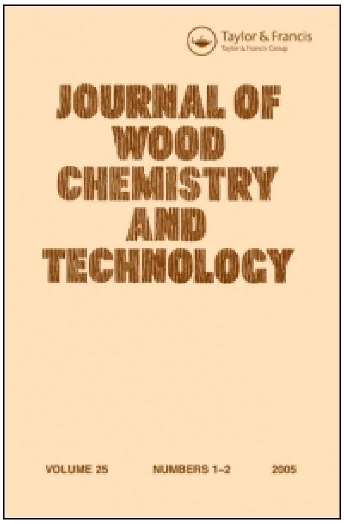

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REACTION OF *p*-HYDROXYCINNAMYL ALCOHOLS WITH TRANSITION METAL SALTS IV. TAILORED SYNTHESES OF β-O-4 TRIMERS[1]

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REACTION OF *p*-HYDROXYCINNAMYL ALCOHOLS WITH TRANSITION METAL SALTS IV. TAILORED SYNTHESES OF β-O-4 TRIMERS[1]

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ABSTRACT

Reaction of coniferyl alcohol or sinapyl alcohol with β-O-4 dimeric model compounds in the presence of manganese(III), copper(II), or vanadium(V) gave trimeric compounds that served as superior models for ^{13}C chemical shift assignments in natural and synthetic lignins. By appropriate choice of dimer and monomer, seven of the eight possible sequences of guaiacyl (G) and syringyl (S) units were prepared: GGG, GGS, GSG, GSS, SSS, SSG, and SGG. Preparaton of the missing sequence (SGS) by this method was not successful, so it was obtained by conventional synthetic techniques.

Stereochemistry in the trimers was also controlled to some extent by utilizing dimers that were predominantly *erythro* (*e*) or *threo* (*t*), and by performing the oxidative coupling under conditions of high stereo-selectivity. The maximum number of geometric isomers in β-O-4 trimers is eight (one pair each of *ee*, *et*, *te*, *tt*). In this study the GGG and GGS trimers contained all eight isomers, the SGG trimer contained

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four isomers, and GSG, GSS, SSS, SSG, and SGS (synthetic) each contained only two isomers.

The chemical shifts of the sidechain carbons in the trimers were compared with corresponding chemical shifts in natural lignins isolated from spruce (*Picea mariana*), birch (*Betula papyrifera*), and hickory (*Carya ovata*). The comparison indicated that GG and SG entities in lignin had *e*/*t* ratios ranging from 2/1 to 1/1, but GS and SS entities were predominantly *e*. This observation was consistent with the isomer composition of linkages formed by oxidative coupling of coniferyl alcohol or sinapyl alcohol with dimers.

INTRODUCTION

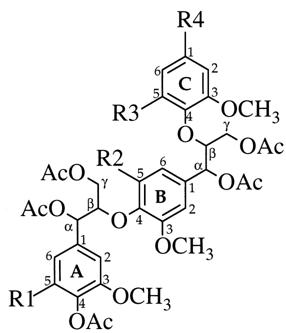
The focus of Part 2 of this series was the reaction of coniferyl alcohol and/or sinapyl alcohol with metal salts for the preparation and characterization of all possible guaiacyl (G), syringyl (S), and G/S dimers with β-O-4, β-5, or β–β linkages.[2] These dimers and their corresponding ^{1}H and ^{13}C NMR spectra were needed to provide a foundation for characterization of trimeric and tetrameric model compounds. During preparation of dimers, five trimers and a tetramer were also isolated but the yields were very low.[2,3] The only exception was when the trimer or tetramer contained the S-r-S entity, which is two S rings connected by a resinol (β–β) linkage. In addition to optimizing the yields of trimers and tetramers, it was of interest to establish improved techniques to prepare additonal trimers not yet available in order to facilitate the ^{13}C NMR characterization of improved dehydrogenation polymers (DHPs)[4] and lignins. In particular, we were interested in obtaining all possible combinations of G and S rings in trimers containing two β-O-4 linkages. We reported that such trimers could be readily obtained by the reacton of *p*-hydroxycinnamyl alcohols with dimeric models in the presence of trivalent manganese or pentavalent vanadium salts.[5] This approach allowed "fixing" two of the rings (B and C) in the target trimer as well as the stereochemistry of the linkage between rings B and C. The results of this approach were generally higher yields of trimer than have previously been obtained and reaction mixtures with fewer isomers.

As previously determined,[6] a trimer is the smallest structure that can serve as an accurate model (in terms of ^{13}C NMR characterization) for native lignin or dehydropolymers (DHPs), because it contains both a free phenolic C9 unit and an "internal" etherified phenolic C9 unit. In the present report, the preparation and ^{13}C NMR characterization of at least one representative of all eight possible combinations of G and S rings in β-O-4 trimers is described. Seven of the eight types were prepared by the biomimetic technique, and only one type (SGS) was prepared by conventional organic synthesis.

The use of NMR spectral simulation to clarify some of the isomeric complexity in guiaicyl β-O-4 trilignols is described along with comparisons of NMR spectra of all the trimers with corresponding spectra of natural lignins isolated from spruce, hickory, and birch.

RESULTS AND DISCUSSION

The structures of selected trimers representing all possible combinations of G and S rings are illustrated in Figure 1. With some trimer types, such as GGG, GGS, GSS, and SSS, more than one compound was prepared that contained either a different R4 group or different isomer composition. Since it has been determined[6] that variance in the R4 group does not have



#	Type	R1	R2	R3	R4
1a	GGG	H	H	H	H
1b	GGG	H	H	H	H
1c	GGG	H	H	H	H
1d	GGG	H	H	H	$CH=CHCH_2OH$
2a	GGS	H	H	OCH_3	H
2b	GGS	H	H	OCH_3	$CHOHCH_3$
3	GSG	H	OCH_3	H	H
4a	GSS	H	OCH3	OCH_3	CH_3
4b	GSS	H	OCH3	OCH_3	CH_3
5a	SSS	OCH_3	OCH_3	OCH_3	$CH=CHCH_2OH$
5b	SSS	OCH_3	OCH_3	OCH_3	CH_3
6	SSG	OCH_3	OCH_3	H	$CHOHCH_3$
7	SGS	OCH_3	H	OCH_3	CH_3
8	SGG	OCH_3	H	H	H

Figure 1. Selected β-O-4 trimers representing all possible combinations of guaiacyl and syringyl rings.

any significant influence on the chemical shifts of the A-ring and associated sidechain (representing phenolic C9 units) or the B-ring and associated side-chain (representing etherified C9 units), only one example of each type is illustrated in Figure 1. However, different isomer compositions within a given trimer type will be noted when applicable and all of the chemical shift data for fourteen trimers is given later in this report (table 5).

Synthesis of Trimers

All but one of the trimers illustrated in Figure 1 were prepared by oxidative coupling reactions utilizing either trivalent manganese or penta-valent vanadium salts[5] according to the reactions illustrated in Table 1. Oxidative coupling of coniferyl alcohol gives the homo-trimer **1d** (R4 = CH=$CHCH_2OH$) and coupling of sinapyl alcohol gives the homo-trimer **5a** (R4 = CH=$CHCH_2OH$). Mixtures of coniferyl alcohol and sinapyl alcohol theoretically lead to all of the hetero-trimer types in addition to homo-trimers. Eluded to in the previous text, the yields of trimeric compounds upon dehydropolymerization of monomers were generally very low; they could be raised substantially by reacting the monomeric alcohol with a dimeric compound. Using this technique, five of the six possible hetero-trimeric model types (**2-4, 6, 8**) were synthesized as well as the two homo-trimers **1a** and **5b**. Because preparation of type **7** by this technique was unsuccessful, it was prepared by conventional synthetic techniques. Other investigators, using a peroxidase/H_2O_2 system, were also unsuccessful in cross coupling sinapyl alcohol with dimeric guaiacyl compounds.[7] They concluded that cross coupling appears to be restricted to phenols of similar oxidation potential.

Table 1. Coupling Reactions Leading to β-O-4 Trimers

1	CA*			GGG
2	CA + G-dimer			GGG
3	CA + S-dimer			GSS
4	CA + GS-dimer			GGS
5	CA + SG-dimer	+ Mn(III)	→	GSG
6	SA*	(or V(V)		SSS
7	SA + S-dimer			SSS
8	SA + G-dimer			SGG
9	SA + GS-dimer			SGS
10	SA + SG-dimer			SSG

*CA = coniferyl alcohol, SA = sinapyl alcohol

Stereochemistry of β-O-4 Trimers

Each trimer contains four asymmetric carbon atoms (Aα, Aβ, Bα, Bβ). This translates into $2^4 = 16$ optical isomers or eight geometric isomers, as listed in Table 2 in RS nomenclature.[8] It is expected that the sidechain carbons and others in close proximity to the asymmetric centers would have different chemical shifts in each isomer. The stereochemistry of a particular trimer depends on several factors, and it can usually be controlled to some extent. One factor that determines the stereochemistry of a particular

Table 2. Possible Isomers in β-O-4 Trimers

	Asymmetric carbons[a]		
Optical isomers	Aα,Aβ	Bα,Bβ	Geometric isomers[b]
1	RR	RR	1 (*tt*)
2	SS	SS	
3	RR	SS	2 (*tt*)
4	SS	RR	
5	RS	RS	3 (*ee*)
6	SR	SR	
7	RS	SR	4 (*ee*)
8	SR	RS	
9	RR	RS	5 (*te*)
10	SS	SR	
11	RR	SR	6 (*te*)
12	SS	RS	
13	RS	RR	7 (*et*)
14	SR	SS	
15	SR	RR	8 (*et*)
16	RS	SS	

[a]A and B refer to the A and B rings of the trimer.
[b]*e* = *erythro*, *t* = *threo*.

Table 3. Possible Combinations of Linkage Stereochemistry in Trimers

Type	A-ring linkage	B-ring linkage	# of isomers
1	*e* + *t*	*e* + *t*	8
2	*e* + *t*	*e*	4
	e	*e* + *t*	4
	e + *t*	t	4
	t	*e* + *t*	4
3	*e*	*e*	2
	e	*t*	2
	t	*e*	2
	t	*t*	2

trimer is how the trimer is prepared – by oxidative coupling of a monomer (Table 1, reactions 1 and 6) or by the coupling of a monomer with a previously prepared dimer (Table 1, reactions 2-5, 7-10). The stereoselectivity of a particular coupling reaction is also a factor and depends in part upon the metal salt, the media, the methoxyl substitution of the substrates, and the mode of addition. Previous studies had established that reaction 1 (Table 1) generally gave an *e*/*t* ratio of 85/15 to 50/50 depending upon the metal salt and media. These situations gave the most complex NMR spectra because all eight geometric isomers were formed, but not necessarily to the same extent. This corresponds to Type 1 in Table 3, which is a tabulation of all possible combinations of linkage stereochemistry in trimers. In contrast, oxidative coupling of sinapyl alcohol (reaction 6) is highly stereospecific and give predominantly *e* linkages with the result that only two geometric isomers predominate (Table 3, Type 3).

A more complex situation exists when coniferyl alcohol or sinapyl alcohol is added to a previously prepared dimer because homocoupling can occur along with monomer-dimer coupling. However, with very slow addition of monomer and metal salt (in separate streams) to the dimer, monomer-dimer coupling usually predominates. If the dimer has a fixed stereochemistry (*e* or *t*), and the coupling of the monomer to the dimer is not stereospecific, then four isomers would be present such as in Type 2 (Table 3). Four isomers would also be obtained by a stereospecific coupling to a "mixed" *e*/*t* dimer. In contrast, only two isomers are formed when the coupling is stereospecific and the dimer is isomerically pure. In this case, only highly expanded ^{13}C NMR spectra of the sidechain region will reveal

Table 4. Isomeric Composition of Trimers (% of major isomer)

Trimer	Type	Dimer entities (% major isomer)	
1a	GGG	GG (∼60*e*)	GG (∼75*e*)
1b*	GGG	GG (100*e*)	GG (100*e*)
1c*	GGG	GG (100*e*)	GG (100*t*)
1d	GGG	GG (>90*e*)	GG (∼60*e*)
2a	GGS	GG (∼50*e*)	GS (∼60*t*)
2b	GGS	GG (∼60*e*)	GS (>80*t*)
3	GSG	GS (>90*e*)	SG (100*t*)
4a	GSS	GS (>90*e*)	SS (>90*t*)
4b	GSS	GS (>90*e*)	SS (>90*e*)
5a	SSS	SS (>90*e*)	SS (>90*e*)
5b	SSS	SS (>90*e*)	SS (>90*e*)
6	SSG	SS (>90*e*)	SG (>90*e*)
7*	SGS	SG (>90*t*)	GS (>90*e*)
8	SGG	SG (∼70*e*)	GG (>90*e*)

*Prepared by conventional synthetic techniques.

the presence of the two magnetically similar isomers. Fortunately, this detail is not observed and thus does not complicate spectra, when dealing with linewidths corresponding to those of typical lignin signals. The approximate isomeric composition of the dimeric entities of the trimers illustrated in Figure 1 is given in Table 4.

Guaiacyl β-O-4 Trimers

The complexity of the guaiacyl β-O-4 trimer **1a**, when several isomers are present, is illustrated in Figure 2 in the top ^{13}C NMR spectrum of the expanded regions of the sidechain carbons. Compared with this complex spectrum is a pure *ee* isomer (**1b**) corresponding to one of the *ee* geometric isomers (3 or 4) in Table 2 and an *et* isomer pair (**1c**) corresponding to geometric isomers 7 and 8 in Table 2 of the same trimer that were prepared by conventional synthetic techniques by others.[9,10] Presumably, in the very narrow chemical shift range of these spectra, concentration effects, solvent interactions, or isomer effects prevail as indicated by the non-additive nature of the bottom spectrum, which is from a physical mixture of the *ee* and *et* samples. Therefore, the partially resolved signals in the top spectrum cannot be reliably assigned by comparison with the pure isomers. However, signals

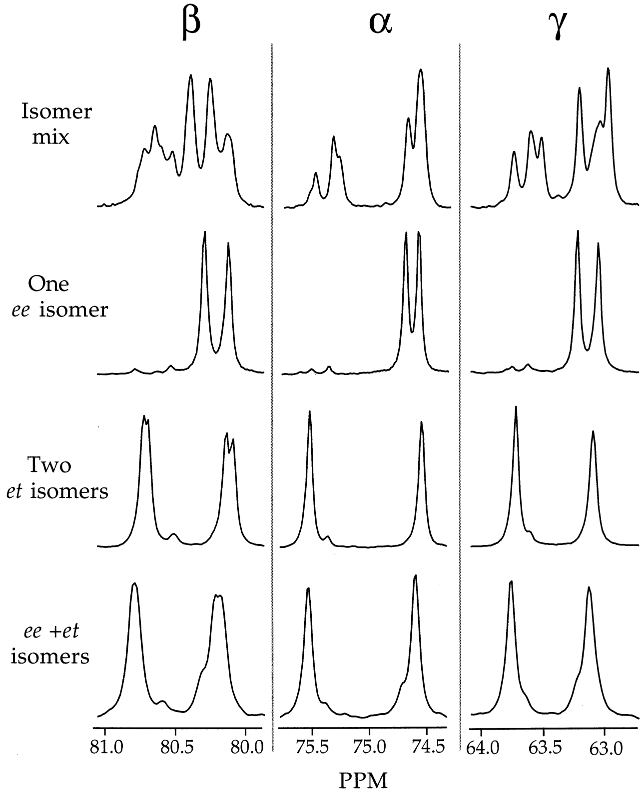


Figure 2. ^{13}C NMR spectra of sidechain region of guaiacyl β-O-4 trimers. Isomer Mix is a mixture of all eight isomers; *ee* + *et* isomers are a mixture of one *ee* isomer and two *et* isomers.

from the *e* carbons and *t* carbons are generally resolved as indicated by the distinctly separate groupings.

With appropriate software, deconvolution of the complex patterns in isomer mixtures can be performed. For example, assuming that all possible isomers are present (but not in equal amounts), one hypothetical solution of the β carbon region of trimer **1a** is shown in the spectrum of simulated individual signals in Figure 3. These component signals represent four pairs of β*e* carbons upfield of 80.5 ppm and four pairs of β*t* carbons downfield of 80.5 ppm of all the isomers listed in Table 2. The bottom spectrum is the sum of the individual signals, which closely matches the experimental spectrum.

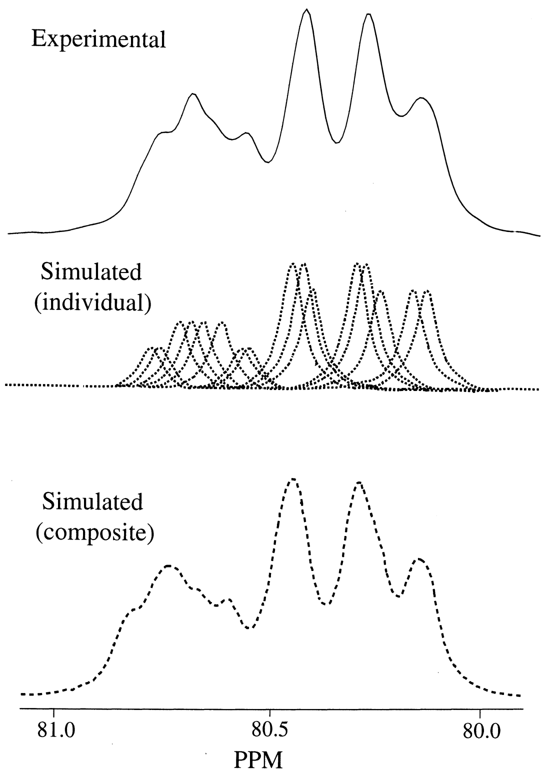


Figure 3. Deconvolution of β carbon in a guaiacyl β-O-4 trimer containing all eight geometric isomers.

Guaiacyl/Syringyl and Syringyl β-O-4 Trimers

As mentioned previously, oxidative coupling of sinapyl alcohol (reaction 6) is highly stereospecific and gives predominantly *e* linkages, with the result that only two geometric isomers (3 and 4, Table 2) predominate. This stereospecificity is generally observed when sinapyl alcohol or coniferyl alcohol is oxidatively coupled to an SG or SS dimer (reactions 3, 5, 7, and 10, Table 1) giving trimers of type GSS, GSG, SSS, and SSG, respectively. This is presumably due to steric hindrance of the additional methoxyl group on the free phenolic end of the dimer. The consequence is that the A-ring sidechain is predominantly *e* and the B-ring sidechain is fixed by the isomeric content of the dimer starting material. Since the SS and SG dimers used for generating the four trimers were greater than 90% pure (*e* or *t*), only one pair of isomers (either *ee* or *et*) predominates. This is confirmed by

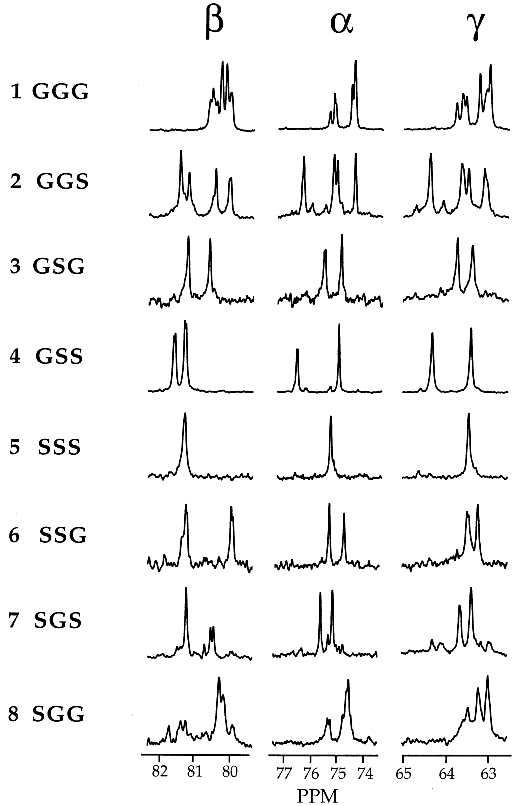


Figure 4. ^{13}C NMR spectra of sidechain region of the eight trimers shown in Figure 1.

the expanded ^{13}C NMR region of the sidechain region of trimers **3–6** illustrated in Figure 4. Trimer **7** of type SGS also appears to contain only one pair of isomers, but since this pair was prepared by conventional synthetic techniques no oxidative coupling was involved.

Since the main function of the trimers is to provide a basis for chemical shift assignments in DHPs and lignins, the fine structure observed with low molecular weight compounds is generally overshadowed by the relatively broad signals in the corresponding spectra of the polymers. The extent to which isomer complexity effects characterization of DHPs and lignins is illustrated in Figure 5, in which the linewidths of the trimer signals are increased to approximately match the corresponding linewidths of the milled wood lignins isolated from spruce, hickory, and birch. As is clear from the figure, much of the fine structure is lost upon line broadening and

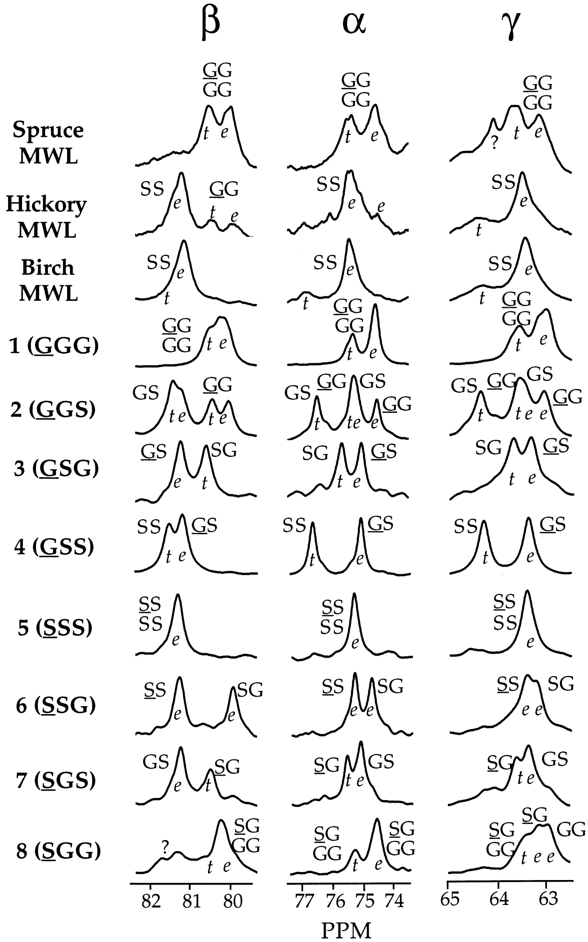


Figure 5. [13]C NMR spectra of sidechain region of spruce, hickory, and birch milled wood lignins (MWLs) along with line-broadened (15-Hz) spectra of the eight trimers.

the remaining resolvable signals generally represent differences between *e* and *t* groupings. Also, with the broader signals, it is no longer feasible to distinguish between phenolic and etherified entities in the sidechain region. By utilizing the data in Figure 5, the chemical shift angles of the various dimeric entities in the trimeric lignin model compounds could be illustrated. As shown in Figure 6, this proved to be a convenient tool to assign β-O-4 sidechain chemical shifts in acetylated DHPs and acetylated lignins.

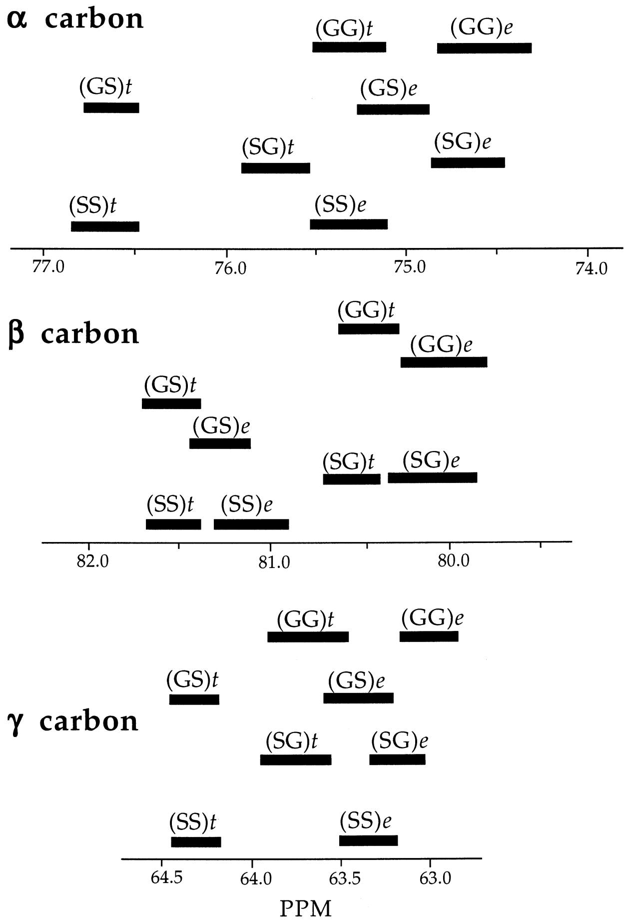


Figure 6. Chemical shifts of sidechain carbons in *e* and *t* dimer entities.

By utilizing both analogy between the trimers and two-dimensional NMR experiments such as short-range and long-range carbon-proton correlations, all the ^{13}C signals were assigned and are listed in Table 5.

CONCLUSIONS

At least one example of all possible combinations of guaiacyl and syringyl C9 units in β-O-4 trimeric model compounds was prepared and characterized by ^{13}C NMR and mass spectroscopy. The ^{13}C signals from sidechain carbons of 14 β-O-4 trimers were compared with each other and with selected spectra of milled wood lignins isolated from spruce, hickory, and a high syringyl fraction of birch wood. From these comparisons, we conclude that the β-O-4 linkages in GG and SG entities in trimers prepared by oxidative coupling and GG β-O-4 entities in milled wood lignins have an *e*/*t* ratio ranging from 1/1 to 2/1. In contrast, we observed that with β-O-4 GS and SS entities in trimers prepared by oxidative coupling and those in milled wood lignins from hickory and birch, the linkages are predominantly *erythro*.

The presence or absence of hetero-dimeric entities (GS or SG) in natural lignins could not be confirmed by ^{13}C NMR spectroscopy because the sidechain signals from both *e* and *t* GS entities overlap the corresponding signals from *e* to *t* SS entities; signals from *e* SG entities overlap those from *e* GG entities; and signals from *t* SG entities overlap those from both *e* SS (α-carbon) and *t* GG (β and γ carbons). However, the difficulty of preparing the SG entity in trimers by oxidative coupling of sinapyl alcohol with GG or GS dimers suggests the absence of SG-polymer entities in lignin. This may be due to the propensity of highly reactive (to oxidative coupling) sinapyl alcohol to dimerize rather than coupling to a relatively unreactive dimer (or oligomer). In contrast, the ease of preparing the GS entity in trimers by the coupling of coniferyl alcohol with SG or SS dimers suggests the presence of the SG-polymer entity in lignin. This is presumably due to the more similar reactivities of coniferyl alcohol and the free phenolic S-unit.

EXPERIMENTAL

Starting Materials

Monomers and milled wood lignins

The coniferyl alcohol and sinapyl alcohol were prepared according to a published procedure.[11] Acetosyringone was obtained from the Aldrich Chemical Co. (Milwaukee, Wisconsin). The spruce (*Picea mariana*) and birch (*Betula papyrifera*) acetylated milled wood lignins were obtained from previous studies.[12,13] The hickory (*Carya ovata*) milled wood lignin was prepared by extracting ball-milled wood with 96%-98% dioxane/water, similar to a procedure described previously.[14]

Table 5. ^{13}C NMR data of β-O-4 trimers[a]

	Compound													
Carbon	**1a** GGG1	**1b** GeGeG1	**1c** GeGtG1	**1d** GGG2	**2a** GGS1	**2b** GGS3	**3** GSG1	**4a** GeStS5	**4b** GeSeS5	**5a** SSS2	**5b** SSS5	**6** SSG3	**7** SGS5	**8** SGG1
A-α	e 74.6	e 74.6	e 74.5	e 74.6	e 74.5	e 74.6	e 75.1	e 75.1	e 75.1	e 75.4	e 75.4	e 75.4	—	e 74.6
	t 75.4	—	—	t 75.4	t 75.3	t 75.4	—	—	—	—	—	—	t 75.7	t 75.4
A-β	e 80.4	e 80.3	e 80.2	e 80.3	e 80.2	e 80.2	e 81.4	e 81.4	e 81.4	e 81.4	e 81.5	e 81.4	—	e 80.3
	t 80.7	—	—	t 80.6	t 80.6	t 80.6	—	—	—	—	—	—	t 80.7	t 80.4
A-γ	e 63.0	e 63.2	e 63.1	e 63.1	e 63.1	e 63.1	e 63.4	e 63.4	e 63.3	e 63.4	e 63.4	e 63.4	—	e 63.2
	t 63.6	—	—	t 63.6	t 63.6	t 63.6	—	—	—	—	—	—	t 63.6	t 63.6
A1	136.6	136.6	136.5	136.6	136.6	136.6	137.1	137.1	137.0	136.6	136.1	136.6	136.2	136.0
A2	112.8	112.8	112.8	112.9[b]	112.7[b]	112.9	112.3	112.3	112.2	104.7	104.6	104.6	105.0	104.9[b]
A3	152.1	152.0	152.0	152.1	152.2	152.1	152.0	152.0	152.0	153.0	153.0	153.0	153.2	153.0
A4	140.8	140.8	140.8	140.8	140.8	140.9	140.5	140.6	140.5	129.4	129.3	129.3	129.7	129.4
A5	123.3	123.3	123.3	123.3	123.3	123.4	123.3	123.3	123.3	153.0	153.0	153.0	153.2	153.0
A6	120.5	120.5	120.5	120.5	120.4	120.6	120.0	120.0	120.0	104.7	104.6	104.6	105.0	104.9[b]
B-α	e 74.6	e 74.6	—	e 74.6	e 75.3	e 75.4	—	—	e 75.4	e 75.4	e 75.4	e 74.9	e 75.2	e 74.6
	t 75.4	—	t 75.5	t 75.4	t 76.5	t 76.5	t 75.7	t 76.7	—	—	—	—	—	—
B-β	e 80.4	e 80.3	—	e 80.3	e 81.4	e 81.4	—	—	e 81.4	e 81.6	e 81.5	e 80.1	e 81.4	e 80.3
	t 80.7	—	t 80.8	t 80.6	t 81.6	t 81.6	t 80.8	t 81.7	—	—	—	—	—	—
B-γ	e 63.0	e 63.2	—	e 63.1	e 63.6	e 63.6	—	—	e 63.3	e 63.4	e 63.4	e 63.4	e 63.4	e 63.0
	t 63.6	—	t 63.7	t 63.6	t 64.4	t 64.4	t 63.7	64.3	—	—	—	—	—	—

B1	136.6	132.7	132.7	136.6	136.6	133.2	133.7	134.2	134.4	134.1	134.2	136.6	133.0	136.6
B2	112.8	113.1	112.9	113.0	112.7[b]	112.9	105.3	105.3	104.8	104.7	104.8	105.5	112.5	113.0
B3	151.6	151.6	151.6	151.6	151.5	151.6	154.0	153.9	153.8	153.9	153.8	153.8	151.4	152.1
B4	148.3	148.4	148.3	148.4	152.2	152.1	136.4	136.3	136.0	136.6	136.6	136.6	148.7	148.2
B5	119.0	118.9	119.0	119.1	118.9	118.6	154.0	153.9	153.8	153.9	153.8	153.8	118.4	118.7
B6	120.1	120.8	120.6	120.5	120.4	120.6	105.3	105.3	104.8	104.7	104.8	105.5	120.3	120.1
C-α	—	—	—	134.2	—	72.7	—	21.7	21.7	134.4	21.7	72.4	21.8	—
C-β	—	—	—	123.3	—	22.6	—	—	—	124.1	—	22.5	—	—
C-γ	—	—	—	65.4	—	—	—	—	—	65.3	—	—	—	—
C1	123.6	123.9	123.6	132.6	124.6[b]	133.2	123.6	134.2	134.2	133.3	134.2	133.6	134.5	121.6
C2	113.7	113.8	113.7	111.4	106.2	104.0	113.7	107.0	106.8	105.0	106.9	111.7	106.9	113.8
C3	152.1	152.1	151.8	152.1	154.2	153.8	151.7	153.7	153.8	154.2	153.8	151.6	153.9	152.1
C4	148.3	148.2	149.1	148.4	133.2	133.7	149.1	135.5	134.2	136.5	134.4	147.8	134.1	148.2
C5	119.6	119.6	119.0	119.1	154.2	153.8	118.9	153.7	153.8	154.2	153.8	118.9	153.9	119.6
C6	121.6	121.6	121.7	120.5	106.2	104.0	121.7	107.0	106.8	105.0	106.9	119.1	106.9	120.8
4AcMe	20.9	20.9	20.9	20.9	20.9	20.9	20.9	20.9	20.9	20.3	20.3	20.3	20.3	20.3
4AcC=O	168.9	168.9	169.0	168.9	168.9	168.9	169.0	168.9	169.0	168.5	168.5	168.5	168.5	168.5

[a]Chemical shifts are of fully acetylated compounds in acetone-d_6 and are given in δ ppm, referred to the center signal of the solvent at 29.83 which is referenced to TMS at 0 ppm. Common signals: OMe, 56.3-56.5; α-AcC=O, 169.9-170.0; γAcC=O, 170.7-170.8; α=AcMe, 20.9; γ-AcMe, 20.6–20.7.

[b]center of *e*/*t* signals.

Oxidants

Manganese(III) was supplied as $Mn(OAc)_3 \cdot 2H_2O$ and copper (II) was supplied as $Cu(OAc)_2 \cdot H_2O$; both were obtained from the Aldrich Chemical Co. Vanadium(V) was supplied as the polyoxoetalate (POM) salt, $K_5(SiVW_{11}O_{40}) \cdot 12H_2O$, which was synthesized according to a published procedure.[15]

Dimeric precursors to trimers **1–8**

All the dimer precursors have been authenticated and are included in the NMR Database of Lignin and Cell-Wall Compounds.[16]

1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propan-1,3-diol, the GG dimer precursor to trimer **1a**, was composed of about 75% of the *e* isomer (compound #101*e* in the database) and 25% of the *t* isomer (#102*t*). This compound was synthesized from acetovanillone and guaiacol according to published procedures.[17,18]

1-(4-hydroxy-3-methoxyphenyl)-2-(2,6-dimethoxyphenoxy)propan-1,3-diol, the GS dimer (compound #179) precursor to trimer **2a** was about 60% *t*. This compound was synthesized from acetovanillone and syringol.[17,18]

1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxyphenoxy)propan-1,3-diol, the pure *t* SG dimer (compound #90) precursor to trimer **3**, was synthesized from acetosayringone and guaiacol.[17,18]

1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2,6-dimethoxy-4-methylphenoxy)-propan-1,3-diol. The *t* isomer of the SS dimer (compound #243) precursor to trimer **4a**, was prepared from acetosyringone and methyl syringol.[17,18,20] The corresponding *e* isomer of the SS dimer precursor to trimer **5a** was synthesized by the oxidative coupling of sinapyl alcohol to 4-methylsyringol with Mn(III) acetate in pyridine.[2] The methyl syringol was obtained by catalytic reduction of syringaldehyde with palladium on charcoal in absolute ethanol.[19]

1-(4-hydroxy-3,5-dimethoxyphenyl)-2-(2-methoxy-4-(ethan-1-ol)phenoxy)-propan-1,3-diol, the *e* SG dimer (*t* isomer, compound #88) precursor to trimer **6**, was synthesized by the usual procedures[17,18] using acetovanillone instead of guaiacol to form the second ring. An alternate synthesis that results in a purer *e* isomer has been published by others.[20]

1-(4-hydroxy-3-methoxyphenyl)-2-(2,6-dimethoxyphenoxy)-propan-1,3-diol, the *e* GS dimer (*t* and *e*, compound #242) precursor to trimer **7**, was prepared from acetovanillone and methyl syringol.[19]

1-(4-hydroxy-3-methoxyphenyl)-2-(2-methoxyphenoxy)propan-1-ol-3-acetoxy, the GG dimer precursor to trimer **8**, was greater than 90% *e*. The only difference between the preparation of this dimer and the first GG dimer was that the di-acetate derivative of the α-keto precursor to the dimer was reduced with zinc borohydride by a method previously described,[18] to give the γ-acetoxy GG dimer.

Trimers 1–8

GGG (**1a**)

A solution of coniferyl alcohol (90 mg, 0.50 mmol) in acetonitrile (10 mL) and a solution of POM (3.16 g, 1.00 mmol) in 1 M sodium acetate (10 mL) were simultaneously added (with peristaltic pumps), over a period of 14 h, to a solution of the GG dimer (160 mg, 0.50 mmol) in a 1/1 mixture of acetonitrile and acetate buffer (5 mL) at room temperature with magnetic stirring under a nitrogen flow. The resulting dark opaque solution was placed on a rotary evaporator under vacuum (~15 mm) at room temperature for about 1 h to remove most of the acetonitrile. The solution was then added to brine (75 mL) and extracted with ethyl acetate (4 x 25 mL). The yellow organic layer ws separated, dried over anhydrous magnesium sulfate, and evaporated on a rotary evaporator, leaving a white foamy solid (245 mg, 98% wt recovery). The foam was acetylated for 2 h at room temperature with 1/1 acetic anhydride/pyridine (5 ml), which upon removal of reagents by azeotroping with toluene followed by acetone, yielded a yellow oil that was applied on a 96 x 5.1 cm column of Bio-Rad Bio-Beads S-X3. Elution with methylene chloride gave a trimer fraction containing the desired product (61 mg, 26% of total applied acetylated material).

GGG (**1d**)

This trimer was isolated in very low yield (~2%) from a mixture of products obtained by the oxidative coupling of coniferyl alcohol with Mn(III) acetate in pyridine as was previously described.[3]

GGS (**2a**)

A solution of coniferyl alcohol (68.4 mg, 0.38 mmol) in acetonitrile (10 mL) and a solution of $Cu(OAc)_2 \cdot H_2O$ (76 mg, 0.38 mmol) in water (10 mL) were simultaneously added, over a period of 14 h, to a solution of the GS dimer (133 mg, 0.38 mmol) in 1/1 acetonitrile/water (10 mL) at room temperature with magnetic stirring under a nitrogen flow. Workup, acetylation, and column fractionation, as described above, gave the desired trimer (39 mg, 16% of total acetylated material).

GGS (**2b**)

Prepared in the same manner as **2a**.

GSG (**3**)

A solution of coniferyl alcohol (56 mg, 0.31 mmol) in acetonitrile (10 mL) and a solution of POM (1.96 g, 0.62 mmol) in 1 M sodium acetate buffer were simultaneously added, over a period of 14 h, to a solution of the SG dimer (160 mg, 0.50 mmol) in a 1/1 mixture of acetonitrile and 1 M sodium acetate buffer (5 mL) at room temperature with magnetic stirring under a nitrogen flow. Workup, acetylation, and column fractionation, as described above, gave the desired trimer (179 mg, 60% of total acetylated material).

GSS (**4a**)

A solution of coniferyl alcohol (74 mg, 0.41 mmol) in acetonitrile (10 mL) and a solution of POM (2.59 g, 0.82 mmol) in 1 M sodium acetate buffer were simultaneously added, over a period of 14 h, to a solution of the *t* SS dimer (160 mg, 0.50 mmol) in a 1/1 mixture of acetonitrile and 1 M sodium acetate buffer (5 mL) at room temperature with magnetic stirring under a nitrogen flow. Workup, acetylation, and column fractionation, as described above, gave a crude product (239 mg) that was applied on a thick-layer silica-gel plate. The major band on the plate was the desired trimer (154 mg, 51% of total acetylated material).

GSS (**4b**)

Prepared in the same manner as **4a** with *e* SS dimer.

SSS (**5a**)

A solution of sinapyl alcohol (57 mg, 0.27 mmol) in pyridine (10 mL) and a soluton of $Mn(OAc)_3 \cdot 2H_2O$ (150 mg, 0.54 mmol) in pyridine (10 mL) were simultaneously added, over a period of 14 h, to a solution of the *e* SS dimer (117 mg, 0.27 mmol) in pyridine (5 mL)/water (0.2 mL) at room temperature with magnetic stirring under a nitrogen flow. Acetic anhydride (3 mL) was then added to the reaction mixture and stirring was continued for 1 h. The solution was added to 0.01 M sodium sulfite solution, followed by concentrated HCl. The resulting suspenson was extracted with ethyl acetate (5 x 25 mL), and the extract was washed with water twice and dried over anhydrous magnesium sulfate. Evaporation of the solvent, application of the oil on a column as described above, and separation of the trimer fraction gave only 18 mg of material; Consequently, the procedure was repeated with 1 mmol sinapyl alcohol, 2 mmol manganese salt, and 1 mmol of SS dimer. The trimer fraction from the second reaction was combined with the first product and re-chromagraphed on Bio-Beads S-X3 to give a total of only 6 mg of the desired trimer in pure form.

SSS (**5b**)

A solution of $Mn(OAc)_3 \cdot 2H_2O$ (134 mg, 0.50 mmol) in pyridine (2 mL) was added dropwise over a 10 min period to a magnetically stirred solution of sinapyl alcohol (105 mg, 0.50 mmol) in pyridine (2 mL). The dark solution was then stirred for an additional 10 min and water (0.1 mL) was added. Acetic anhydride (2 mL) was added after 5 min, and acetylation was continued for 1.5 h. The resulting olive-drab solution was added dropwise to water (100 mL); to the resulting amber suspension a few milligrams solid sodium bisulfite was added to destroy excess Mn(III). The white suspension was then extracted with ethyl acetate (3 x 30 mL). The yellow extract was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the solvent and application of the orange oil on an S-X3 column as described above gave a fraction containing the desired trimer (19 mg, 25% of total product) along with 25% of the SS dimer and 46% of high molecular weight material.

SSG (**6**)

A solution of sinapyl alcohol (63 mg, 0.30 mmol) in pyridine (5 mL) and a solution of $Mn(OAc)_3 \cdot 2H_2O$ (166 mg, 0.60 mmol) in pyridine (5 mL) were simultaneously added, over a period of 14 h, to a solution of the *e* SG dimer (118 mg, 0.30 mmol) in pyridine (5 mL)/water (0.1 mL) at room temperature with magnetic stirring under a nitrogen flow. Workup, acetylation, and chromatography as in the previous experiment gave a trimer fraction (76 mg, 34% of total acetylated material) that was contaminated with adjacent fractions. Therefore, the fraction was re-applied to the same column and a much narrower fraction was collected to give the desired pure trimer (18 mg, 8% of the original acetylated material).

SGS (**7**)

Acetosyringone was acetylated and brominated according to usual procedures,[17,18,19] and the product was then condensed with the α,γ-diacetate of the *e* GS dimer. The resulting trimer was treated with formaldehyde in dioxane reduced with sodium borohydride to give a *t* linkage between the A- and B-rings,[18] and fully acetylated to give the desired trimer.

SGG (**8**)

A solution of sinapyl alcohol (56 mg, 0.26 mmol) in pyridine (10 mL) and a solution of $Mn(OAc)_3{\cdot}2H_2O$ (144 mg, 0.52 mmol) in pyridine (10 mL) were simultaneously added, over a period of 14 h, to a solution of GG dimer (96 mg, 0.26 mmol) in pyridine (5 mL)/water (0.2 mL) at room temperature with magnetic stirring under a nitrogen flow. Workup, acetylation, and chromatography as in the preparation of the SSS trimer gave a fraction (23 mg, 13% of total acetylated material) that was contaminated with adjacent fractions. Re-application of the product on an S-X3 column did not appreciably increase the purity of the trimer. The overall yield from monomer and dimer was less than 5%.

Spectroscopy

NMR

The NMR data were obtained with a Bruker DPX-250 spectrometer (62.9 MHz ^{13}C) with 6 - 25 mg of sample in 0.4 mL acetone-d_6 at ambient temperature. Unless noted otherwise, a line broadening of 2 Hz was used. All chemical shifts are given in δ ppm and are referred to the centerline of the solvent at 29.83 ppm, which is based on tetramethylsilane ($\delta = 0.0$).

The deconvolution spectra were obtained with MacNuts software obtained from Acorn NMR Inc. (www.acornnmr.com).

Mass

Mass spectra of selected trimers were obtained with a Finnigan GCQ spectrometer, source temp = 180°C.

EIMS (probe) 70eVm m/z (relative intensity):

1a M^+726(7), 323(100), 281(27), 263(29), 221(93), 222(39), 179(18), 178(39), 160(32), 124(37).

2a M^+756(2), 323(18), 281(6), 263(7), 221(20), 222(59), 180(30), 179(39), 162(85), 154(100), 131(17).

3 M^+756(1), 434(7), 323(100), 264(17), 221(68), 179(8), 178(17), 175(18), 124(6).

4a M^+800(1), 323(100), 281(7), 263(18), 221(86), 209(14), 179(33), 168(26), 167(17).

5a M^+830(1), 478(1), 353(47), 311(29), 293(36), 253(100), 252(77), 209(50), 208(15), 168(42).

6 M^+800(not present), 353(34), 311(33), 293(32), 252(58), 251(100), 209(75), 208(48), 207(37), 206(37), 177(58).

7 M^+800(3), 471(10), 411(17), 353(24), 323(32), 311(19), 293(23), 281(12), 251(60), 209(40), 168(100).

8 M^+756(1), 711(3), 353(37), 311(20), 293(33), 253(38), 252(80), 251(42), 209(30), 208(38), 207(37), 206?(47), 190(42), 182(43), 160(41), 124(100).

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