Acta Chemica Scandinavica, 1995: 49: 623–624
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ACTA
CHEMICA SCANDINAVICA
ISSN 0904–213X

Short Communication

Synthesis of Guaiacylglycerol β-Guaiacyl Ether

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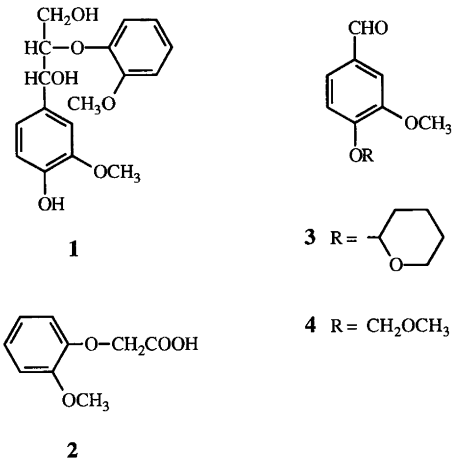
Li, S., Lundquist, K. and Paulsson, M., 1995. Synthesis of Guaiacylglycerol β-Guaiacyl Ether – Acta Chem. Scand. 49: 623–624 © Acta Chemica Scandinavica 1995.

A previous paper[1] describes the synthesis of a series of lignin model compounds of the arylglycerol β-guaiacyl ether type. In the initial step an aromatic aldehyde was reacted with the α-lithiated lithium salt of (2-methoxyphenoxy)ethanoic acid (**2**). The crude mixtures of 3-hydroxypropionic acids obtained were reduced with borane–dimethyl sulfide complex. Pure *erythro* and *threo* forms of arylglycerol β-guaiacyl ethers could be isolated from the reduction products by chromatography on SiO_2 followed by ion-exchange chromatography.

The phenolic model 1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol (**1**) was synthesized using the tetrabutylammonium salt of vanillin and (2-methoxyphenoxy)ethanoic acid (**2**) as starting materials.[1] The yield was rather low (27%). Higher yields could be obtained with benzyl as a protecting group[2] but such synthesis requires additional reaction steps. This paper reports a synthesis of **1** (yield, 47%) starting from **2** and the tetrahydropyran-2-yl ether of vanillin (**3**). No separate deprotection step was required since removal of the tetrahydropyran-2-yl group occurred spontaneously during the reaction of **3** with α-lithiated **2** (or during the work-up procedure). We have also prepared **1** using **2** and the methoxymethyl ether of vanillin (**4**) as starting materials (yields were in the range 40–50%). In this case a separate reaction step was required to remove the methoxymethyl group. The intermediate 3-hydroxypropionic acid derivative was deprotected by acid hydrolysis.

The separation of the *erythro* and *threo* forms of **1** was accomplished by ion-exchange chromatography according to the method described in Ref. 1 but the acetone in the eluent was replaced by ethanol (cf., Ref. 3). Under these conditions the *threo* form of **1** exhibited a slight tailing while some heading could be observed in experiments with the *erythro* form of **1**. However, complete separation of the isomers could be achieved. No tailing or heading phenomena were observed in separation experiments with non-phenolic arylglycerol β-guaiacyl ethers.



Scheme 1.

Experimental

*The tetrahydropyran-2-yl ether of vanillin (**3**).* Vanillin (6.09 g, 40 mmol) was derivatized essentially according to a method[4] for the preparation of tetrahydropyran-2-yl ethers of alcohols. An excess of 3,4-dihydro-2*H*-pyran (80 mmol) was used. Unchanged vanillin was removed by extraction with aqueous NaOH. Crystallization from methanol gave a product melting at 42–43 °C (lit.[5] 44–46 °C). Yield: 5.14 g (54%). ^{1}H NMR [400 MHz, $CDCl_3$, $(CH_3)_4Si$, 300 K]: δ 1.5–2.2 [6 H, m, C–$(CH_2)_3$–C], ≈3.63 (1 H, m, C–CH_2–O), ≈3.90 (1 H, m, C–CH_2–O), 3.93 (3 H, s, OCH_3), 5.55 (1 H, ≈t, J = 3.2 Hz, O–CH–O), 7.2–7.5 (3 H, m, aromatic protons), 9.86 (1 H, s, CHO).

*The methoxymethyl ether of vanillin (**4**).* Vanillin (5.33 g, 35 mmol) was derivatized using dimethoxymethane as the reagent. A procedure developed for the preparation of methoxymethyl ethers of alcohols[6] was adopted but the

amounts of reagent and catalyst (P_2O_5) added were reduced to one third of those calculated from Ref. 6. The solids in the reaction mixture were removed prior to work-up. Unchanged vanillin was removed by extraction with 0.5 M NaOH. Crystallization from ethanol gave a product melting at 39°C (lit.[7] 39–40°C). Yield: 57%. ^{1}H NMR [400 MHz, $CDCl_3$, $(CH_3)_4Si$, 300 K]: δ 3.53 (3 H, s, CH_3O–C–O), 3.96 (3 H, s, OCH_3), 5.33 (2 H, s, O–CH_2–O), 7.2–7.5 (3 H, m, H-Ar), 9.88 (1 H, s, CHO).

1-(4-Hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)-1,3-propanediol (**1**). (2-Methoxyphenoxy)ethanoic acid (**2**) (3.64 g, 20 mmol) and the tetrahydropyran-2-yl ether of vanillin (**3**) (4.72 g, 20 mmol) were used as starting materials. The synthesis was performed essentially according to the 'general procedure' for the synthesis of arylglycerol β-guaiacyl ethers described in Ref. 1 (p. 150). The condensation step was modified in that the intermediate α-lithiated lithium salt of **2** was prepared by reacting **2** with a lithium diisopropylamide solution obtained by injecting 29 ml 1.5 M lithium diisopropylamide in cyclohexane (Aldrich) into 50 ml tetrahydrofuran (cf. *Erratum*). Fifty-five ml 3 M HCl were used for the acidification of the reaction mixture; the reaction mixture was exposed to acid conditions for about 1 h during the work-up procedure. Reduction of the crude product (6.56 g) with borane–dimethyl sulphide complex gave 5.66 g of an oil. Purification by chromatography on SiO_2 gave a product weighing 3.96 g. Further purification and separation of the *erythro* and *threo* forms was accomplished by ion-exchange chromatography according to the method described in Ref. 1 but the acetone in the eluent was replaced by ethanol (cf. Ref. 3). Yield: 2.98 g (1.45 g of the *threo* form, 1.53 g of the *erythro* form), (47%).

Erratum. In Ref. 1 (p. 150) it is said that diisopropylamine is reacted with '43 ml 1.6 M solution' of butyllithium. The amount of butyllithium used was 43 mmol (27 ml 1.6 M solution) and the reaction was performed at 0°C.

Acknowledgements. Financial support from *Stiftelsen Nils och Dorthi Troedssons Forskningsfond* is gratefully acknowledged.

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Received November 30, 1994.