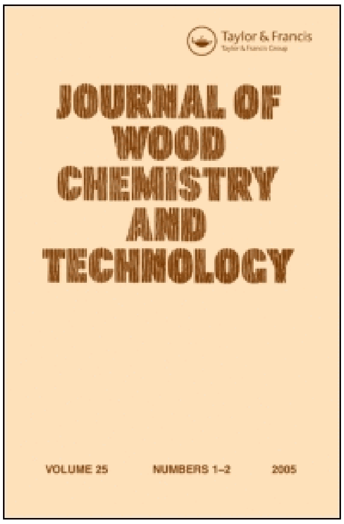

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THE SYNTHESIS OF 1,2-DIARYLPROPANE-1,3-DIOLS via THE IVANOFF REACTION

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ABSTRACT

The synthesis of two β-1 lignol dimers, 1,2-bis-(4-hydroxy-3-methoxyphenyl)-1,3-propanediol (VIa) and 1-(3-ethoxy-4-hydroxyphenyl)-2-(4-hydroxy-3-methoxyphenyl)-1,3-propanediol (VIb) was performed using the Ivanoff Reaction in the key synthetic step. The erythro forms of VIa and b were isolated as crystalline solids in yields of approximately 15%, while the threo isomers were obtained as oils. The ratio of threo:erythro isomers was approximately 3:1.

INTRODUCTION

As part of a continuing study of the reactions of lignin model compounds with alkaline hydrogen peroxide under technical bleaching conditions[1-5], it became necessary to synthesize lignin model dimers containing an interunitary β-1 linkage. At the outset of this project in 1978, two syntheses for β-1 diols had been published. The first, reported in 1965[6], involved the symmetrical benzoin condensation of benzyl vanillin. The second, reported in 1975[7], was based on the condensation of methyl benzylhomovanillate with benzyl syringaldehyde. Since 1978, three additional syntheses have been reported[8,9,10], each having its own merits with respect to simplicity, yield, and stereoisomeric purity. The synthetic sequence shown in Figure 1 was developed in this laboratory. It represents an improvement in terms of simplicity and of product yield and purity compared to the initially reported syntheses, and an alternative approach to the synthesis developed by Lundquist[10] in which homovanillic acid was converted to an α-lithiated carboxylic acid salt using lithium diisopropylamide at 0°C and subsequently condensed with benzyl vanillin.

DISCUSSION

The key synthetic step depicted in Figure 1 is the Ivanoff[11] reaction from which the Ⓖ—p(β-1)—Ⓖ skeleton is obtained. The Ivanoff[11] reaction is basically a Grignard reaction in which benzylhomovanillic acid (I) reacts with an excess of isopropyl magnesium chloride forming the dienolate intermediate (II). Nucleophilic

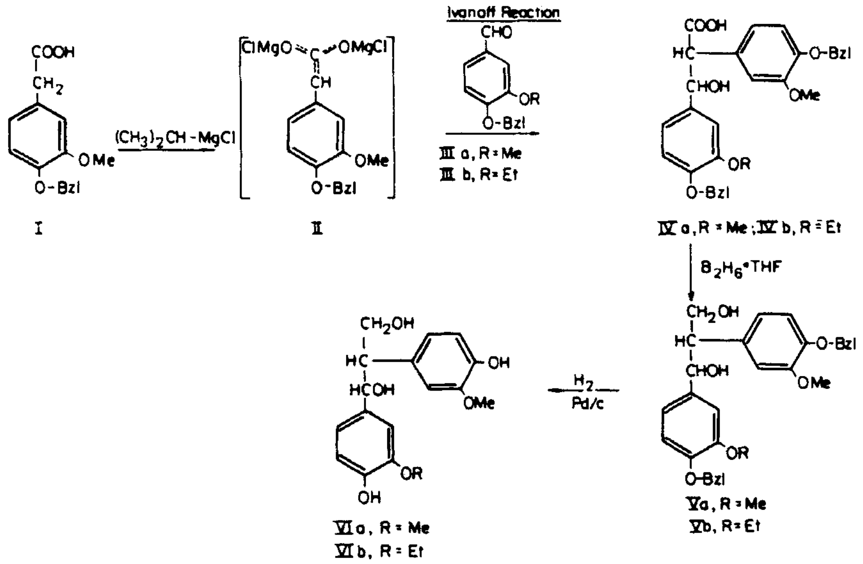

FIGURE 1. Sequence for the Synthesis of β-1 Diols via the Ivanoff Reaction

addition of this intermediate to benzylvanillin (IIIa) or 4-O-benzyl-3-ethoxybenzaldehyde (IIIb) at ambient temperature affords the β-hydroxypropionic acid (β-1 acid, IV). The erythro form of this acid, as determined by a comparison with published melting point data for acid IVa[10] and ^{1}H NMR data for the corresponding diol tetraacetates of VIa[7] and b, is readily isolated as a precipitate in the product mixture. Reduction of acids IVa or IVb with excess diborane in THF followed by debenzylation with hydrogen in the presence of Pd on carbon yields either 1,2-bis-(4-hydroxy-3-methoxyphenyl)-1,3-propanediol, VIa, or its ethoxy analog, VIb, shown in Figure I.

Since the β-1 diol dimers isolated from spruce and birch wood meal[12] have been shown to be of the erythro configuration[7], the synthesis detailed below is concerned mainly with this isomer.

EXPERIMENTAL

Synthesis

The benzyl ethers of vanillin (IIIa) and 3-ethoxy-4-hydroxybenzaldehyde (IIIb) were prepared following the procedure outlined by Omori and Dence[5]. Yield (benzyl vanillin), 80%; mp (after recrystallization from light petroleum ether:acetone, 4:1), 60-61°C (Lit.[4,5] 60-61°C). Yield, 4-O-benzyl-3-ethoxybenzaldehyde, 80%; mp (after recrystallization) 49-50°C.

Homovanillic acid was benzylated using a modification of the procedure cited above: homovanillic acid (5.0g; 0.027 mole, Aldrich Chemical Co.) was added to a prewarmed (50°C) solution of absolute ethanol (100 ml) and potassium hydroxide (0.07 mole) under a continuous nitrogen purge. The foregoing solution was gently refluxed while 7.0 ml (0.06 mole) of benzyl chloride dissolved in 10 ml of ethanol was added dropwise over a 15-minute period. After 2 hours of refluxing, 1.0g of potassium hydroxide dissolved in 20 ml of water was added, and the mixture was refluxed an additional 20 minutes. The mixture was cooled, acidified, and diluted with

1200 ml of water. The resulting precipitate was recrystallized from diethyl ether-acetone by suspending the solids in 50 ml of hot ether and adding 20 ml of acetone. Yield, 80%; mp 116-117° (Lit.[13] 116°C).

2-(4-Benzyloxy-3-methoxyphenyl)-3-(4-benzyloxy-3-ethoxyphenyl)-3-hydroxypropionic acid (erythro IVb) was prepared following essentially the procedure described by Zimmerman and Traxler[14] for the condensation of phenylacetic acid and benzaldehyde. Benzyl homovanillic acid (3.7g or 0.014 mole) suspended in 100 ml of dry freshly distilled diethyl ether, was added dropwise under nitrogen to an ether solution which contained 0.035 mole of isopropyl magnesium chloride (i.e., 0.035 mole each of isopropyl chloride, magnesium turnings, and 50 ml of dry diethyl ether). The resultant slurry was stirred magnetically at 30°C for 15 hours while under a continuous nitrogen purge. Subsequently, 0.014 mole (3.5g) of 4-O-benzyl-3-ethoxybenzaldehyde dissolved in 50 ml of diethyl ether was added dropwise, and the mixture was refluxed for 5 hours. After cooling, the mixture was stirred vigorously while 400 ml of water and 50 ml of concentrated HCl were added. The spongy precipitate that formed was hydrolyzed by the acid and dissolved in the ether layer. The aqueous phase was re-extracted with ether (4 × 100 ml), and the combined ether extracts were extracted with water (2 × 100 ml), dried over anhydrous sodium sulfate, and concentrated *in vacuo* at room temperature to 50-100 ml. A white precipitate formed (~1.0g) upon cooling, which corresponded to the erythro β-1 acid (IVb) based on ^{1}H NMR spectrometry of the corresponding diol tetraacetate of VIb. Upon further evaporation of the ether extract, ~6.0g of a light yellow oil were recovered which contained additional erythro (~10%) and substantial amounts of the threo β-1 acid. These isomers were separated by column chromatography (silica gel) and high-performance liquid chromatography (5μ silica gel) as described elsewhere[10,15]. Total yield, erythro isomer (IVb) 1.2g or 16%; mp 167-70°C (with decomposition). The mass spectral fragmentation pattern (70 eV) was identical to literature data[10]: 528 (m^+, absent), 510 (0.1%), 483 (0.01%), 466 (6.3%), 375 (19.6%), 284 (2.3%), 272 (9.0%), 256 (5.2%), 181 (2.5%), 165 (1.0%), 91 (100%).

The procedure used to prepare 2,3-bis(4-benzyloxy-3-methoxyphenyl)-2-hydroxypropionic acid was identical to the one described above. Yield erythro isomer, 1.0g or ~15%; mp 181-3° (Lit.[10] 185°C); MS:[10] 514 (m^+, absent), 496 (0.02%), 452 (11.6%), 362 (8.8%), 361 (41.0%), 272 (1.0%), 271 (2.5%), 149 (5.3%), 91 (100%).

Erythro 1-(4-benzyloxy-3-ethoxyphenyl)-2-(4-benzyloxy-3-methoxyphenyl)-1,3-propanediol was obtained by the reduction of acid IVb following essentially the procedure of Brown et al.[16] An excess of diborane-tetrahydrofuran complex (2.0 ml, B_2H_6·THF, 1M, Aldrich Chemical Co.) was added slowly under nitrogen to a stirred solution of acid IVa or IVb (1.0g) in THF. After 1 hour at 30°C, the excess diborane was destroyed with 50 ml of 1:1 water-THF, and the boric acid was removed by saturating the mixture with potassium carbonate. The THF layer and subsequent THF extracts (3 × 50 ml) were combined, dried over anhydrous sodium sulfate, and evaporated. Yield erythro diol, Vb, after recrystallization from diethyl ether:petroleum ether (1:1), 80-90%; mp, 95-98°C; MS: 514 (m^+, absent), 496 (0.1%), 482 (0.03%), 466 (1.0%), 375 (3.4%), 284 (1.0%), 257 (2.0%), 240 (11.1%), 167 (2.5%), 149 (7.5%), 91 (100%).

The erythro bis-1,2-(4-benzyloxy-3-methoxyphenyl)-1,3-propanediol was prepared as described for the ethoxy derivative. Yield, 80-90%; mp, 105-7°C (Lit.[8,9] 106-8°C). MS: 500 (m^+,absent), 482 (0.6%), 468 (0.1%), 452 (2.7%), 361 (1.0%), 272 (15.6%), 240 (21.0%), 91 (100%).

The debenzylation of erythro dibenzyl diols Va,b was accomplished by low pressure hydrogenation in the presence of 5% Pd on carbon as described by Omori and Dence.[5] Yield of ethoxy β-1 diol VIb, 80-90%, mp 126-30°C. MS(diol): 334(m^+,absent), 316 (4.9%), 286 (54.0%), 167 (22.3%), 151 (17.7%), 150 (100%), 137 (15.7%), 123 (4.3%). MS (tetraacetatete): 502 (m$^+$, 1.6%), 460 (3.6%), 400 (1.0%), 251 (14.8%), 209 (66.3%), 192 (16.3%), 167 (85.7%), 150 (100%), 149 (25.4%), 137 (16.9%). ^{1}H NMR (tetraacetate[7], δ ppm, $CDCl_3$): 1.34 (3H,t), 1.98 (6H,s), 2.28 (3H,s), 2.31 (3H,s), 3.38 (1H,m,H_β), 3.75 (3H,s), 3.92 (2H,q), 4.22 (1H, dd, J = 6.6 and 11.0, H_γ), 4.38 (1H,dd, J = 7.0 and 11.0, H_γ), 6.10 (1H,d, J = 6.0, H_α), 6.62-7.02 (6H,m).

Yield of bis-guaiacyl β-1 diol (VIa), 80-90%; mp, 145-7°C (Lit. 146.5-9°C[8], 158-9°C[9], 143.5[12]). Tetraacetate; mp, 133.5°C (Lit. 132-3°C[8], 132-4°C[12]). MS (diol[17],: 320 (m$^+$, absent), 302 (1.8%), 272 (30.0%), 167 (5.9%), 150 (100%), 137 (9.0%) 123 (3.5%). MS (tetraacetate, taken on a Perkin Elmer RMU6 spectrometer): m$^+$,488 (3.1%), m/e 446 (3.4%), m/e 386 (1.2%), m/e 344, (1.0%), m/e 237 (0.1%), m/e 209 (14.4%), m/e 195 (42.0%), m/e 167 (3.4%), m/e 153 (46.5%), m/e 149 (2.0%), m/e 135 (4.3%), m/e 43 (100%). ^{1}H NMR (tetraacetate[7], δ ppm, $CDCl_3$): 1.97 (6H,s), 2.28 (6H,d), 3.36 (1H,t,H_β), 3.73 (3H,s), 3.77 (3H,s), 4.16 (1H,dd, J = 6.4 and 11.0, H_γ), 4.35 (1H,dd, J = 7.1 and 11.0, H_γ), 6.11 (1H,d, J = 6.4, H_α), 6.62-7.02 (6H,m).

The ratio of the erythro and threo forms of the dimer acid, IVa, was determined by HPLC separation of the two isomers in the Ivanoff product mixture and measurement of their corresponding peak heights.

Spectrometric methods

^{1}H NMR spectra were taken on a Varian XL-100 spectrometer using tetramethylsilane as a reference and $CDCl_3$ as a solvent. Mass spectra (MS) were taken on a Finnigan 4000 gas chromatograph/ mass spectrometer using the solid probe and temperature programming from -10°C→180°C in a period of 20 minutes.

Chromatographic procedures

Thin layer chromatography (TLC) was performed using silica gel 60F-254 on aluminum sheets (E. Merck, Darmstadt, Germany) with toluene, ethyl formate, formic acid (5:4:1) to develop the plates. The components were detected by spraying the plates with 20% sulfuric acid followed by heating at 105°C for 10 minutes.

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