New Synthetic Routes to Lignin Model Compounds of the Arylglycerol-β-aryl Ether Type

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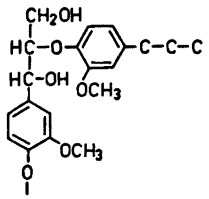
The arylglycerol-β-aryl ether type of structure (*1*) has long been considered to constitute the most prominent substructure in lignin.[1] Lignin model compounds of type *1* are therefore useful in research concerning lignin. Syntheses of such compounds have been described by several authors.[2]



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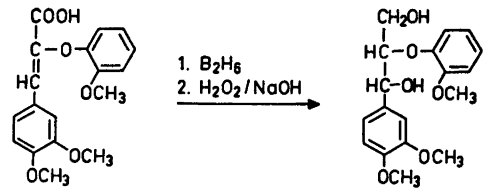
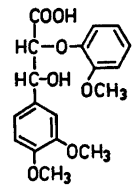
We wish to report two new synthetic routes to model compounds for structure *1*. One of these involves hydroboration of an α-aryloxycinnamic acid as the key step. α-Aryloxycinnamic acid *2* was prepared by a Claisen reaction (*cf.* Refs. 2b and 3) from veratraldehyde and the methyl ester of 2-methoxyphenoxyacetic acid, as well as by a Perkin reaction (*cf.* Ref. 4) from veratraldehyde and 2-methoxyphenoxyacetic acid. The Perkin reaction provides the simplest route to acid *2*, but gives only poor yields. A higher yield (20 %) was obtained by a Claisen reaction using sodium hydride as condensing agent and toluene as solvent. We intend to further investigate methods for the preparation of acids of type *2*. The product obtained on hydroboration of compound *2* (Fig. 1) was identified as the *erythro* form [5] of compound *3* (yields were about 40 %). Since hydroboration is known to proceed by *cis* addition, we assume that the starting material has the *trans* configuration. Additional compounds present in the reaction mixtures were guaiacol, 3,4-dimethoxycinnamyl alcohol, 3-(3,4-dimethoxyphenyl)-1,2-propanediol, and 3-(3,4-dimethoxyphenyl)-1-propanol. The formation of the by-products can be explained in the following way. The organoborane derivative, formed on reduction by and addition of diborane to acid *2*, undergoes an elimination reaction yielding guaiacol and 3,4-dimethoxycinnamyl alcohol; the additional two by-products result from subsequent reactions of the 3,4-dimethoxycinnamyl alcohol formed (*cf.*



2 *3*

Fig. 1. Preparation of lignin model compound *3* by hydroboration of α-aryloxycinnamic acid *2*.

Ref. 6). Brown and co-workers [6] have studied reactions of the types assumed to be involved in the formation of the above-mentioned by-products. Their results suggest that it should be possible to increase the yield of compound *3* considerably by optimizing the reaction conditions.



4

Acid *4* was obtained as a by-product in the preparation of acid *2* by the Claisen reaction. In accord with earlier observations in similar syntheses,[2b] decreased reaction temperature favored the formation of β-hydroxy acid (*i.e.* in our case acid *4*). We have obtained acid *4* in 25 % yield; the product was a mixture of the two possible diastereomers. These were partially separated by chromatography on silica gel. The configuration of the isomers was determined by reduction to compound *3* and examination of the product by spectral comparisons with the known [5] diastereomers of this compound.

It was found that acid *4* can be alternatively prepared from veratraldehyde and lithium α-lithio(2-methoxyphenoxy)acetate (yield 60 %). Preparation of acids of type *4* by this method and subsequent reduction to compounds of type *3* represents a second new route to lignin model compounds of type *1*. Syntheses of such model compounds from acids of type *4*, obtained by the Claisen reaction, have been carried out by Freudenberg and Müller.[2b] It is noteworthy that in the preparation of acid *4* by the Claisen reaction, the *threo* form dominated in the product, while more *erythro* form than *threo* form was present in the product obtained using lithium α-lithiocarboxylate.

Experimental. NMR spectra were recorded on a Varian A-60 instrument with TMS as internal standard. *Mass spectra* were taken using an

AEI MS 902 instrument and this equipment was also used for accurate mass measurements of molecular ions.

Thin layer chromatography (TLC) was performed with silica gel, using benzene-dioxan-acetic acid (90:25:4)[7] as eluent. Spots were made visible by spraying with formalin-H_2SO_4 (1:9) and subsequent heating. R_F values: *4* (*threo* form), 0.06; *4* (*erythro* form), 0.11; 3-(3,4-dimethoxyphenyl)-1,2-propanediol, 0.13; *3* (*erythro* and *threo* forms), 0.28; *2*, 0.35; 3-(3,4-dimethoxyphenyl)-1-propanol, 0.36; 3,4-dimethoxycinnamyl alcohol, 0.38; guaiacol, 0.56.

Preparation of α-(2-methoxyphenoxy)-3,4-dimethoxycinnamic acid (2) by the Perkin reaction. 2-Methoxyphenoxyacetic acid (10.0 g), veratraldehyde (9.2 g), NaH (2.7 g of a 50 % dispersion in mineral oil), and acetic anhydride (20 ml) were heated at 150 °C for 10 h. The reaction mixture was cooled and some water was added to decompose excess acetic anhydride. The mixture was then dissolved in 150 ml ether. The ether solution was extracted with 5 % aqueous Na_2CO_3 ($100+2\times50$ ml). Acidification of the extract with 2 M HCl gave a precipitate, which, according to TLC, consisted essentially of compound *2* and 3,4-dimethoxycinnamic acid. The latter compound was removed from the precipitate by repeated extraction with boiling water and, finally, with a small amount of acetone at room temperature. A crystalline residue (m.p. 201 °C) consisting of compound *2* (TLC) weighing 1.5 g (8 %) was obtained. Recrystallization from acetone raised the m.p. to 202 °C. Accurate mass measurements of the molecular ion gave *m/e* 330.1073. Calc. for $C_{18}H_{18}O_6$: *m/e* 330.1103. NMR spectrum (δ units, 60 °C; solvent, $CDCl_3$): 3.72 (3 H, s; OCH_3), 3.87 (3 H, s; OCH_3), 3.93 (3 H, s; OCH_3), 6.6—7.6 (8 H, m; aromatic protons and the vinyl proton); 9.32 (1 H, s; COOH). The IR spectrum showed a strong band at 1690 cm^{-1} (C=O).

Hydroboration of α-(2-methoxyphenoxy)-3,4-dimethoxycinnamic acid (2). Ten ml of a solution of B_2H_6 in tetrahydrofuran[8] ($\approx$0.8 M) were added to a solution of compound *2* (990 mg, 3 mmol) in tetrahydrofuran (N_2 atmosphere). After an initial evolution of hydrogen, the reaction mixture turned yellow. The yellow colour disappeared after about 30 min (separate experiments indicated that the disappearance of the yellow colour was associated with the consumption of starting material). After 3 h, the excess of B_2H_6 was decomposed by addition of water (4 ml). To oxidize C—B bonds the reaction mixture was treated with 6 ml 3 M NaOH and, in portions, with a total of 0.6 ml 30 % H_2O_2. The mixture was stirred vigourously at 30—40 °C for 1 h. After addition of 30 ml H_2O, the reaction mixture was extracted with chloroform ($60+2\times30$ ml). The extract was dried over Na_2SO_4 and solvent removed by film evaporation. The residue (0.92 g) was dissolved in 20 ml ether and kept in a refrigerator for some days. Crystals precipitated (0.28 g) which were identified as the *erythro* form of 2-(2-methoxyphenoxy)-1-(3,4-dimethoxyphenyl)-1,3-propandiol (*3*) (m.p. 99 °C, lit.[5] 97.5—98.5 °C). Column chromatography [20 g SiO_2; eluent, benzene-ethyl acetate (1:1)] gave 90 mg of the same compound (eluate 120—240 ml). Total yield: 37 %. Additional fractions from the column consisted of guaiacol (eluate 25—40 ml; identified by IR and TLC), 3,4-dimethoxycinnamyl alcohol (eluate 60—70 ml, 106 mg; identified by TLC, IR, NMR, and m.p. (75—76 °C, lit.[9] 79—80 °C), 3-(3,4-dimethoxyphenyl)-1-propanol (eluate 90—120 ml, 42 mg; identified by TLC and IR), and a mixture of the latter two compounds (eluate 70—90 ml, 87 mg; NMR). Continued elution with ethyl acetate gave 3-(3,4-dimethoxyphenyl)-1,2-propanediol (identified by TLC and IR). This compound and guaiacol are left in part in the aqueous layer and the yields of these compounds have therefore not been determined.

Preparation of acid 4, using lithium α-lithiocarboxylate. The method described by Moersch and Burkett[10] was used (work-up procedure B). 2-Methoxyphenoxyacetic acid (9.1 g) and veratraldehyde (8.3 g) were used as starting materials. As indicated by TLC the crude product (16 g) consisted mainly of a mixture of the two possible diastereomers of acid *4*. The two isomers were separated by chromatography on silica gel (210 g) with, successively, dichloromethane and mixtures of dichloromethane and ethyl acetate (9:1, 4:1, 7:3, 1:1) as eluent. The *erythro* form was eluted somewhat more rapidly than the *threo* form. Fractions of the *erythro* form (2.8 g, impure crystals), the *threo* form (1.3 g, oil), and a mixture of the two isomers (6.3 g, oil) were obtained. Total yield: 60 %. The fraction consisting of the *erythro* form of acid *4* was heated briefly with 30 ml benzene and the solid filtered off the following day. A product (2.5 g) melting at 119—121 °C was obtained. Recrystallization from benzene raised the m.p. to 121—122 °C. Accurate mass measurement of the molecular ion showed that the elemental composition was $C_{18}H_{20}O_7$ which is in accord with structure *4*. NMR spectrum (δ units; chloroform-*d* solution treated with D_2O): 3.83 (9 H, s; OCH_3), 4.63 (1 H, d, $J=5.2$ Hz; $-CO-CH<$), 5.16 (1 H, d, $J=5.2$ Hz; $Ar-CH<$), 6.6—7.2 (7 H, multiplet; aromatic protons). The IR spectrum showed a strong band at 1725 cm^{-1} (C=O). The *erythro* configuration was demonstrated by reduction with B_2H_6 and identification of the product as the *erythro* form of compound *3*. Structural proof for the *threo* form of acid *4* was obtained with the same methods as those used for the *erythro* form. NMR spectrum (δ units; conditions as above): 3.80 (9 H, s; OCH_3), 4.63 (1 H, d, $J=3.4$ Hz; $-CO-CH<$), 5.24 (1 H, d, $J=3.4$ Hz; $Ar-CH<$), 6.6—7.2 (7 H, aromatic protons). The IR spectrum showed a strong band at 1750 cm^{-1}.

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5,6-*O*-Isopropylidene-D-glucofuranose

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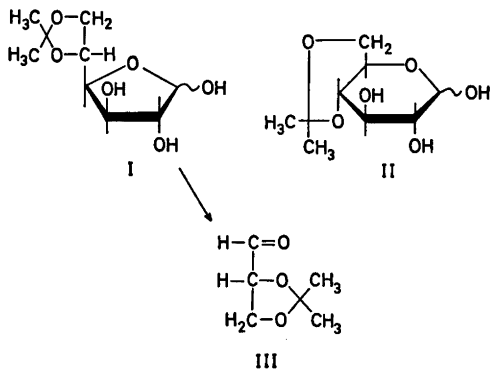
Treatment of D-galactose with acetone containing 15 – 20 % *N*,*N*-dimethylformamide and anhydrous cupric sulfate at reflux temperature, was found in a previous work [1] to give among other products 5,6-*O*-isopropylidene-D-galactofuranose in 16 % yield. A claim that the corresponding D-glucose derivative is formed by partial acid hydrolysis of 1,2:5,6-di-*O*-isopropylidene-3-*O*-vinyl-α-D-glucofuranose [2] is questionable, and the product obtained has later been suggested to be 1,2-*O*-isopropylidene-α-D-glucofuranose, based on the way of preparation and the given melting point.[3] An investigation of the possibility to prepare 5,6-*O*-isopropylidene-D-glucofuranose by treatment of D-glucose with anhydrous cupric sulfate in acetone-*N*,*N*-dimethylformamide was therefore undertaken, and is the subject of the present report.



Refluxing of D-glucose for 24 h with these reagents, led to the formation of several products, of which two exhibited chromatographic mobility indicating the presence of one *O*-isopropylidene group. These compounds were isolated by column chromatogtaphy on silica gel. The slowest moving compound was indistinguishable from 4,6-*O*-isopropylidene-D-glucopyranose (II)[3,4] whereas the fastest moving, obtained in 14 % yield, was identified as 5,6-*O*-isopropylidene-D-glucofuranose (I). The identification was based on the facts that oxidation with periodate gave 2,3-*O*-isopropylidene-D-glyceraldehyde (III), and the mass spectrum (Fig. 1a) was almost identical with that of 5,6-*O*-isopropylidene-D-galactofuranose [1] (Fig. 1b). A peak of high intensity in the mass spectrum at *m/e* 101 is strongly indicative of the