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

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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.

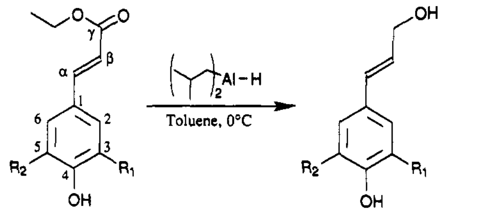
We now report that simple DIBAL-H reduction of ethyl ferulate (**1a**) rapidly and cleanly affords coniferyl alcohol (**2a**) in good yield and allows large-scale preparation. The method works equally well for preparing sinapyl (**2b**) and *p*-coumaryl (**2c**) alcohols.

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, $J_{\gamma-\gamma OH} \approx J_{\gamma\beta}$ = 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



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a $R_1 = OCH_3$, $R_2 = H$
b $R_1 = R_2 = OCH_3$
c $R_1 = R_2 = H$

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); ^{1}H 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; ^{1}H 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 ^{1}H 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. ^{1}H 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 ethylester. *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.