Rapid Proton NMR Method for Determination of Threo:Erythro Ratios in Lignin Model Compounds and Examination of Reduction Stereochemistry

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Threo:erythro ratios of β-aryl ether lignin model compounds are rapidly obtained by integration of α-OH proton signals at ca. 4.5 ppm in proton NMR spectra in acetone-d_6 sovlent containing traces of water. The excellent separation of these sharp signals (ca. 0.11 ppm), which is unaffected by etherification of the phenol, and the additional dispersion of the β-proton signals make NMR in this solvent ideal for homonuclear correlation spectroscopy. Sodium borohydride reduction of precursor ketones shows a substantial solvent effect: for example, in ethanol, isopropyl alcohol or *tert*-butyl alcohol the erythro isomer is mildly favored (ca. 40:60 threo:erythro), whereas in 50% aqueous alcohols the stereochemistry reverses to a marked threo preference (ca. 80:20 threo:erythro).

INTRODUCTION

To date, most papers on synthetic methods for lignin model compounds have not reported isomer composition, yet this detail is often of critical concern in the selection of a synthetic method and can be of extreme importance in reactivity studies. Nakatsubo and Higuchi (1975) proposed a method based on phenylboronate derivatives for determining isomers. More recently we introduced a simplified method that allowed for rapid determination of threo:erythro ratios of β-ether lignin model dimers (Ralph and Wilkins, 1985). That method has considerable advantages over the traditional methods of acetylation/proton NMR, quantitative ^{13}C NMR, or Nakatsubo's phenylboronate method: the preparation of trifluoroacetate derivatives can be done quickly in the NMR tube, without the need for workup; small amounts of compound can be used because the spectroscopy involved sensitive proton or ^{19}F NMR; the resolution of threo and erythro isomers, at least for the parent guaiacylglycerol β-guaiacyl ether (GGβGE, alcohol GG-1a, Figure 1), is quite good at moderate field strengths; and, if required, the materials can be recovered from their trifluoroacetate derivatives simply by stirring the chloroform solution with sodium borohydride on silica. However, the best resolution of isomers is achieved by the use of ^{19}F NMR, and this has presented some barrier to the acceptance of the method. When we reported the method, we were not able to proton-decouple our ^{19}F spectra, and this also limited its attractiveness. If only proton NMR is to be used, the presence of an ether protecting group on the phenolic OH gives poor resolution of the α-proton doublets.

This paper describes a simplified method using just proton NMR of underivatized models that works exceptionally well, gives greater dispersion between threo and erythro isomers, and is equally effective for free phenolic and phenol-etherified models. The dispersion between threo and erythro isomers of the α-OH protons, and the β protons, allows for simplified homonuclear correlation experiments as illustrated by COSY and relayed coherence transfer COSY experiments. Additionally, we report solvent effects on reduction stereochemistry of α-keto precursors to β-aryl ether lignin model compounds.

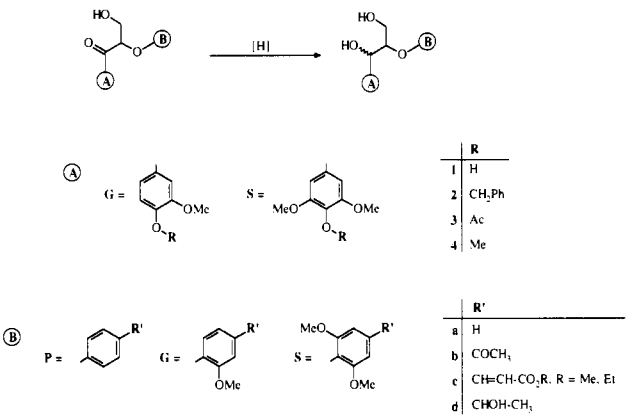

Figure 1. Ketones and their corresponding alcohols, from reduction. Naming goes as ketone AB-RR′ and alcohol AB-RR′, e.g., ketone SG-3a.

EXPERIMENTAL PROCEDURES

Proton NMR spectra of acetone-d_6 solutions (typically 2–5 mg of sample in ca. 0.3 mL of solvent in a 5-mm NMR tube) were determined at 25–30 °C with a variety of Bruker instruments ranging from 200 to 500 MHz. The central peak of the residual acetone-d_5 proton was used as internal reference (2.04 ppm). Distilled water, 1-2 μL, was added when necessary (see Results and Discussion). Magnitude-mode COSY spectra were run by using the standard COSY.AU microprogram with a 90° mixing pulse (Aue et al., 1976; Nagayama et al., 1980). The COSY spectrum in Figure 3 was acquired at 500 MHz with 256 increments of 4 transients. The final 1K by 512 (2.16 Hz/point) matrix was zero-filled to 2K by 1K and transformed by using sine-bell weighting in both domains. Three-step relayed coherence transfer (magnitude mode) COSY spectra (Bax and Drobny, 1985) were run by using Bruker's COSYRCT3.AU microprogram using delays of 62, 62, and 26 ms for the $0.5/(1.6J)$ coherence periods (corresponding to approximate coupling constants of 5, 5, and 12 Hz). The matrix size and apodization were the same for the COSYRCT3 experiment in Figure 4 as for the COSY experiment, Figure 3. Plots were made directly into a Macintosh computer using the program NMR-Plot (see Acknowledgment) and annotated in Claris MacDraw II 1.1.

Ketone reductions were done by standard procedures. On small sample sizes, $NaBH_4$ was used in considerable excess. For example, for $NaBH_4$ reductions on a ca. 20-mg scale, the ketone was dissolved in 5 mL of alcohol or, for reductions in 50% alcohol, dissolved in 2.5 mL of alcohol and 2.5 mL of water added. $NaBH_4$

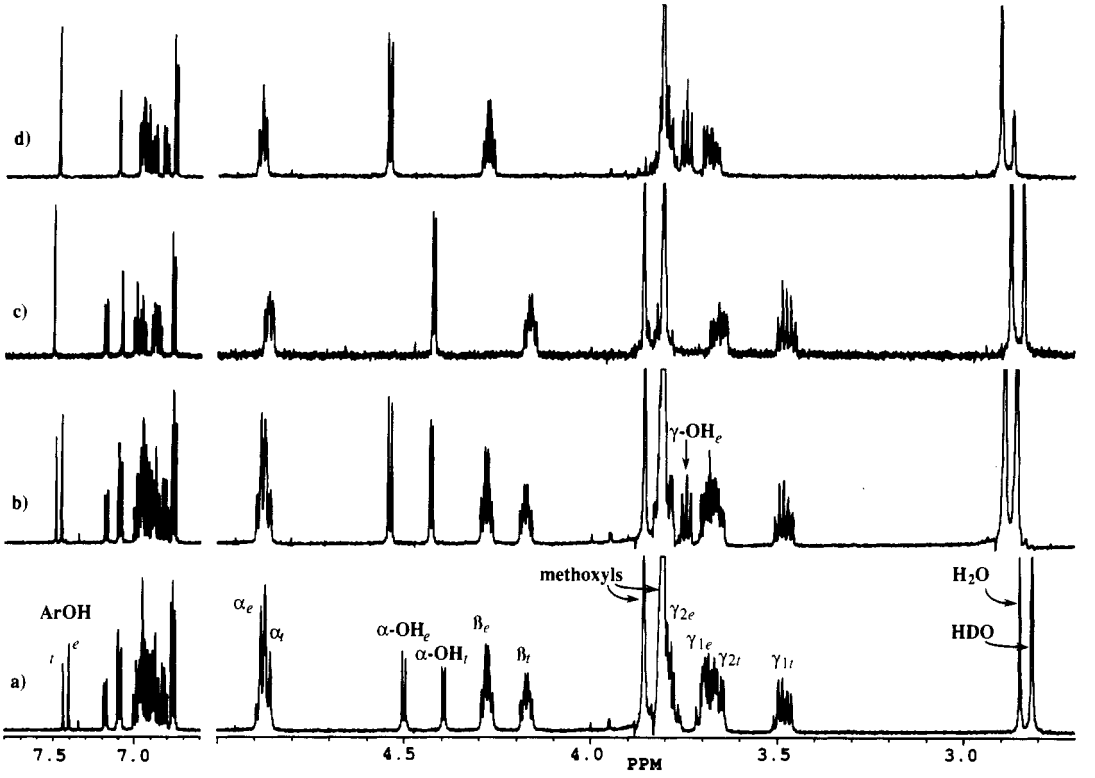

Figure 2. Proton NMR spectra (500 MHz) of alcohol GG-1a. Note: the aromatic and phenolic region is on a different horizontal and vertical scale than the aliphatic region in these plots. (a) Threo + erythro ($t < e$). (b) Same as (a) but with 1 μL of H_2O added. Note the increased H_2O peak, the increased intensity of phenolic and α-OH peaks, and the migration of all OH peaks. (c) Threo isomer. (d) Erythro isomer.

(2.5 equiv) was added and the mixture stirred overnight (the reaction usually does not need much more than 1 h). Saturated ammonium chloride solution was added to destroy the excess borohydride, and the mixture was extracted with methylene chloride. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was removed to yield the alcohol in typically 95% yield.

RESULTS AND DISCUSSION

Determination of Stereochemistry by ^{1}H NMR. The method is straightforward and requires only slight modification of the way any NMR spectrum would be run with acetone-d_6 as solvent. The model, 1–5 mg, or less if sample is limited, is dissolved in acetone-d_6 in a 5-mm NMR tube. A proton NMR spectrum is run in the normal way (with little regard to pulse width or relaxation delays) and the narrow α-OH proton doublets near δ 4.5 are integrated. For free phenolic models, the phenolic OH protons near δ 7.5 should also be integrated. If the α-OH proton doublets are not evident in the spectrum, 1–2 μL of H_2O is added and the spectrum is rerun.

Acetone-d_6 is a commonly used solvent for NMR spectroscopy, second only in usage to $CDCl_3$. It has a sharper lock signal and is therefore a superior solvent for high-resolution work. For some reason the appearance (Figure 2) of proton spectra of β-ether lignin model compounds in this solvent has escaped comment in the literature. At first sight the α proton at about 4.9 ppm, normally a clean doublet (coupled to the β proton), appears complex, and extra peaks are evident in the region between the methoxyl protons and Hα. Closer inspection shows these excess doublets to be the OH protons on the α-hydroxyl group. In acetone they do not exchange in the NMR time frame as they do in $CDCl_3$ and therefore appear as sharp doublets (coupled to the α protons). Similar coupling of the proton on the γ-OH group also complicates the splitting patterns of the Cγ protons. So for characterizing the compound of interest, acetone is a poor choice for proton NMR as it leads to considerable complication of the spectra. This complication can of course be removed by adding a drop of D_2O, causing conversion of OH to OD. Since the H–C–O–D coupling constant is 7-fold lower than the H–C–O–H coupling constant, the signal appears uncoupled, perhaps slightly broadened. If excess D_2O is added, the exchange rate increases so that coupling information to these exchangeable protons is completely lost. However, in acetone-d_6, the threo and erythro α-OH protons are sharp and extremely well resolved, so this solvent is an excellent choice for determining isomer ratios. For free phenolic models, the phenolic OH protons near δ 7.5 are also resolved and can also be used (Figure 2). The NMR field strength is no longer a crucial factor because of the excellent dispersion of the critical signals, typically 0.12 ppm for the α-OH protons and 0.03 ppm for the phenolic OH protons.

One initially disturbing feature was that the integral value (area) of the hydroxyl proton signals was always lower than that for the other protons in the molecule. The initial assumption that it was a relaxation time (T_1) problem and that we were pulsing too rapidly and losing part of the signal was easily disproved by extending the relaxation delay between scans. Only a small increase in the relative integral was obtained. Measurement of the T_1's (by inversion recovery) further showed that this was unlikely to be the source of the problem as the T_1 values of the OH protons were not excessive (Table I). These T_1 values do, however, reveal why the OH doublets are so sharp (the T_1 is longer than for other protons in the molecule) and why the isomer ratio is correctly determined even if pulsing is too rapid to allow efficient relaxation (the T_1's of the threo and erythro OH protons are similar).

The observation that the phenolic protons in alcohol GG-1a (Figure 1), relatively well resolved at about δ 7.5

Table I. Proton NMR Data[a] for Selected Protons, Compound GG-1a in Acetone-d_6

	threo	erythro		threo	erythro
α-OH			Ar-OH		
δ	4.42	4.54	δ	7.51	7.48
$J_{HO-H\alpha}$, Hz	3.6	4.6	T_1, s	3.1	3.1
T_1, s	3.0	2.9	α		
β			δ	4.88	4.86
δ	4.17	4.28	T_1, s	1.9	1.9
T_1, s	1.7	1.7			

(Figure 2), integrated exactly the same as the α-OH protons led to the conclusion that OH protons were being lost due to exchange. Indeed, a minor impurity in the acetone-d_6 was D_2O which, along with moisture from the air, results in observable signals due to HDO and H_2O. Aldrich Chemical Co. confirmed that deuterated water is an impurity in their product. A simple way therefore to return the compound's hydroxyls to the protonated variety is to add a little extra H_2O. Indeed, adding 1–2 μL of H_2O improves the relative integral value substantially (Figure 2b).

Of note here is that it is not necessary to add water to the sample to obtain accurate isomer ratios. There is no differential selectivity in the initial exchange, and the lowering of the integral for any of the OH's in the molecule simply reflects the statistical portion of exchangeable H to D in the sample. However, if extremely small quantities of model are used for the determination, it would be possible to swamp the OH signals with the residual D_2O in the acetone. In that case, simply adding water would improve the integral substantially and, provided the water concentration does not become too high, would not interfere with the isomer determination since the OH protons on H_2O and HDO appear near δ 2.9, 0.03, ppm apart (with H_2O at lower field, higher δ) when in low concentrations in acetone-d_6 (Figure 2). [Examination of these peaks is an excellent indicator of how much H_2O/HDO is in the NMR tube relative to the amount of compound. If the H_2O peak is much smaller than the HDO peak, it is generally beneficial to add a few microliters of H_2O. The high-field HDO proton appears as a 1-Hz 1:1:1 triplet (coupled to D) if resolution enhanced sufficiently.] If too much water is added, the H_2O signal migrates up the spectrum and H–D exchange becomes rapid on the NMR time scale, causing a complete loss of the α-OH protons and the return of the α-proton singlets to clean doublets. Interestingly, these doublets are nicely separated in acetone-d_6/H_2O and could be integrated for alcohol GG-1a. The best recommendation is not to use a freshly opened bottle of solvent—use an old one. It will contain more H_2O because of exposure to atmospheric water and will give more satisfactory performance.

It is also worth noting that in acetone-d_6 solvent, unlike in other solvents or with other derivatives of these compounds, the β protons of the threo and erythro isomers are well dispersed, at 4.17 and 4.28 ppm, respectively (Table I; Figure 2). They are still complex peaks because of their coupling to H_α and the two H_γ's but the 0.11 ppm chemical shift separation allows better interpretation of COSY-type spectra (Aue et al., 1976; Nagayama et al., 1980). Even in mixtures of the two isomers, the correlations between α-OH and H_α and H_β and (H_{γ^1} and H_{γ^2}) and, sometimes, to γ-OH become totally resolved in this solvent (Figure 3). In Figure 3, the evenly spaced dashed lines show this connectivity in the threo isomer, statring from the threo α-OH proton, while the irregular dashes trace out the corresponding connectivity in the erythro isomer.

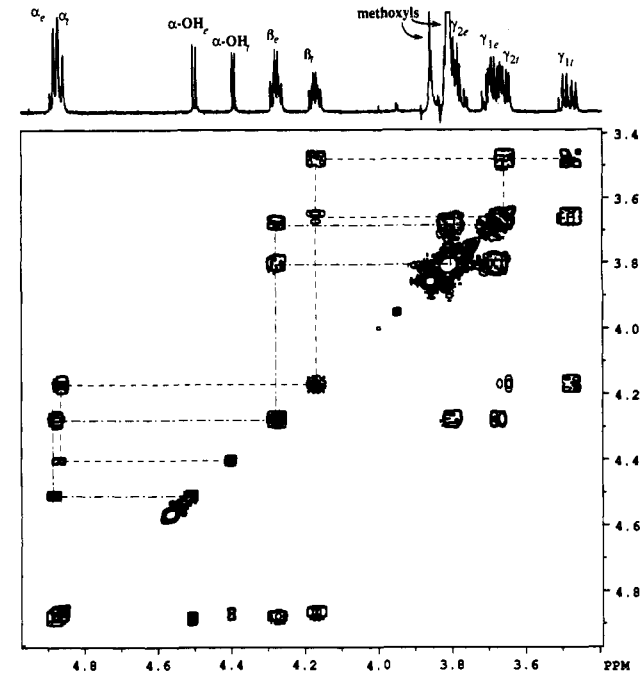

Figure 3. COSY spectrum (500 MHz) of GG-1a, threo + erythro, showing the connectivities α-OH to α to β to γ_1 and γ_2. Because of the excellent dispersion of the β protons in this solvent, the γ protons are unambiguously correlated.

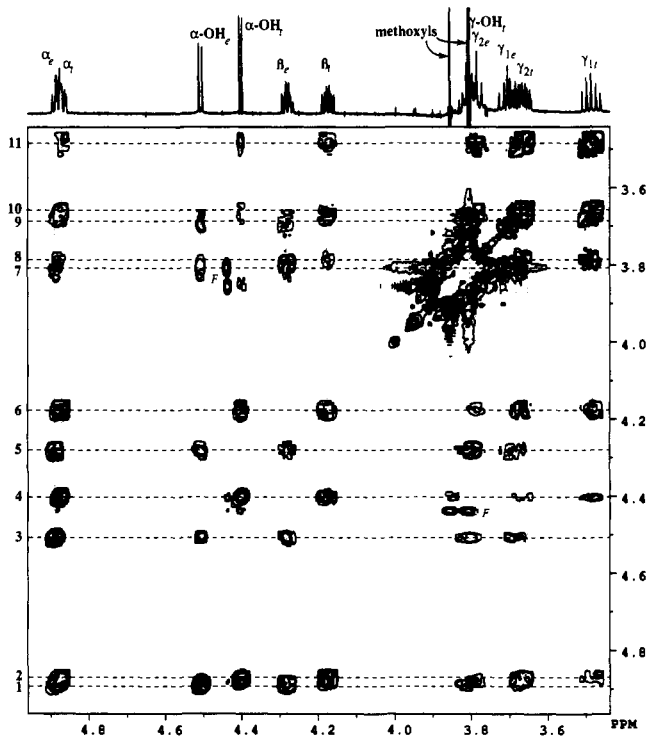

Figure 4. COSYRCT3 (three-step relayed coherence transfer COSY) spectrum (500 MHz) of GG-1a, threo + erythro, showing how each α-OH proton correlates with all other protons in the same coupling network, allowing full assignment of all side-chain protons. See Experimental Procedures for details.

From this experiment it is very clear that both γ_t protons are upfield of the γ_e protons.

Even more useful for mixed isomers or more complex mixtures are the correlations between all protons in a coupling network identified in an experiment such as relayed coherence transfer COSY (Bax and Drobny, 1985) (Figure 4). [Note: a more appropriate experiment to yield this kind of connectivity in considerably less time is the TOCSY or HOHOHA experiment (Braunschweiler and

Ernst, 1983; Davis and Bax, 1985), but instruments with the capability to perform those experiments were not available to us at the time. The COSYRCT3 experiment shown in Figure 4 illustrates how excellent results can be obtained with older instruments.] For example, from line 3 of Figure 4, it is clear that the erythro α-OH proton correlates with all the other side-chain protons in the erythro isomer. Similarly, from line 4, the threo α-OH proton correlates with all the other side-chain protons in the threo isomer. The other lines reveal essentially the same correlations, with the correlation peak intensities being dictated by the efficiency of coherence transfer at the delays chosen in the experiment (see Experimental Procedures). The γ_{1t} line, line 11, also shows clearly that the γ-OH proton for the threo isomer is buried under the γ_{2e} multiplet. It is likely that the γ-OH proton for the erythro isomer is also in the same region—certainly the erythro γ-OH proton can be seen in Figure 2, parts d and b, but its shift is sensitive to the amount of water in the sample as it is buried, presumably under γ_{2e} again, in Figure 2a.

Reduction Stereochemistry. There has been a growing interest in the reduction stereochemistry of precursor α-keto lignin model compounds, particularly in the β ethers. In 1975, Nakatsubo et al. described a synthesis yielding largely the erythro isomer of alcohol GG-1a by a method that produced an α-hydroxy compound with good stereochemical control (ca. 75:25; Nakatsubo et al., 1978). Most other synthetic methods in common use require the reduction of α-keto precursors. Ralph and Young (1981) developed a procedure for improved threo selectivity using L-Selectride and reported ratios for LAH and Pd/C reductions. The L-Selectride method has been superseded now by simpler reductions using $NaBH_4$ (Hoysoya et al., 1972; Brunow et al., 1988). Interestingly, we, and others, had been using $NaBH_4$ for reductions for many years but had always observed very poor stereoselectivity and usually a slight favoring for the erythro isomer (Ralph, 1982). It was a surprise to learn that Brunow et al. were achieving high stereoselectivity using $NaBH_4$. Both groups repeated their work and the difference remained. It became clear that the reduction method was critical and that the choice of solvent played a marked role in the stereochemical outcome. Table II summarizes the stereochemical outcome of various reductions of β-ether models from our own data over a number of years. It is clear from the table that the stereochemistry of the reduction of ketone GG-2a by $NaBH_4$ in hydroxylic solvents is strongly dependent on the solvent system used. Whereas reduction in pure alcohols (ethanol, isopropyl alcohol, and *tert*-butyl alcohol) preferentially forms the erythro isomer to a minor degree (ca. 40:60 threo:erythro), when water is added to the reaction solvent, the reduction yields a marked predominance of the threo isomer (ca. 80:20 threo:erythro). Reductions in methanol are capricious but generally give high threo selectivity, as previously noted by Barrelle et al. (1989). Ketones with a syringyl moiety at ring B (e.g., GS-3c, SS-3b) show significantly higher selectivity, favoring the threo isomer by over 90%, while the *p*-hydroxyphenyl moiety at ring B gives slightly lower selectivity than the ring B guaiacyl compounds. Ring A substitution exerts a lesser influence. Lithium aluminum hydride (LAH) reduction is more variable. On looking back through records for these reductions in THF over 10 years, the ratio ranges from 25:75 threo:erythro (Ralph and Young, 1981) to 60:40. It is not clear how these differences arise. In the most recent evaluations (1985, Table II) the order of addition of ketone and LAH seemed to have no effect, but the influence of temperature was not assessed.

Table II. Stereochemistry of Reduction of β-Ether Lignin Model Ketones

model ketone	reducing agent	solvent, conditions[a]	*t*:*e* ratio	year
GP-3c	$NaBH_4$	EtOH:H_2O (50:50)	76:24	1990
GP-3c	$NaBH_4$	MeOH:H_2O (54:46)	77:23	1990
GG-2a	$NaBH_4$	MeOH	80:20	1990
GG-2a	$NaBH_4$	MeOH:H_2O (50:50)	82:18	1990
GG-2a	$NaBH_4$	MeOH:H_2O (50:50)	86:14	1990
GG-2a	$NaBH_4$	MeOH:H_2O (60:40)	54:46	1990
GG-2a	$NaBH_4$	MeOH:H_2O (90:10)	63:37	1990
GG-2a	$NaBH_4$	MeOH:H_2O (90:10)	81:19	1990
GG-2a	$NaBH_4$	EtOH	40:60	1985
GG-2a	$NaBH_4$	EtOH	40:60	1985
GG-2a	$NaBH_4$	EtOH, 95%	56:44	1990
GG-2a	$NaBH_4$	EtOH:H_2O (50:50)	77:23	1989
GG-2a	$NaBH_4$	EtOH:H_2O (50:50)	82:18	1989
GG-2a	$NaBH_4$	*i*PrOH	36:64	1990
GG-2a	$NaBH_4$	*i*PrOH:H_2O (50:50)	79:21	1990
GG-2a	$NaBH_4$	*t*BuOH	39:61	1990
GG-2a	$NaBH_4$	*t*BuOH:H_2O (50:50)	81:19	1990
GG-3c	$NaBH_4$	EtOH:H_2O (50:50)	80:20	1990
GG-3c	$NaBH_4$	MeOH:H_2O (50:50)	71:29	1990
GS-1b	$NaBH_4$	EtOH	86:14	1985
GS-3c	$NaBH_4$	MeOH:H_2O (58:42)	>95:5	1990
SG-3a	$NaBH_4$	EtOH:H_2O (50:50)	80:20	1990
SG-3b	$NaBH_4$	EtOH:H_2O (50:50)	77:23	1990
SS-3b	$NaBH_4$	EtOH:H_2O (50:50)	93:7	1990
SP-3b	$NaBH_4$	EtOH:H_2O (50:50)	77:23	1990
GG-2a	LAH	THF	25:75	1979
GG-2a	LAH	THF	30:70	1979
GG-2a	LAH	THF[b]	60:40	1985
GG-2a	LAH	THF[c]	60:40	1985
GG-2a	LAH	Et_2O[d]	50:50	1985
GG-2a	L-Selectride	THF, −78 °C	80:20	1981
GG-2a	L-Selectride	THF, −78 °C	85:15	1981
GG-2a	H2-Pd/C	EtOH	40:60	1981
GG-2a	H2-Pd/C	95% EtOH:dioxane (90:10)	55:45	1985

[a] Room temperature unless otherwise noted. [b] LAH dissolved first, ketone dropwise. [c] Ketone dissolved, LAH solid added. [d] Ketone suspended, LAH solid added.

L-Selectride reduction of GG-2a exhibited high selection for the threo isomer (Ralph and Young, 1981) but suffers from the additional complexity of the procedure over using $NaBH_4$ in alcohol/water mixtures. Catalytic H_2-Pd/C reductions also vary slightly with solvent but generally favor the erythro isomer (Lundquist, 1972; Ralph, 1982). To date, there does not appear to be a particularly selective reduction method to obtain the erythro isomer. For related model compounds with a simple methyl group rather than a hydroxymethyl group at the γ position, reduction using $NaBH_4$, L-Selectride, $ZnBH_4$, or LAH invariably gives at least 90% erythro (Adler, 1966; Ralph, 1982; Samuels et al., 1986). Reasonable explanations for some of the stereochemical observations have been presented (Ralph, 1982; Samuels et al., 1986; Brunow et al., 1986; Barelle et al., 1989), but we hope to shed further light on these observations through molecular modeling studies.

CONCLUSION

With the threo:erythro ratio determination method described above, it is straightforward to determine these ratios on small quantities of compound without the need for derivatization. Samples prepared for NMR in this way are also excellent for full assignment and connectivity analysis using COSY and relayed coherence transfer COSY

experiments and should be equally valuable for TOCSY (HOHOHA), NOESY, and various C–H correlation experiments. The stereochemistry of ketone reductions by a variety of reducing agents is often dependent on solvent. As the stereochemistry of a lignin model is often of critical importance, we hope that this will be reported now that a simplified method for stereoisomer determination is available.

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Registry No. **GG-1a** ketone, 22317-34-6; *threo*-**GG-1a**, 7572-88-5; *erythro*-**GG-1a**, 7595-27-9; **GG-2a** ketone, 20730-75-0; *threo*-**GG-2a**, 78561-49-6; *erythro*-**GG-2a**, 78561-50-9; **GG-3c** ketone, 132260-65-2; *threo*-**GG-3c**, 132260-73-2; *erythro*-**GG-3c**, 132260-74-3; **GP-3c** ketone, 132260-64-1; *threo*-**GP-3c**, 132260-71-0; *erythro*-**GP-3c**, 132260-72-1; **GS-1b** ketone, 132260-66-3; *threo*-**GS-1b**, 132297-29-1; *erythro*-**GS-1b**, 132297-30-4; **GS-3c** ketone, 132260-67-4; *threo*-**GS-3c**, 132260-75-4; *erythro*-**GS-3c**, 132297-31-5; **SG-3a** ketone, 132260-68-5; *threo*-**SG-3a**, 132260-76-5; *erythro*-**SG-3a**, 132260-77-6; **SG-3b** ketone, 132260-69-6; **SP-3b** ketone, 132260-70-9; **SS-3b** ketone, 132297-28-0; *threo*-**SS-3b**, 132297-32-6; *erythro*-**SS-3b**, 132297-33-7; LAH, 16853-85-3; THF, 109-99-9; $NaBH_4$, 16940-66-2; EtOH, 64-17-5; H_2O, 7732-18-5; MeOH, 67-56-1; *i*-PrOH, 67-63-0; *t*-BuOH, 75-65-0; Et_2O, 60-29-7; Pd, 7440-05-3; L-Selectride, 38721-52-7; dioxane, 123-91-1; lignin, 9005-53-2.