithiated carboxylic acid salt as intermediate (Scheme 1). A mixture of the diastereomers of acid *6* was obtained. The isomers could be separated by column chromatography. Each isomer of acid *6* was converted into the corresponding isomer of diarylpropanediol *1* by reduction with borane dimethylsulfide complex followed by catalytic hydrogenation.

Synthesis of the *erythro* as well as the *threo* form of *1* by a method involving a Prins reaction has recently been published by Brežný and Pufflerová.[7] Their stereochemical assignments were made on the basis of comparisons of *J* values for the coupling between H_α and H_β and are in agreement with our results. In connection with ^{1}H NMR studies of lignin model compounds[8] it was found that the correct structure could not always be derived from $J_{\alpha\beta}$ values. However, the identification of the isomers of compound *1* could be corroborated by extended ^{1}H NMR spectral comparisons with diarylpropanediols of known structure.

Experimental. Mass spectra (MS) were taken on an AEI model MS 902 instrument.

Thin layer chromatography (TLC) was performed on silica gel, using benzene – dioxane – acetic acid (90:25:4) as eluent. Spots were made visible by spraying with formalin-H_2SO_4 (1:9) and subsequent heating (140 °C). R_F values: 4-hydroxy-3-methoxyphenylacetic acid, 0.32; acid *6* (*threo* form), 0.33; vanillic acid, 0.38; acid *6* (*erythro* form), 0.46; 4-benzyloxy-3-methoxyphenylacetic acid (*4*), 0.48.

Preparation of 1,2-bis(4-benzyloxy-3-methoxyphenyl)-1-ethanone (2). A mixture of 1,2-bis(4-hydroxy-3-methoxyphenyl)-1-ethanone[9] (2.9 g, 0.01 mol), benzyl chloride (3.0 g, 0.024 mol), K_2CO_3 (6.91 g, 0.05 mol), and ethanol (150 ml) were refluxed for 12 h. Water (100 ml) and 2 M NaOH (50 ml) were added to the reaction mixture. Precipitated material was filtered off, washed with water, and dried *in vacuo*. Recrystallization from ethanol gave 3.5 g product melting at 145 – 146 °C (lit.[1] 146.5 – 147.5 °C).

4-Hydroxy-3-methoxyphenylacetic acid was prepared by oxidation of eugenol acetate with permanganate, essentially according to the procedure described in Ref. 10. The crude product was found to contain vanillic acid as a contaminant (TLC). Purification was accomplished by chromatography on crosslinked polyvinylpyrrolidon (Polyclar AT, BDH) with acetone – water (2:1) as eluent (*cf.* Ref. 11). About 10 g of the crude product was dissolved

in 75 ml of the eluent and applied to a column packed with 100 g Polyclar AT. The eluate was collected in 25 ml fractions which were examined by TLC. Fractions 22 – 52 contained 4-hydroxy-3-methoxyphenylacetic acid (vanillic acid was detected in fractions 56 – 100). Removal of solvents by film evaporation gave a crystalline residue which was chromatographically pure and melted at 141 – 142 °C (lit.[12] 141 – 142 °C).

4-Benzyloxy-3-methoxyphenylacetic acid (4) was prepared by benzylation of 4-hydroxy-3-methoxyphenylacetic acid by means of a procedure used by Grewe and Fischer[13] for the benzylation of 3-hydroxy-4-methoxyphenylacetic acid. Recrystallization from benzene gave a product melting at 110 – 111 °C (lit.[14] 116 °C). Yield: 65 %.

1,2-Bis(4-benzyloxy-3-methoxyphenyl)-3-hydroxypropionic acid (6) was prepared from 4-benzyloxy-3-methoxyphenylacetic acid (*4*) (5.4 g, 0.02 mol) and 4-benzyloxy-3-methoxybenzaldehyde (*5*) (4.8 g, 0.02 mol). The general procedure for the preparation of β-hydroxyacids using α-lithiated carboxylic acid salts given by Moersch and Burkett[6] was followed. Redistilled isopropylamine, tetrahydrofuran (distilled over sodium), and butyllithium in hexane (Merck) were used in the synthesis. Work-up procedure B[6] was applied. The final ether extract contained a crystalline precipitate (0.54 g) which was examined separately. The residue obtained on removal of solvents from the ether extract weighed 10.1 g. This product was chromatographed on silica gel (350 g) with mixtures of dichloromethane and successively increasing amounts of ethyl acetate (9:1, 3:1 and 3:2) as eluent. The eluate was collected in 25 ml fractions which were examined by TLC. A crystalline product (0.40 g, m.p. 180 – 185 °C) was obtained from fractions 178 – 197. Recrystallization from chloroform raised the m.p. to 185 °C. The crystalline product was found to be identical with the one obtained from the ether extract (see above). ^{1}H NMR (270 MHz, DMSO-d_6, 300 K): δ 3.71 (1 H, d, J = 9 Hz; H_β), 3.74 (3 H, s; OCH_3), 3.76 (3 H, s; OCH_3), 4.97 (1 H, d, J = 9 Hz; H_α), 5.05 (2 H, s; CH_2), 5.06 (2 H, s; CH_2), ≈7.0 (6 H, m; aromatic protons), ≈7.4 (10 H, m; aromatic protons). The IR spectrum showed a strong band at 1695 cm^{-1} (C=O). On the basis of spectral data and its conversion to the *erythro* form of compound *1* (see below), the product could be identified as the *erythro* form of acid *6*.

Fractions 202 – 261 gave a crystalline product (3.93 g) melting at 135 °C. Recrystallization from benzene gave a product melting at 95 – 96 °C. This product gave crystals from dichloromethane melting at 135 – 137 °C. Fractions 262 – 317 gave an additional amount (0.56 g) of the same compound which contained traces of a contaminant (R_F 0.28).

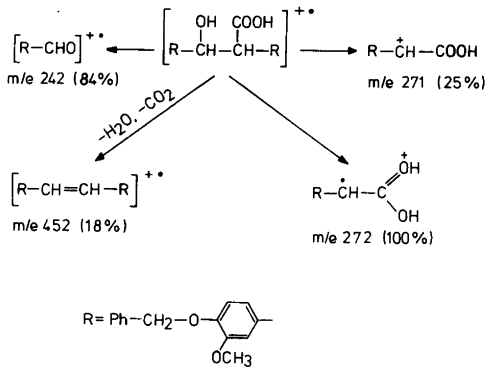

Fig. 1. Mass spectrometric fragmentation of the *threo* form of acid *6*. No molecular ion (*m/e* 514) appeared in the mass spectrum. The elemental compositions of fragment ions at *m/e* 242, 272 and 452 were confirmed by exact mass measurements. Additional peaks in the upper mass range appeared at *m/e* 361 (30 %) and 362 (33 %). The MS of the *erythro* form of acid *6* resembled largely the one obtained from the *threo* form.

^{1}H NMR (270 MHz, DMSO-d_6, 300 K): δ 3.62 (3 H, s; OCH_3), 3.63 (3 H, s; OCH_3), 3.64 (1 H, d, J = 10 Hz, H_β), 4.96 (1 H, d, J = 10 Hz; H_α), 4.97 (4 H, s; CH_2), ≈6.7 (6 H, m; aromatic protons), ≈7.4 (10 H, m; aromatic protons). ^{13}C NMR (67.88 MHz, $CDCl_3$, 315 K): δ 56.2 (OCH_3), 56.3 (OCH_3), 59.6 (C_β), 71.4 (CH_2), 76.3 (C_α), 100 – 150 (signals from carbon atoms in aromatic rings), 177.5 (COOH). MS data are given in Fig. 1. The IR spectrum showed a strong band at 1710 cm^{-1} (C=O). The compound could be converted to the *threo* form of diarylpropanediol *1* (see below). On the basis of this fact and spectral data, the structure of the compound was determined as the *threo* form of acid *6*.

Preparation of 1,2-bis(4-hydroxy-3-methoxyphenyl)-1,3-propanediol (1) from acid 6. A stirred solution of acid *6* of m.p. 135 – 137 °C (0.20 g) in tetrahydrofuran (3 ml) was treated with $BH_3.S(CH_3)_2$ (0.3 ml) at room temperature overnight (nitrogen atmosphere). (The carboxylic acid group in acid *6* is converted into a methylol group by this treatment, *cf.* Ref. 15.) Excess $BH_3.S(CH_3)_2$ was decomposed by adding methanol (1 ml) to the cooled reaction mixture. Addition and removal of methanol (1 ml) was performed twice to secure a complete removal of boric acid possibly present in the product. Purification on a silica gel column [40 g SiO_2; eluent, dichloromethane – ethyl acetate (3:1)] gave 0.16 g of a liquid product of structure *7* (^{1}H NMR). ^{1}H NMR spectrum of the acetate derivative (270 MHz, $CDCl_3$): δ 2.00 (3 H, s; CH_3C),

2.08 (3 H, s; CH_3C), 3.37 (1 H, m; H_β), 3.70 (3 H, s; OCH_3), 3.73 (3 H, s; OCH_3), 4.34 (1 H, dd, $J=5.3$ and 11 Hz; H_γ), 4.49 (1 H, dd, $J=7.1$ and 11 Hz; H_γ), 5.08 (4 H, s; CH_2), 5.92 (1 H, d, $J=8.4$ Hz; H_α), ≈ 6.5 (6 H, m; ar, guaiacyl), ≈ 7.4 (10 H, m; ar, phenyl).

Benzyl groups were removed by hydrogenation in dioxane solution with 10 % Pd/C as catalyst. An oil was obtained. ^{1}H NMR spectrum of the acetate derivative (270 MHz, $CDCl_3$): δ 2.03 (3 H, s; CH_3C), 2.11 (3 H, s; CH_3C), 2.26 (3 H, s; CH_3C), 2.27 (3 H, s; CH_3C), 3.42 (1 H, m; H_β), 3.63 (3 H, s; CH_3O), 3.65 (3 H, s; CH_3O), 4.36 (1 H, dd, $J=5.9$ and 11 Hz; H_γ), 4.53 (1 H, dd, $J=7.0$ and 11 Hz; H_γ), 5.98 (1 H, d, $J=7.8$ Hz; H_α), 6.4 – 7.0 (6 H, m; aromatic protons). On the basis of comparisons with ^{1}H NMR data for acetylated 1,2-diaryl-1,3-propanediols,[4,5] it could be concluded that the product obtained is the *threo* form of compound *1*.

Similar treatments of acid *6* (m.p. 185 °C) gave a crystalline product (m.p. 158 – 159 °C) identical with the one obtained in the synthesis of compound *1* according to the procedure described in Ref. 1. The intermediate dibenzyl ether (*7*) melted at 106 – 108 °C (lit.[7] 106 – 108 °C). ^{1}H NMR spectrum of the acetate derivative (270 MHz, $CDCl_3$): δ 1.97 (3 H, s; CH_3C), 1.98 (3 H, s; CH_3C), 2.28 (3 H, s; CH_3C), 2.29 (3 H, s; CH_3C), 3.38 (1 H, m; H_β), 3.69 (3 H, s; CH_3O), 3.73 (3 H, s; CH_3O), 4.18 (1 H, dd, $J=6.5$ and 11.4 Hz; H_γ), 4.39 (1 H, dd, $J=7.0$ and 11.4 Hz; H_γ), 6.10 (1 H, d, $J=6.5$ Hz; H_α), 6.5 – 7.0 (6 H, m; aromatic protons). Primarily on the basis of its ^{1}H NMR spectral properties, the product was identified as the *erythro* form of diarylpropanediol *1*.

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