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Synthesis of Guaiacylglycerol-β-Coniferyl and β-Coniferyl Aldehyde Ethers

Fumiaki NAKATSUBO* and Takayoshi HIGUCHI*

Abstract——A new synthetic method for the preparation of guaiacylglycerol-β-coniferyl and β-coniferyl aldehyde ethers, representing the most important lignin substructure are described as one in a series of synthetic studies of lignin model compounds.

Introduction

The arylglycerol-β-aryl ether substructure is the most important in lignins. It has been reported that 30 to 50% or more of the phenylpropane units are found in these structures[1,2]. For this reason, guaiacylglycerol-β-guaiacyl ether has been used as a lignin model compound for studying various lignin reactions, such as in pulping, in chemical utilization and in biodegradation. However, this compound is not truly representative of the lignin structure, because the β-aryl ether residues in lignins contain C_3-side chains. To study the effect of chemical changes on functional groups in the side chains of β-aryl ether substructures, it is desirable to use structural models containing ally alcoholic or ally aldehyde type side chains, which do occur in lignins. Guaiacylglycerol-β-coniferyl (5) and β-coniferyl aldehyde (4) ethers, therefore, are suitable model compounds. Guaiacylglycerol-β-coniferyl and β-coniferyl aldehyde ethers have been isolated in low yields as lignin hydrolysis products[3,4], and as products formed by the oxidative coupling of coniferyl alcohol[5,6]. However, the separation and purification of the two ethers are difficult because many other products are formed both in the hydrolysis and in the dehydrogenation, and compounds are obtained as a mixture of *erythro* and *threo* isomers which cannot be purified by crystallization.

The present paper, one in a series of synthetic studies of lignin model compounds, reports the new synthetic method for preparing guaiacylglycerol-β-coniferyl (5) and β-coniferyl aldehyde (4) ethers.

Results and Discussion

The synthetic method for the target ethers is analogous to that used to prepare guaiacylglycerol-β-guaiacyl ether[7] and a trilignol composed of phenylcoumaran and β-O-4 structures[8]. For the present synthesis (Fig. 1), coniferyl aldehyde and vanillin

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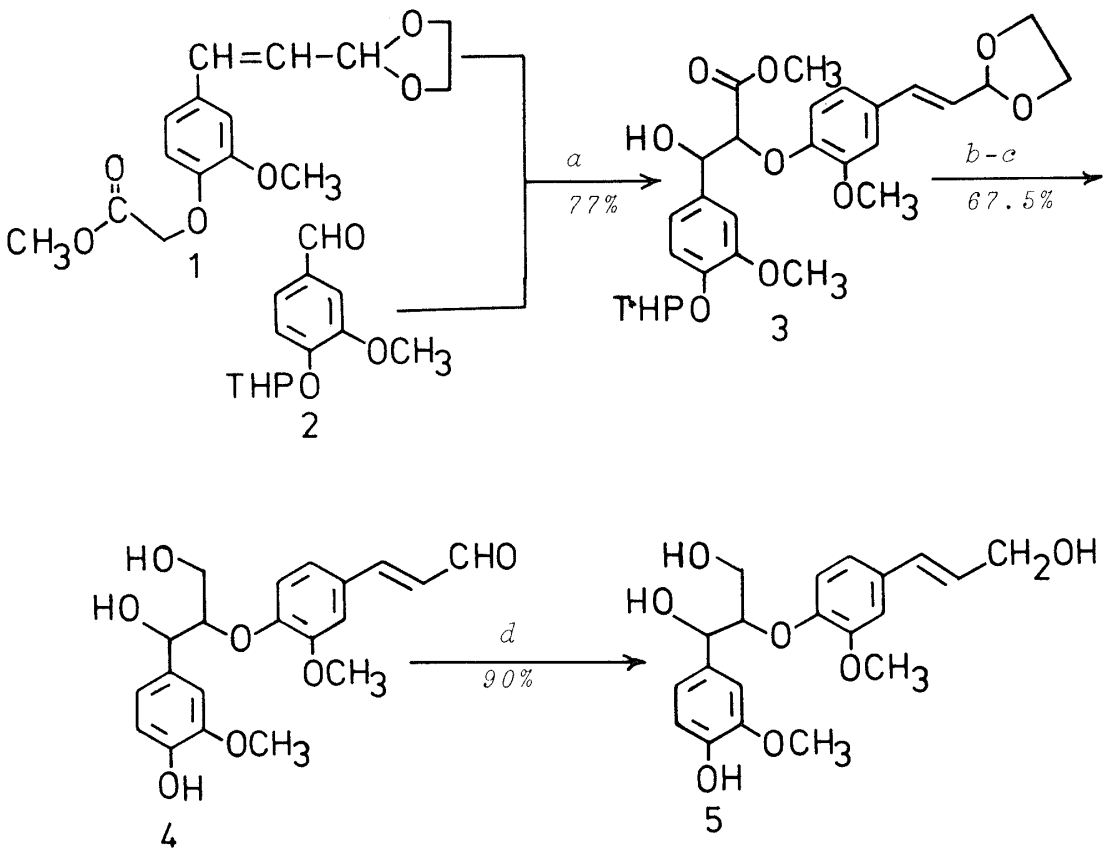

Fig. 1. Synthetic route of guaiacylglycerol-β-coniferyl (5) and β-coniferyl aldehyde (4) ethers. [a]Lithium diisopropyl amide/THF/−78°C [b]$LiAlH_4$/THF/50°C [c]1N-HCl/THF/0°C [d]$NaBH_4$/MeOH/0°C

are used as the starting materials instead of guaiacol and the phenylcoumaran.

The condensation of compound (1) with (2) by the use of lithium disiopropyl amide (LDA) gives the expected compound (3), with the small amounts of the starting materials and polar impurities. Purification by silica gel TLC (PF-254 Merck), developed with ethyl acetate/*n*-hexane (1:1), gives the pure compound (3). The use of silica gel chromatography (Wako gel C-100) for large-scale preparation, resulted in a partial deacetalization. Thus, the purification is carried out after the subsequent LAH reduction or at the stage of compound (4). The structure of compound (3) is supported by IR, which shows the absorption of the ester group at 1760 cm^{-1}, and by NMR spectra. The compound (3) is a mixture consisting of the *erythro* and *threo* isomers; the ratio was found to be about 3.5:1.0 by the NMR spectrum, which shows clearly distinguishable peaks of the ester protons at δ3.55 (s, *threo*) and δ3.68 (s, *erythro*) and of the β-methin proton at δ4.48 (d, J=6.0, *threo*) and δ4.66 (d, J=5.3, *erythro*). The *erythro* isomer might be expected to predominate from the reaction mechanism involving a six-membered transition state intermediate.

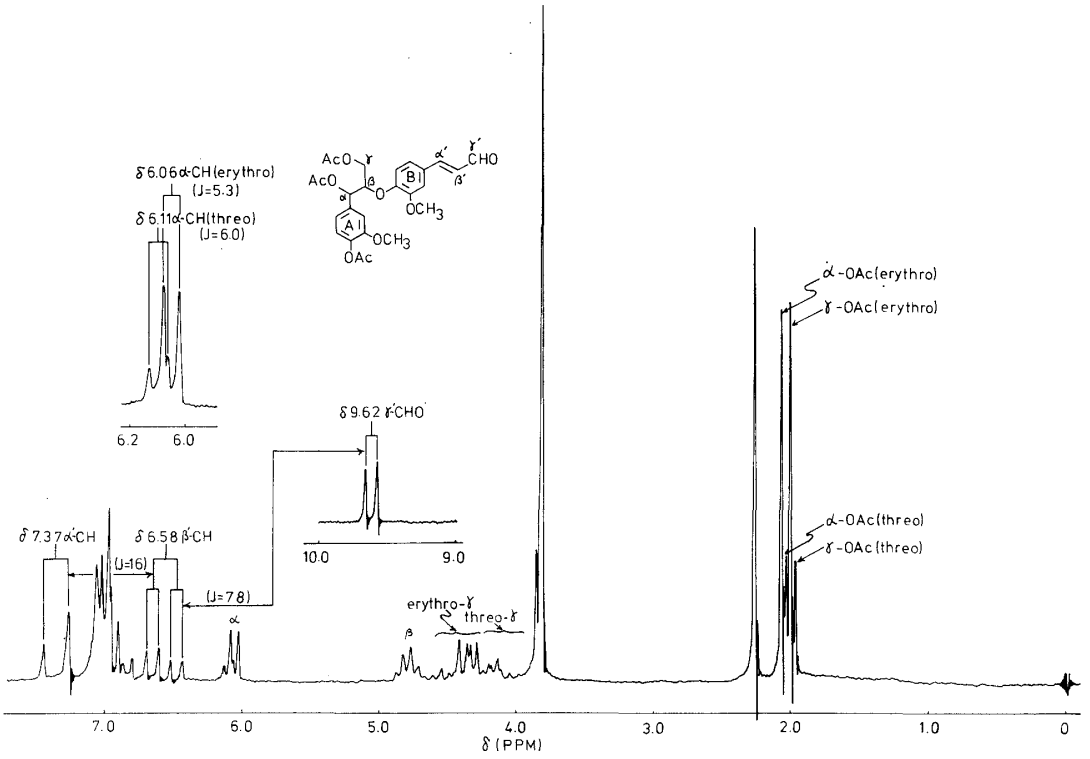

Fig. 2. NMR spectrum of acetylated guaiacylglycerol-β-coniferyl aldehyde ether (4)

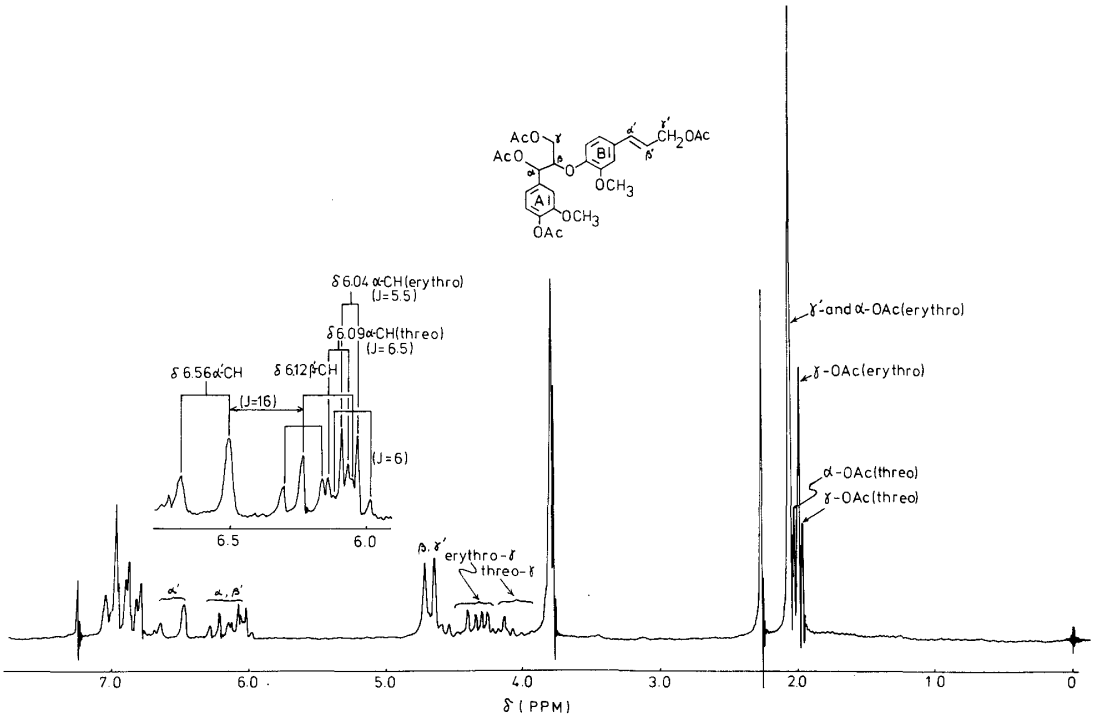

Fig. 3. NMR spectrum of acetylated guaiacylglycerol-β-coniferyl ether (5)

Compound (3) was subjected sequentially to lithium aluminium hydride reduction in THF at 50°C (75%), and to hydrolysis with 1N-HCl/THF (1:2) at 0°C (90%) to afford the expected compound (4). The yield of compound (4) from the starting material (1) is about 52%. Compound (4) was converted to the final compound (5) by sodium borohydride reduction in methanol at 0°C (90%). The structures of compound (4) and (5) are supported by UV, IR, MS and NMR, as described in the Experimental section. The NMR spectra of the acetyl derivatives are shown in Figs. 2 and 3. It is noteworthy that the peaks of the α-methin, γ-methylene and α, γ-alcoholic acetyl are clearly distinguishable between the *erythro* and *threo* isomers in the NMR spectra. The assignment of these protons based on the presumed reaction mechanism, which gives predominantly the *erythro* siomer, and also by comparision with the NMR spectra of the compound consisting of *erythro*/*threo* (about 1.0:1.1 ratio) obtained by the oxidative coupling of coniferyl alcohol. α-Methin protons in *erythro* isomers, having a smaller coupling constant, appear at higher magnetic fields than in *threo* isomers. γ-Methylene and also γ-alcoholic acetyl protons of *erythro* isomers appear at lower magnetic fields than these in the *threo* isomers.

Experimental

A HITACHI model 200-20 double beam spectrometer and a JASCO model IR-S were used for UV and IR spectra, respectively. NMR spectra were taken with a HITACHI R-22 high resolution NMR spectrometer (90 Mz), with TMS as internal standard. Chemical shifts and coupling constants are given in δ-values and Hz, respectively. Mass spectra were taken with a SHIMADZU -LKB 9000 gas chromatograph—mass spectrometer; the relative aboundance of each peak is designated in parentheses. Kieselgel 60 PF-254 Gipshaltig (Merck) was used for silica gel TLC plates.

Compounds (**1**) *and* (**2**)

These compounds were prepared by the method reported previously[8,9], and stored in a refrigerator to avoid partial decomposition of the acetals at room temperature.

Compound (3)

To a stirred solution of lithium diisopropyl amide (5.6 mM) in 20 ml of anhydrous THF, 1.37 g (4.66 mM) of coumpound (1) in 15 ml of THF was added dropwise over a period of about 40 min at −78°C under nitrogen. The reaction mixture gradually turned to an orange-red color. The mixture was stirred for an additional 30 min, and 1.1 g (4.66 mM) of compound (2) in 15 ml of THF was added dropwise over a period of 30 min at the same temperature. The orange-red color of the solution

gradually disappeared during the addition of compound (2) and finally turned to a slightly yellow. After stirring for an additional 30 min, the reaction mixture was neutralized by the addition of powdered dry-ice. The solution was partitioned between ethyl acetate and brine. The ethyl acetate layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give a yellow-colored oil (2.5 g) which was used for the subsequent LAH reduction without purification. An aliquot of the product obtained above was purified by silica gel TLC developed with ethyl acetate/*n*-hexane (1:1) for the NMR and IR measurements.

IR$\nu_{max}^{CH_2Cl_2}$ cm^{-1}:1760. NMR($CDCL_3$) δ: 1.4–2.0(6H,m,–CH_2–of THP), 3.4–3.7 (2H,m, –CH_2–O– of THP), 3.55(s, *threo*) and 3.63(s, *erythro*) (3H, two singlets, CH_3– of methyl ester), 3.79 and 3.80(6H, two singlets, CH_3– of methoxyl), 3.7–4.1(4H,m, –CH_2– of acetal), 4.48(d,J=6.0, *threo*) and 4.66(d, J=5.3, *erythro*) (1H, two doublet, β-CH–), 5.0–5.2(1H,m, α–CH–), 5.25–5.45(1H,m, –O–CH–O– of THP), 5.32(1H,d,J =5.7, –O–CH–O– of acetal), 5.59(1H, dd,J=15.5, 5.7, β′=CH–), 6.59(1H,d,J= 15.5, α′–CH=), 6.6–7.1(6H,m, aromatic).

Compound (**4**)

To a stirred solution of LAH (497.8 mg, 13.1 mM) suspended in 20 ml of anhydrous THF, 2.3 g of the crude yellow oil obtained above in 20 ml of THF was added dropwise over a period of 50 min at 50°C under nitrogen. After stirring for an additional 30 min, the reaction mixture was cooled to 0°C and about 1 ml of water in 5 ml of THF was added dropwise to the solution to decompose the excess hydride. After the addition of dry-ice to the solution, the reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate. The combined ethyl acetate solution was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give a slightly yellow glass (2.3 g). An aliquot of the product was purified by silica gel TLC developed twice with ethyl acetate/*n*-hexane (3:2) for NMR analysis.

NMR($CDCl_3$) δ: 1.9–2.0(6H,m, –CH_2– of THP), 3.4–3.7(2H,m, –CH_2–O– of THP), 3.78(6H,s, CH_3– of methoxyl), 3.80–4.10(4H,m, –CH_2–O– of acetal), 4.8–5.0 (1H,m, α–CH), 5.2–5.4(1H,m, –O–CH–O– of THP), 5.32(1H,d,J=6, –O–CH–O– of acetal), 5.96(1H,dd,J=16, 6, β′=CH–), 6.60(1H,d,J=16, α′–CH=), 6.15–7.10 (6H,m, aromatic.)

The product obtained above was purified on a silica gel column (Wakogel C-100 40 g, 2.6×10 cm) eluted with ethyl acetate/*n*-hexane (1:1) to give the expected diol product (1.36 g, 58% overall yield from compound (1)) containing some partly hydrolyzed aldehyde; this mixture was used for the subsequent reaction as follows.

To a stirred solution of the diol derivative (1.36 g, 2.71 mM) obtained above in 15 ml of THF, 7.5 ml of 1N-HCl was added dropwise at 0°C under nitrogen. After stirring for 2 hours, the solution was partitioned between ethyl acetate and brine. The

ethyl acetate solution was washed with brine until the washings became neutral, and then dried over Na_2SO_4. Evaporation of the solvent *in vacuo* afforded a yellow glass which was purified by TLC developed twice with 3% methanol/methylene chloride to give the expected compound (4), pure by TLC, as a slightly yellow glass (913 mg, 90%).

UV_{max}^{MeOH} nm(log ε): 230(4.14), 336.5 (4.27). IR ν_{max}^{KBr} cm^{-1}: 3500, 1665, 1625, 1595, 1520, 1510, 1465, 1450, 1425, 1275, 1220, 1130, 1020, 965. MNR(d_6-acetone) δ: 3.40–3.80(2H,m, –CH–), 3.82(3H,s, CH_3O– of A-ring), 3.88(*erythro*) and 3.92 (*threo*) (3H, two singlets, CH_3O– of B-ring), 4.51(1H, broad q, J=4.5, β–CH), 4.91(1H, broad d,J=5.5, α–CH–), 6.60(dd,J=16, 7.5, *erythro*), and 6.62(dd,J=16, 7.5, *threo*) (1H, β′=CH–), 6.63–7.35(6H,m, aromatic), 7.50(*erythro*) and 7.52(*threo*) (1H, two doublets, J=16, α′–CH=), 9.57(d,J=7.5, *erythro*) and 9.58(d,J=7.5, *threo*) (1H, γ′–CHO). MS m/e(%): 374(M^+, 0.9), 356(4.2), 338(4.2), 326(33.2), 297(7.3), 265(7.3), 237(3.9), 204(48.8), 178(100), 161(29.3), 151(38), 147(38), 137(61), 135 (46.3), 124(23.4), 119(24.4), 107(41), 91(35.6), 89(32.7), 77(52.7), 65(34.1), 51(40.5).

Compound (**5**)

To a stirred solution of compound (4) (194.2 mg, 0.52 mM) in 4 ml of methanol, 9.5 mg (0.26 mM) of $NaBH_4$ was added at 0°C under nitrogen. After 30 min, the product was partitioned between ethyl acetate and brine. The ethyl acetate solution was dried over Na_2SO_4 and evaporated *in vacuo* to give a colorless glass which was purified by TLC developed with 5% methanol/methylene chloride to afford the pure compound (5) (176 mg, 90%) as a colorless glass.

$UV\lambda_{max}^{MeOH}$ nm(log ε): 265.6(4.22). IR ν_{max}^{KBr} cm^{-1}: 3500, 1605, 1520, 1270, 1155, 1130, 1085, 1028, 965, 855. NMR(d_6-acetone) δ: 3.82(3H,s, CH_3O– of A-ring), 3.85(CH_3O– of *erythro* B-ring) and 3.89(CH_3O– of *threo* B-ring) (3H, two singlets), 4.23(2H, broad d, J=5.0, γ′–CH_2, in one drop of D_2O), 4.43(1H,q,J=5, β–CH· in one drop of D_2O), 4.94(1H, broad d,J=5, α–CH, in one drop of D_2O), 6.23(*erythro*) and 6.24(*threo*) (1H, two dt,J=16, 5.0, β′=CH–), 6.53(1H, broad d,J=16, α′–CH=), 6.65–7.15(6H,m, aromatic). MS m/e(%): 376(M^+, 3.7), 358(3.7), 340(1.8), 328 (12.9), 326(5.2), 206(48), 180(60), 162(23), 151(37), 137(100), 131(25), 124(48), 119(38), 91(49), 77(33), 65(33).

Acetates of compounds (**4**) *and* (**5**)

About 50 mg of compound (4) or (5) dissolved in 2 ml of THF was treated with 2 ml of acetic anhydride/pyridine (1:1) overnight at room temperature. The reaction mixture was evaporated *in vacuo* and acetic anhydride/pyridine was removed azeotropically by evaporation with benzene. The products were purified by TLC(ethyl acetate/*n*-hexane=1:1) for the NMR measurements.

NMR spectrum of acetyl compound (4) (Fig. 2) ($DCCl_3$) δ: 1.98(*threo*) and 2.02 (*erythro*) (3H, two singlets, γ′-OAc), 2.04(*threo*) and 2.09(*erythro*) (3H, two singlets,

α′–OAc), 2.26(3H, phenolic–OAc), 3.83(CH_3O– of A-ring and *erythro* B-ring) and 3.87(CH_3O– of *threo* B-ring) (6H, two singlets), about 3.95–4.25(*threo*) and 4.26–4.70 (*erythro*) (2H,m, γ–CH_2), 4.80(1H, broad q,J=5, β–CH), 6.06(d,J=5.3, *erythro*) and 6.11(d,J=6.0, *threo*) (1H, α-CH), 6.58(1H,dd,J=16, 7.8, β′=CH–), 6.78–7.20(6H,m, aromatic), 7.37(1H,d,J=16, α′–CH=), 9.62(1H,d,J=7.8, γ′–CHO).

NMR spectrum of acetyl compound (5) (Fig. 3) ($CDCl_3$) δ: 1.96 (*threo*) and 2.00 (*erythro*) (3H, two singlets, γ–OAc), 2.02(*threo* α–OAc), and 2.08(erythro α-OAc and γ′–OAc) (6H, two singlets, methoxyl), about 3.9–4.2(*threo*) and 4.2–4.6(*erythro*) (2H,m, γ–CH_2), 4.5–4.8(1H,m, β-CH), 4.68(2H, broad d,J=6, γ′–CH_2), 6.04(d,J=5.5, *erythro*) and 6.09(d,J=6.5, *threo*) (1H, two doublets, α–CH), 6.12(1H,dt,J=16, 6,β′=CH–), 6.56(1H, braod d,J=16, α′–CH=), 7.65–7.10(6H,m, aromatic).

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