Facile Large-Scale Synthesis of Coniferyl, Sinapyl, and *p*-Coumaryl Alcohol

Stéphane Quideau and John Ralph*

U.S. Dairy Forage Research Center, Agricultural Research Service, U.S. Department of Agriculture, 1925 Linden Drive West, Madison, Wisconsin 53706, and Department of Forestry, University of Wisconsin—Madison, Madison, Wisconsin 53706

Coniferyl, sinapyl, and *p*-coumaryl alcohols are rapidly and cleanly prepared by selective 1,2-reduction of the corresponding cinnamate esters using diisobutylaluminum hydride (DIBAL-H) in toluene as reducing agent.

INTRODUCTION

Lignin biosynthesis is initiated by an enzyme-catalyzed phenol dehydrogenation of mixtures of *p*-hydroxy-*trans*-cinnamyl alcohol monomers, namely coniferyl (**2a**), sinapyl (**2b**), and *p*-coumaryl (**2c**) alcohols. A copolymerization follows during which resonance-stabilized phenoxy radicals produced from monomers and from the growing polymer couple in a variety of ways to build up the lignin macromolecule (Sarkanen, 1971; Harkin, 1967, 1973; Adler, 1977).

Lignin-like dehydrogenation polymers (DHPs) can be made in vitro, using mushroom laccase or horseradish peroxidase preparations (Freudenberg, 1956, 1968; Higuchi, 1971; Brunow and Wallin, 1981). Although synthetic dehydrogenative polymerization is a simplification of the lignification processes, it constitutes a unique tool to elucidate the lignin structural patterns and to study the possible chemical pathways followed during lignin biogenesis (Ralph et al., 1992; Higuchi, 1980) and degradation (Kirk et al., 1975; Kern et al., 1985; Faix et al., 1985; Kondo et al., 1990). However, such investigations have always been made difficult by the poor accessibility of the *p*-hydroxycinnamyl alcohols.

In the past, lithium aluminum hydride reduction of ethyl ferulate (**1a**) was the most commonly used synthetic route toward coniferyl alcohol (**2a**) (Allen and Byers, 1949; Freudenberg and Hübner, 1952; Freudenberg and Swaleh, 1969). Sodium bis(2-methoxyethyl)aluminum hydride was later used as reductant to obtain better 1,2-selectivity in the reduction of the conjugated ester **1a** (Minami et al., 1974; Kirk and Brunow, 1988). In both cases, varying amounts of saturated alcohol were observed due to competing 1,4- vs 1,2-attack by hydride. Newman et al. (1986) used the "ate" complex generated from diisobutylaluminum hydride and *n*-butyllithium (Kim and Ahn, 1984) to achieve the desired chemoselective reduction of **1a** in 64% yield. Over the years, different synthetic routes leading to *p*-hydroxycinnamyl alcohols have been reported, but all demand several steps and/or give only moderate overall yields (Nakamura and Higuchi, 1976; Steglich and Zechlin, 1978; Zanarotti, 1982). Finally, Rothen and Schlosser (1991) have synthesized coniferyl alcohol (**2a**) by metallation of eugenol with *n*-butyllithium/potassium *tert*-butoxide followed by dimethoxyborylation–oxidation in 81% yield, but the procedure is more demanding than are reduction methods.

We now report that simple DIBAL-H reduction of ethyl ferulate (**1a**) rapidly and cleanly affords coniferyl alcohol (**2a**) in good yield and allows large-scale preparation. The method works equally well for preparing sinapyl (**2b**) and *p*-coumaryl (**2c**) alcohols.

EXPERIMENTAL PROCEDURES

Melting points are uncorrected. NMR spectra were run in acetone-d_6 on a Bruker AMX-360 instrument, operating at 360.13 MHz ^{1}H (90.55 MHz ^{13}C). The central solvent signal was used as internal reference (^{1}H, 2.04 ppm; ^{13}C, 29.8 ppm). Unambiguous assignments were obtained from proton-detected C–H chemical shift correlation spectra run with Bruker's INVBTP pulse program (Bax and Subramanian, 1986). For coniferyl alcohol (**2a**), the oxygenated aromatic carbons C_3 and C_4 were unambiguously assigned from proton-detected long-range C–H chemical shift correlation spectra run with Bruker's INV4LPLRND pulse program (Bax and Summers, 1986).

Coniferyl Alcohol (2a). Ethyl ferulate (**1a**) was prepared from ferulic acid (Sigma) by stirring overnight with EtOH/HCl, produced by adding 10 mL of acetyl chloride to 100 mL of ethanol (Fieser and Fieser, 1967), and crystallized from ethyl acetate/petroleum ether. **1a** (2.13 g, 9.58 mmol) in toluene (100 mL, freshly distilled), under nitrogen, was cooled in an ice–water bath, and diisobutylaluminum hydride (Aldrich, 27 mL of 1.5 M solution, 40.5 mmol, 4.2 equiv) in toluene was slowly added via syringe over ca. 10 min. After addition was complete, stirring was continued for ca. 1 h. The reaction mixture was then carefully quenched with ethanol (5–10 mL). The solvents were partially removed in vacuo at 40 °C. Water (50 mL) was added, and the aqueous layer, containing a gelatinous precipitate of aluminum salts, was extensively extracted with ethyl acetate (4 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness in vacuo at 35 °C to give coniferyl alcohol (**2a**) generally as a white–pale yellow solid but sometimes as an oil (1.69 g, 98%). ^{1}H NMR of this crude **2a** showed only traces of 1,4-reduction products. Crystallization from dichloromethane/petroleum ether (bp 40–60 °C) gave **2a** as colorless plates (1.33 g, 77%): mp 77.9–78.6 °C (lit. 74–76 °C; Freudenberg and Hübner, 1952); ^{1}H NMR δ 3.78 (1 H, t, $J_{\gamma OH\text{-}\gamma}$ = 5.65 Hz, OH_γ), 3.85 (3 H, s, OCH_3), 4.18 (2 H, td, $J_{\gamma\text{-}\gamma OH} \approx J_{\gamma\beta}$ = 5.6 Hz, $J_{\gamma\alpha}$ = 1.5 Hz, H_γs), 6.22 (1 H, dt, $J_{\beta\alpha}$ = 15.9 Hz, $J_{\beta\gamma}$ = 5.5 Hz, H_β), 6.49 (1 H, dt, $J_{\alpha\beta}$ = 15.9 Hz, $J_{\alpha\gamma}$ = 1.5 Hz, H_α), 6.76* (1 H, d, J_{56} = 8.1 Hz, H_5), 6.84* (1 H, dd, J_{65} = 8.1 Hz, J_{62} = 1.9 Hz, H_6), 7.04 (1 H, d, J_{26} = 1.9 Hz, H_2), 7.63 (1 H, s, Ar OH); ^{13}C NMR δ (see Table I). (*ABq pattern, J_{AB} = 8.10 Hz, $\Delta\nu_{AB}$ = 31.88 Hz.)

For large-scale preparation (10–20 g), the DIBAL-H solution in toluene was transferred to a dropping funnel via a double-tipped needle (Aldrich Technical Information Bulletin AL-134). Addition was accomplished dropwise over ca. 1 h. After quenching with ethanol, the precipitated aluminum salts were removed by filtration and thoroughly washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness to

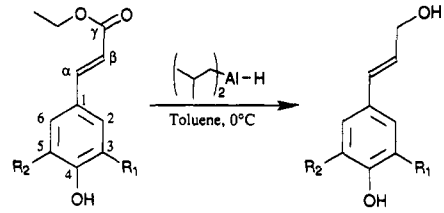

Figure 1. Reduction of ethyl cinnamates **1a–c** by DIBAL-H in toluene to give hydroxycinnamyl alcohols **2a–c**.

Table I. ^{13}C NMR Shifts of *p*-Hydroxy-*trans*-cinnamyl Alcohols (Solvent: Acetone-d_6)

	α	β	γ	OCH_3	1	2	3	4	5	6
2a	130.4	128.0	63.4	56.1	130.2	109.9	148.4	147.1	115.7	120.6
2b	130.6	128.3	63.3	56.5	129.0	104.6	148.7	136.5	148.7	104.6
2c	130.1	127.7	63.4		129.7	128.3	116.1	157.8	116.1	128.3

yield crude **2a**. Crystallization from methylene chloride/petroleum ether afforded pure **2a** in 65–70% yield.

Sinapyl Alcohol (2b). Ethyl sinapate (**1b**) was reduced as described for **1a** to yield crude sinapyl alcohol (**2b**) as an oil. Crystallization from methylene chloride/petroleum ether gave pure **2b** as white–yellow needles, in 70% yield: mp 66.5–67.3 °C (lit. 63–65 °C; Freudenberg and Dillenburg, 1951); ^1H NMR δ 3.88 (1 H, t, $J_{\gamma OH\text{-}\gamma}$ = 5.65 Hz, OH_γ), 3.82 (6 H, s, OCH_3), 4.20 (2 H, td, $J_{\gamma\text{-}\gamma OH} \approx J_{\gamma\beta}$ = 5.6 Hz, $J_{\gamma\alpha}$ = 1.5 Hz, H_γs), 6.24 (1 H, dt, $J_{\beta\alpha}$ = 15.8 Hz, $J_{\beta\gamma}$ = 5.5 Hz, H_β), 6.48 (1 H, dt, $J_{\alpha\beta}$ = 15.8 Hz, $J_{\alpha\gamma}$ = 1.5 Hz, H_α), 6.71 (2 H, s, H_2/H_6), 7.30 (1 H, s, Ar OH); ^{13}C NMR δ (see Table I).

***p*-Coumaryl Alcohol (2c).** Ethyl *p*-coumarate (**1c**) was reduced as described for **1a** to yield crude *p*-coumaryl alcohol (**2c**) as a white–pale yellow solid. Crystallization from acetone/petroleum ether gave pure **2c** as white fine crystals, in 92% yield: mp 89.3–90.5 °C; ^1H NMR δ 3.85 (1 H, t, $J_{\gamma OH\text{-}\gamma}$ = 5.65 Hz, OH_γ), 4.19 (2 H, td, $J_{\gamma\text{-}\gamma OH} \approx J_{\gamma\beta}$ = 5.6 Hz, $J_{\gamma\alpha}$ = 1.6, H_γs), 6.19 (1 H, dt, $J_{\beta\alpha}$ = 15.9 Hz, $J_{\beta\gamma}$ = 5.6 Hz, H_β), 6.50 (1 H, dt, $J_{\alpha\beta}$ = 15.9 Hz, $J_{\alpha\gamma}$ = 1.6 Hz, H_α), 6.78 (2 H, m, H_3/H_5), 7.25 (2 H, m, H_2/H_6), 8.40 (1 H, s, Ar OH); ^{13}C NMR δ (see Table I).

RESULTS AND DISCUSSION

Diisobutylaluminum hydride (DIBAL-H) is well-known as one of the most versatile reducing agents used in organic synthesis because of its ability to achieve stereo- and chemoselective reductions, particularly in the case of unsaturated carbonyl compounds (Winterfeldt, 1975). Thus, coniferyl (**2a**), sinapyl (**2b**), and *p*-coumaryl (**2c**) alcohols were obtained from their corresponding ethyl cinnamate derivatives (**1a–c**) via DIBAL-H reduction in toluene at 0 °C, in 77%, 70%, and 92% yield, respectively, as described under Experimental Procedures. The alcohols were characterized by ^1H and ^{13}C NMR spectroscopy (Table I; Experimental Procedures). Unambiguous spectral assignments were made using short- and long-range C–H chemical shift correlation experiments. We have concluded that the use of the "ate" complex from DIBAL-H and *n*-BuLi (Newman et al., 1986; Kim and Ahn, 1984) is unnecessary, since it affords no improvement in achieving 1,2-selectivity in these reductions. In addition, large-scale preparation can be easily accomplished with similar results by using a slightly modified procedure (see Experimental Procedures). Furthermore, the preparation of labeled *p*-hydroxycinnamyl alcohols is considerably easier than that by the Rothen and Schlosser method, since the ethyl cinnamate derivatives (**1a–c**) can be readily prepared with ^{13}C (or ^{14}C) labeling at any side-chain position (Newman et al., 1986). Such specifically labeled alcohols are of key importance in studies of lignin biosynthesis and biodegradation.

LITERATURE CITED

Adler, E. Lignin chemistry—past, present and future. *Wood Sci. Technol.* **1977**, *11* (3), 169–218.

Allen, C. F. H.; Byers, J. R. A synthesis of coniferyl alcohol and coniferyl benzoate. *J. Am. Chem. Soc.* **1949**, *71*, 2683–2684.

Bax, A.; Subramanian, S. Sensitivity-enhanced two-dimensional heteronuclear shift correlation NMR spectroscopy. *J. Magn. Reson.* **1986**, *67*, 565–569.

Bax, A.; Summers, M. F. ^1H and ^{13}C assignments from sensitivity-enhanced detection of heteronuclear multiple-bond connectivity by 2D multiple quantum NMR. *J. Am. Chem. Soc.* **1986**, *108*, 2093–2094.

Brunow, G.; Wallin, H. Studies concerning the preparation of synthetic lignin. *Ekman-Days 1981, Int. Symp. Wood Pulping Chem.* **1981**, *4*, 125–127.

Faix, O.; Mozuch, M. D.; Kirk, T. K. Degradation of gymnosperm (guaiacyl) vs. angiosperm (syringyl/guaiacyl) lignins by Phanerochaete chrysosporium. *Holzforschung* **1985**, *39* (4), 203–208.

Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; p 668.

Freudenberg, K. *Angew. Chem.* **1956**, *68* (16), 508–512.

Freudenberg, K. In *Constitution and Biosynthesis of Lignin*; Freudenberg, K., Neish, A. C., Eds.; Springer-Verlag: New York, 1968; pp 47–122.

Freudenberg, K.; Dillenburg, R. *Chem. Ber.* **1951**, *84* (1), 67–69.

Freudenberg, K.; Hübner, H. H. *Chem. Ber.* **1952**, *85* (12), 1181–1191.

Freudenberg, K.; Swaleh, M. *Chem. Ber.* **1969**, *102*, 1316–1319.

Harkin, J. M. Lignin—a natural polymeric product of phenol oxidation. In *Oxidative Coupling of Phenols*; Taylor, W. I., Battersby, A. R., Eds.; Dekker: New York, 1967; pp 243–321.

Harkin, J. M. Lignin. In *Chemistry and Biochemistry of Herbage*; Butler, G. W., Bailey, R. W., Eds.; Academic Press: New York, 1973; Vol. 1, pp 323–373.

Higuchi, T. Formation and biological degradation of lignins. *Adv. Enzymol.* **1971**, *34*, 207–283.

Higuchi, T. Biochemistry of lignification. *Wood Res.* **1980**, *66*, 1–16.

Kern, H. W.; Haider, K.; Pool, W.; deLeeuw, J. W.; Ernst, L. Comparison of the action of Phanerochaete chrysosporium and its extracellular enzymes (lignin peroxidases) on lignin preparations. *Holzforschung* **1989**, *43* (6), 375–384.

Kim, S.; Ahn, K. H. Ate complex from diisobutylaluminum hydride and n-butyllithium as a powerful and selective reducing agent for the reduction of selected organic compounds containing various functional groups. *J. Org. Chem.* **1984**, *49*, 1717–1724.

Kirk, T. K.; Connors, W. J.; Bleam, W. D.; Hackett, W. F.; Zeikus, J. G. Preparation and microbial decomposition of synthetic (^{14}C) lignins. *Proc. Natl. Acad. Sci. U.S.A.* **1975**, *72* (7), 2513–2519.

Kirk, T. K.; Brunow, G. Synthetic ^{14}C-labeled lignins. *Methods Enzymol.* **1988**, *161*, 65–73.

Kondo, R.; Iimori, T.; Imamura, H.; Nishida, T. Polymerization of DHP and depolymerization of DHP-glucoside by lignin oxidizing enzymes. *J. Biotechnol.* **1990**, *13*, 181–188.

Minami, K.; Sakai, H.; Fukuzumi, T. Synthesis of coniferyl alcohol with a new reducing reagent from acetylferulic acid ethyl-ester. *J. Jpn. Wood Res. Soc.* **1974**, *20* (1), 42–44.

Nakamura, Y.; Higuchi, T. New synthesis of coniferyl aldehyde and alcohol. *Wood Res.* **1976**, *59/60*, 101–105.

Newman, J.; Rej, R. N.; Just, G.; Lewis, N. Synthesis of (1,2-^{13}C), (1-^{13}C) and (3-^{13}C) coniferyl alcohol. *Holzforschung* **1986**, *40* (6), 369–373.

Ralph, J.; Helm, R. H.; Quideau, S.; Hatfield, R. D. Incorporation of feruloyl esters into coniferyl alcohol dehydrogenation polymers, *J. Chem. Soc., Perkin Trans. 1* **1992**, in press.

Rothen, L.; Schlosser, M. A one-pot synthesis of coumaryl, coniferyl and sinapyl alcohol. *Tetrahedron Lett.* **1991**, *32* (22), 2475–2476.

Sarkanen, K. V.; Ludwig, C. H. Precursors and their polymerization. In *Lignins, Occurrence, Formation, Structure and Reactions*; Sarkanen, K. V., Ludwig, C. H., Eds.; Wiley-Interscience: New York, 1971; pp 95–163.

Steglich, W.; Zechlin, L. Synthesis of fomentariol——a new method for the synthesis of cinnamyl alcohols. *Chem. Ber.* **1978**, *111*, 3939–3948.

Winterfeldt, E. Applications of diisobutylaluminum hydride (DIBAH) and triisobutylaluminum (TIBA) as reducing agents in organic synthesis. *Synthesis* **1975**, 617–630.

Zanarotti, A. Preparation and reactivity of 2,6-dimethoxy-4-allylidene-2,5-cyclohexadien-1-one (vinyl quinone methide). A novel synthesis of sinapyl alcohol. *Tetrahedron Lett.* **1982**, *23* (37), 3815–3818.

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Registry No. **1a**, 4046-02-0; **1b**, 41628-47-1; **1c**, 2979-06-8; **2a**, 458-35-5; **2b**, 537-33-7; **2c**, 3690-05-9; DIBAL-H, 1191-15-7; ferulic acid, 1135-24-6.