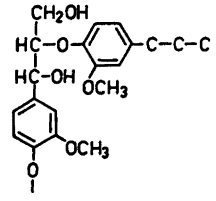
On the Synthesis of Lignin Model Compounds of the Arylglycerol-β-aryl Ether Type

INGMAR BERNDTSSON and
KNUT LUNDQUIST

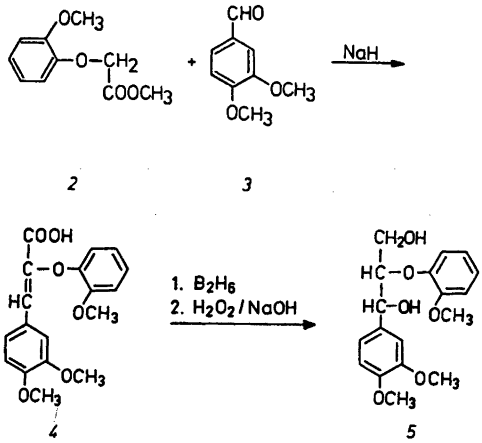
Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, S-402 20 Göteborg 5, Sweden

In a previous paper [1] new synthetic routes for the preparation of lignin model compounds of the arylglycerol-β-aryl ether type (*1*) were described. Syntheses of such model compounds have also recently been reported by Nakatsubo *et al.*[2] One of the syntheses of model compound *5* described in Ref. 1 involves preparation of aryloxycinnamic acid *4* by a Perkin reaction [1] or by a Claisen reaction followed by hydroboration of acid *4* (Scheme 1). The present paper



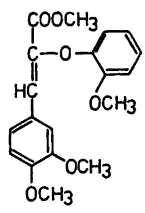
1

describes the synthesis of acid *4* by the Claisen reaction and improvements of the yield in the conversion of this compound into compound *5* by hydroboration. In addition the separation of the two possible diastereomers of compound *5* by ion exchange chromatography is described.

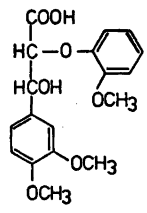


Scheme 1.

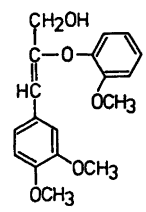
Synthesis of acid *4* by a Perkin reaction gave only poor yields.[1] Attempts have been made to increase the yield by replacing acetic anhydride with pivalic anhydride in the reaction mixture. However, the yield of acid *4* was about the same. Preparation of acid *4* by the Claisen reaction from the methyl ester of 2-methoxyphenoxyacetic acid (*2*) and veratraldehyde (*3*) using sodium hydride as a condensing agent (Scheme 1) gave a higher yield. We have made a series of experiments to find suitable conditions for this synthesis. The best results were obtained when an equimolar solution of the ester and the aldehyde was dropped into a suspension of sodium hydride in toluene at 60 °C (yield 41 %). Under these conditions the acid *4* is obtained and not its methyl ester (*6*), which was the expected product. Apparently the ester *6* formed is saponified in the reaction mixture (the condensation reaction involves an elimination of the elements of water) or, possibly, during an initial phase of the work-up procedure. Lower reaction temperatures result in the formation of considerable amounts of acid *7*. If the reaction temperature is increased, the disproportionation of the aldehyde (*cf.* Ref. 3) becomes important, which in our case



6



7



8

resulted in the presence of considerable amounts of 3,4-dimethoxybenzyl alcohol and veratric acid in the reaction mixtures. Similarly, dropping a solution of the ester alone into a solution of veratraldehyde containing sodium hydride favors the disproportionation reaction.

Earlier [1] hydroboration experiments with acid *4* gave model compound *5* in about 40 % yield. From hydroboration studies by Brown and co-workers [4] it was concluded that it should be possible to increase the yield considerably by modifying the reaction conditions. In fact, treatment with diborane at a lower temperature together with modifications of the subsequent

oxidation with hydrogen peroxide gave compound *5* in a considerably higher yield (68 %). Hydroboration of acid *4* gives the pure *erythro* form of compound *5*.[1] Preparation of this compound by other described methods for the synthesis of arylglycerol β-aryl ethers (Refs. 1 and 2 and literature cited therein) must involve a separation of diastereomers.

One way of obtaining the *erythro* as well as the *threo* form of compound *5* is the separation of these compounds from reaction products consisting of mixtures of the two diastereomers; several synthetic routes which provide such mixtures are known (Ref. 1 and literature cited therein). We wish to report that this separation can be done by chromatography on an anion exchanger, using borate solution as an eluent. The *threo* form is eluted more rapidly than the *erythro* form, which implies that the latter compound gives the strongest borate complex (*cf.* Ref. 5). This result is in accord with electrophoresis studies [6] of the two borate complexes.

Experimental. Conditions for TLC were those given in Ref. 1. The *methyl ester of 2-methoxyphenoxyacetic acid (2)* was prepared from 2-methoxyphenoxyacetic acid and methanol with H_2SO_4 as a catalyst (m.p. 33 °C, lit.[7] 33 °C). Alternatively compound *2* can be prepared from guaiacol and methyl chloroacetate.[7]

Preparation of α-(2-methoxyphenoxy)-3,4-dimethoxycinnamic acid (4) by the Claisen reaction. Compound *2* (15.0 g) and veratraldehyde (12.7 g) were dissolved in toluene (87 ml). The solution was dropped from a pressure-equalizing funnel into a stirred suspension of NaH (8.6 g of 55 – 60 % NaH in mineral oil) in toluene (20 ml) kept at 60 °C. Initially a few ml of the solution was added. As indicated by the evolution of hydrogen, the reaction started after 15 min. The rest of the solution was added during 1 h. Stirring at 60 °C was continued for 7 h. The reaction mixture was neutralized with conc. hydrochloric acid-water (1:1) and transferred to a separatory funnel by means of ether (375 ml) and 5 % $NaHCO_3$ solution (250 ml). After shaking, the layers were separated and the ether layer extracted with 2 × 250 ml of 5 % $NaHCO_3$ solution. The combined aqueous layers were acidified (pH 2) with conc. hydrochloric acid-water (1:1) under stirring. A crystalline precipitate was formed (18.9 g), which was treated with 75 ml of ether overnight. The residue (13.9 g) consisted according to TLC essentially of acid *4*. Recrystallization from acetone gave 10.4 g of acid *4* with m.p. 202 °C, lit.[1] m.p. 202 °C (yield 41 %).

Hydroboration of α-(2-methoxyphenoxy)-3,4-dimethoxycinnamic acid (4). Acid *4* (990 mg) was treated with B_2H_6 as described in Ref. 1, but the reaction mixture was kept at 0 °C. The reaction can be followed by direct examination of the reaction mixture by TLC, although the chromatograms only approximately reflect the composition of the final reaction product obtained after oxidation with H_2O_2. It was found suitable to interrupt the reaction, when an intermediate (or by-product) with R_F value 0.41 tends to disappear. This compound has been isolated by column chromatography according to the procedure described in Ref. 1 and has been identified by spectral data as compound *8*. [^{1}H NMR spectrum (δ units; solvent, chloroform-*d*): 2.2 (1 H, s; OH), 3.74 (3 H, s; OCH_3), 3.84 (3 H, s; OCH_3), 3.90 (3 H, s; OCH_3), 4.16 (2 H, s; $-CH_2-$), 6.08 (1 H, s; vinyl proton), ≈ 7.0 (7 H, m; aromatic protons)]. After 5 h the reaction mixture was oxidized with H_2O_2 and worked up as described in Ref. 1, with the exception that H_2O_2 was added to the reaction mixture prior to 3 M NaOH (which was added slowly during a 15 min period). Crystallization from ether gave 0.57 g of the *erythro* form of compound *5* (m.p. 98 °C, lit.[6] 97.5 – 98.5 °C). An additional amount (0.11 g) of the same compound was obtained from the mother liquor (column chromatography [1]). Yield: 68 %.

Separation of the two diastereomers of compound 5 by ion exchange chromatography. A column of an anion exchanger (QAE-Sephadex A-25, 20 g) was packed and several hundred ml of the eluent [0.06 M $K_2B_4O_7$ in water-acetone (4:1)] was allowed to pass the column. A mixture of the diastereomers of compound *5* (0.15 g) was dissolved in 9 ml of the eluent and applied to the column. The eluate was collected in 5 ml fractions which were pooled on the basis of an examination by TLC. The organic constituents were separated from the pooled fractions by chloroform extraction. From fractions 17 – 21, 89 mg of the *threo* form of compound *5* (^{1}H NMR) was obtained, and fractions 22 – 26 contained 40 mg of the *erythro* form of compound *5* (^{1}H NMR).

Acknowledgements. We thank Dr. K. Larsson and Prof. M. Nilsson for valuable discussions and Mrs. I. Somfai for skilful technical assistance.

1. Lundquist, K. and Remmerth, S. *Acta Chem. Scand. B 29* (1975) 276.
2. Nakatsubo, F., Sato, K. and Higuchi, T. *Holzforschung 29* (1975) 165.
3. Swamer, F. W. and Hauser, C. R. *J. Am. Chem. Soc. 68* (1946) 2647.
4. Brown, H. C. and Cope, O. J. *J. Am. Chem. Soc. 86* (1964) 1801; Brown, H. C. and Gallivan, R. M. *Ibid. 90* (1968) 2906; Brown, H. C. and Sharp, R. L. *Ibid. 90* (1968) 2915.
5. Larsson, K. and Samuelson, O. *Carbohydr. Res. 50* (1976) 1.
6. Gierer, J. and Norén, I. *Acta Chem. Scand. 16* (1962) 1976.
7. Myška, J. *Czech. Pat.* 96,577 (1960).

Received May 16, 1977.