

Synthesis of Trimeric Lignin Model compounds Composed of β -Aryl Ether and Phenylcoumaran Structures

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Summary

Four lignin models representing β -aryl ether/ β -aryl ether and β -aryl ether/phenylcoumaran trimers have been synthesized as mixtures of isomers. The use of pure isomers of lignin model dimers in some syntheses gave fewer stereoisomers and facilitated their NMR characterisation.

Schlüsselwörter (Sachgebiete)

Ligninmodellverbindungen

Trimere

β -Arylether

Phenylcoumaran

Stereoisomer

NMR

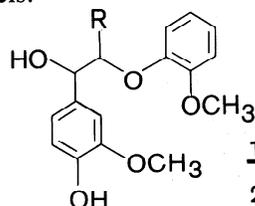
Synthese von trimeren Ligninmodellverbindungen aus β -Arylether- und Phenylcoumaran-Strukturen

Zusammenfassung

Vier Ligninmodellverbindungen mit β -Arylether/ β -Arylether und β -Arylether/Phenylcoumaran Trimeren wurden als Mischungen von Isomeren synthetisiert. Bei Verwendung von reinen Isomeren von Ligninmodell-Dimeren bei einigen Synthesen ergaben sich weniger Stereoisomere und ihre NMR Kennzeichnung war leichter.

Introduction

Dimeric lignin model compounds such as **1** and **2** have been extensively used in mechanistic studies to model single interunit linkage types in the lignin polymer. Nakatsubo and others have also synthesized a series of *trimeric* model compounds including phenylcoumaran/ β -0-4 (Nakatsubo and Higuchi 1980a), phenylcoumaran/ β -1 (Nakatsubo and Higuchi 1980b) and β -0-4/syringaresinol (Kamaya et al. 1980) models.



1 R=H

2 R=CH₂OH

3 R=CO₂Et

Associated with our investigations into reactions of anthrahydroquinone and anthranol with lignin model compounds and lignin itself, we have been interested in models containing the β -aryl ether unit, as a free-phenolic end group, attached to the most predom-

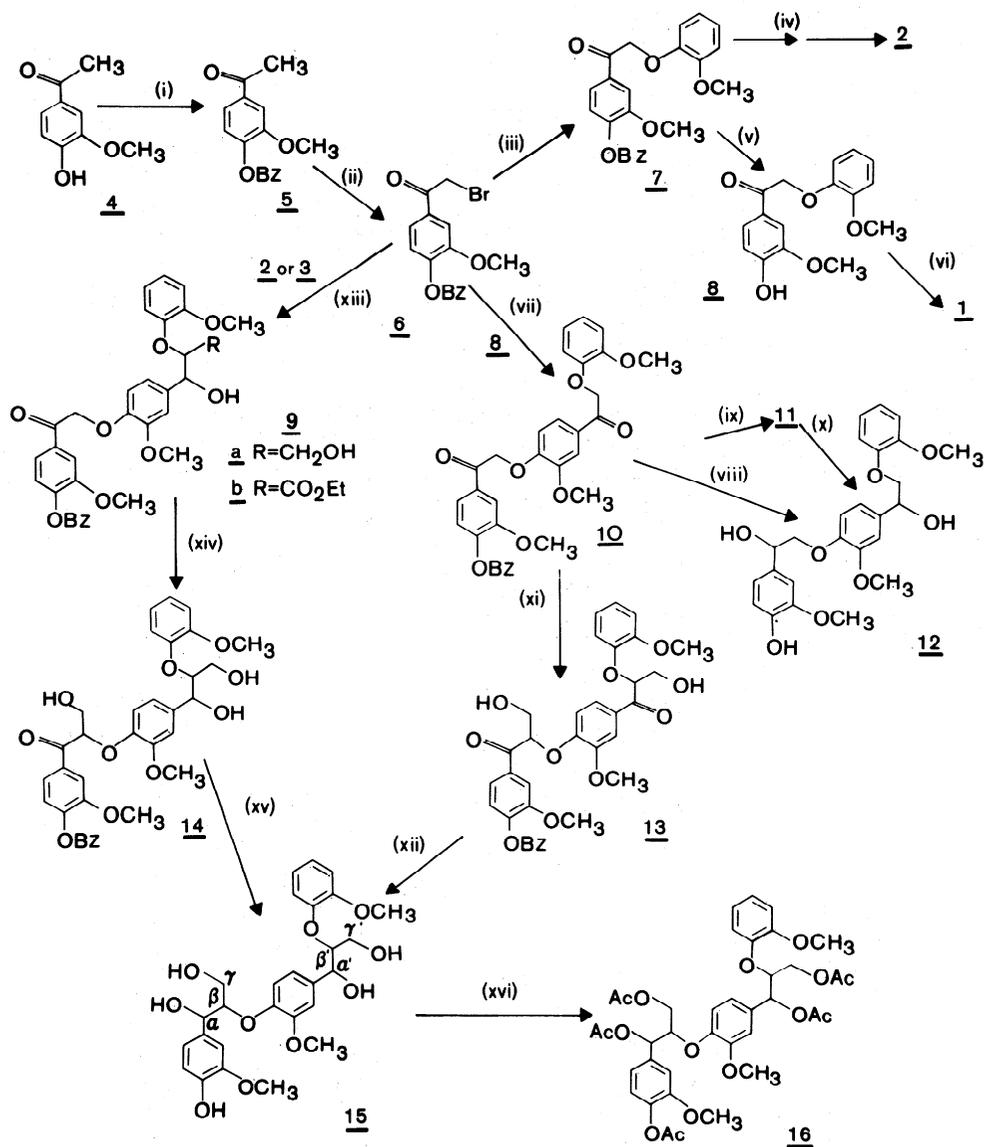
inant units in the lignin structure. These include β -0-4/ β -0-4 and β -0-4/phenylcoumaran models for which syntheses have not previously been reported.

Results

The syntheses of compounds **12** and **15** (Scheme 1), and **20** and **23** (Scheme 2) follow traditional (and non-convergent) methods. They have the advantage that many of the intermediates used are in common with those in lignin model dimer syntheses. The general methods are anticipated to work for variations on the specific models chosen.

Preparation of β -ether/ β -ether model trimers

The synthetic schemes for preparation of the trimers with both 2-carbon (ethyl) and 3-carbon (propyl) sidechains are given in Scheme 1. Essentially, this scheme is a modification of schemes previously used to prepare the dimeric lignin models **1** and **2** (e.g. Landucci et al 1981; and references therein). Thus, in Scheme 1, the steps to **5**, **6**, **7**, **8**, **1** and **2** are well known.



Scheme 1. Route to β -ether/ β -ether trimers

(i) $\text{PhCH}_2\text{Cl}/\text{EtOH}/\text{KOH}$ or $\text{PhCH}_2\text{Cl}/\text{K}_2\text{CO}_3/\text{KI}/\text{Me}_2\text{CO}$, (ii) $\text{Br}_2/\text{CCl}_4/\text{CHCl}_3$, (iii) guaiacol/ $\text{K}_2\text{CO}_3/\text{Me}_2\text{CO}$, (iv) a. $\text{H}_2\text{CO}/\text{K}_2\text{CO}_3/\text{EtOH}$ b. $\text{Pd-C}/\text{H}_2/\text{EtOH}$, 2 atm (200 kPa), (v) $\text{Pd-C}/\text{H}_2/\text{THF}$, 1 atm (100 kPa), (vi) LAH/THF , (vii) $\text{K}_2\text{CO}_3/\text{Me}_2\text{CO}$, 100%, (viii) $\text{Pd-C}/\text{H}_2/\text{EtOH}$, 2 atm (200 kPa), 72%, (ix) $\text{Pd-C}/\text{H}_2/\text{THF}$, 1 atm (100 kPa), 51% (not optimised), (x) LAH/THF , (xi) $\text{H}_2\text{CO}/\text{EtOH}/\text{K}_2\text{CO}_3$ 39%, (xii) $\text{Pd-C}/\text{H}_2/\text{EtOH}$, 1 atm (100 kPa), 90%, (xiii) $\text{K}_2\text{CO}_3/\text{Me}_2\text{CO}$, 100%, (xiv) $\text{H}_2\text{CO}/\text{EtOH}/\text{K}_2\text{CO}_3$, 50–86%, (xv) a. $\text{Pd-C}/\text{H}_2/\text{EtOH}$ b. LAH/THF , 86%, (xvi) $\text{Ac}_2\text{O}/\text{py}$, 96%.

A variety of phenolic protecting groups have been used but the most popular for syntheses of β -ether dimers are probably the benzyl ether and the benzoate groups. The benzyl derivative was found to be more suitable for the arylpropyl models as some hydrolysis of the benzoate group occurred in the formaldehyde addition steps.

The key reaction step was the $\text{S}_{\text{N}}2$ displacement of bromide in **6** by a free-phenolic dimeric moiety. This phenol may be either a precursor which can be subsequently functionalised and modified (such as **8** or **3**) or a dimeric model compound such as **2**, which needs no further structural elaboration.

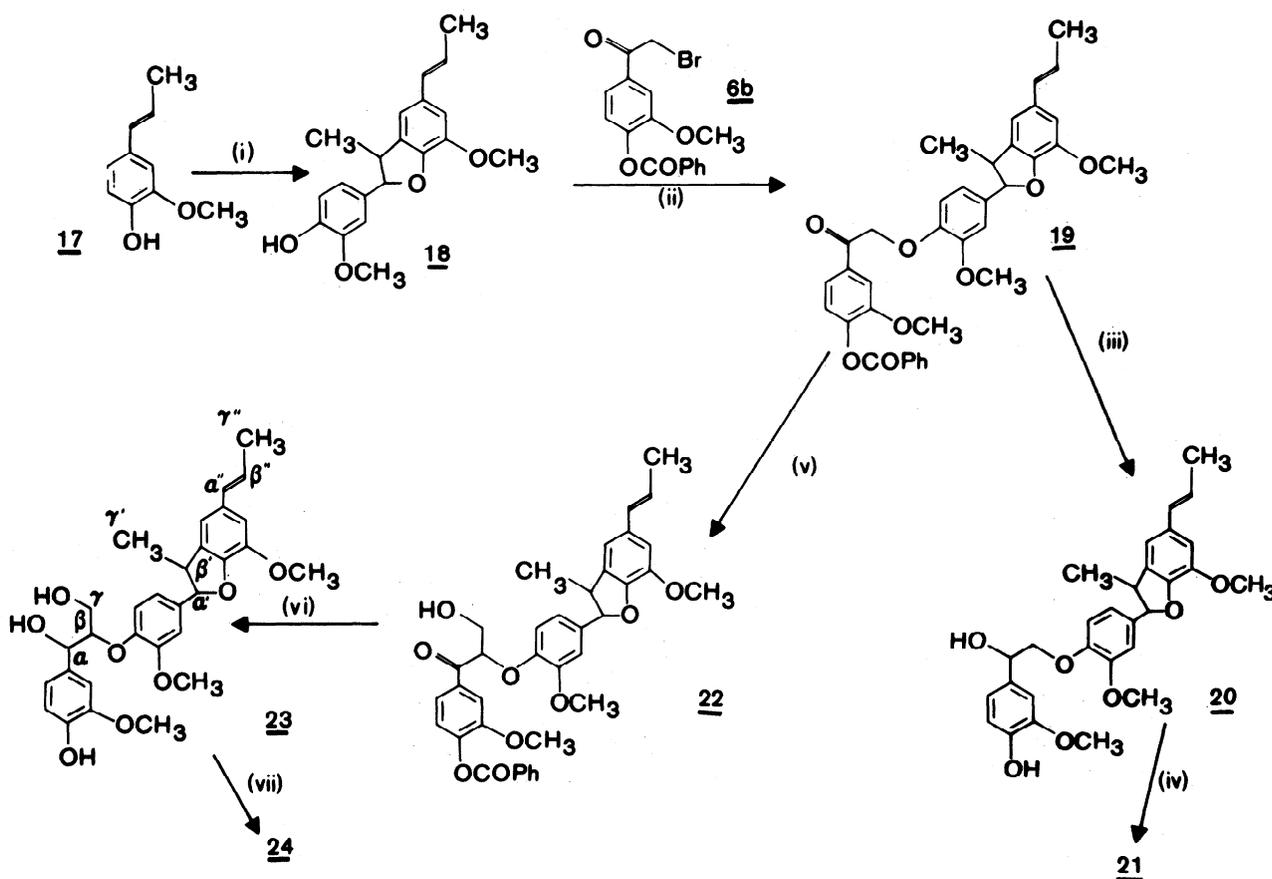
The arylethyl trimer **12** was obtained by reduction/debenzylation of **10**.

Formaldehyde addition to the ketone (e.g. **9a** to **14**)

by a classical aldol reaction extended the sidechain to be representative of arylpropyl lignin models, but was a difficult step. Finally, reduction and debenzylation (e.g. **14** to **15**, **13** to **15**) gave the required model **15**.

Preparation of β -ether/phenylcoumaran trimers

The synthetic scheme to the two β -ether/phenylcoumaran trimers **20** and **23** (Scheme 2) is essentially analogous to the β -ether/ β -ether trimer synthesis. Although the benzyl ether protecting group is the most satisfactory for the β -ether/ β -ether trimers, the final catalytic reductive debenzylation step is not compatible with the phenylcoumaran moiety, which is itself a benzyl ether. Hence, the benzoate group was chosen



Scheme 2. Route to β -ether/phenylcoumaran trimers

(i) $\text{FeCl}_3/\text{EtOH}/\text{H}_2\text{O}$, 30%, (ii) $\text{K}_2\text{CO}_3/\text{Me}_2\text{CO}$, 90%, (iii) LAH/THF , 81%, (iv) $\text{Ac}_2\text{O}/\text{py}$, 94%, (v) $\text{H}_2\text{CO}/\text{EtOH}/\text{K}_2\text{CO}_3$, 53%, (vi) LAH/THF , 83%, (vii) $\text{Ac}_2\text{O}/\text{py}$, 63%.

to protect the phenol for the β -ether/phenylcoumaran models. The phenylcoumaran dimer **18** itself was added directly to bromide **6b** because it can be prepared in a single step from isoeugenol **17** (Leopold 1950). Reduction with lithium aluminium hydride (LAH) gave the arylethyl trimer **20** directly. Hydroxymethylation of the sidechain (**19** to **22**) again proved to be the difficult step of the arylpropyl model synthesis with some hydrolysis of the benzoate group occurring. The yield of **22** was only 53%. LAH reduction of **22** gave the required trimers **23**.

Discussion

The syntheses of the lignin model trimers by the above methods is straightforward and most steps occur in high yields (>80%).

In particular the displacement of bromide in **6** by any of the phenols tried occurred cleanly in essentially quantitative yield. It is assumed that the more ideal phenylcoumaran model, dehydridiconiferyl alcohol, and phenolic models representing the β -C-1, pinoresinol or other linkages would add equally well and give a simple route into a diverse class of trimers containing a β -ether unit linked to another structural unit.

The problems with the formaldehyde addition steps were not envisaged based on the high yields obtained on dimeric products using the method of Landucci et al. (1981). Although the yields in these steps were as low as 50%, the required products were readily separated from the reaction mixtures and, because of the compatibility with dimeric model syntheses, the method is convenient. Attempts at other procedures to add formaldehyde or other $-\text{CH}_2\text{OH}$ synthons proved no more successful. Alternative strategies employing convergent synthetic approaches can be envisaged and may be examined at a later date.

The ability to have synthetic control over the isomer of at least the second unit of the trimers (by adding a diastereomerically pure phenol to bromide **6**) is another point in favour of this approach. Thus, the addition of the dimer guaiacylglycerol- β -guaiacyl ether **2** to bromide **6** to give **9a** allowed simpler hydroxymethylation to **14** in higher yield and provided a means of reducing the number of isomers in the final product **15**. Compound **15** has *threo/erythro* isomerism possible in both moieties of the trimer but from the 16 possible stereoisomers (8 distinct compounds) there are four classes of interest, namely ee, et, te, tt (where ee = *erythro-erythro*, etc.). How-

ever, since each isomer of **2** is available in diastereomerically pure form, i.e., *threo* and *erythro* forms (e.g. Ralph and Young 1981; Nakatsubo *et al.* 1975; Hosoya *et al.* 1980; Ahvonen *et al.* 1983), the use of a single diastereomer of **2** in the reaction would yield a product **15** as four distinct compounds in only two of the above classes. E.g., when *threo*-**2** was used, trimer **15** was a mixture of *et* and *tt* isomers.

Pure *erythro*-**2** and pure *threo*-**2** both added to bromide **6** cleanly to give **9a** as did pure *erythro*-**3**, available from the synthetic method of Nakatsubo *et al.* (1975) to give **9b**. The remainder of the scheme was not carried out with the product from **6** and **3** (i.e., **9b**). It is assumed that one should analogously be able to add *threo* and *erythro* β -C-1 models, to give the required β -ether/ β -C-1 trimers.

Although no attempt has been made to separate these trimers into their component isomers, nor to induce selectivity into the ketone reduction steps of **13**, **14** or **22**, it is assumed that both should be possible by methods used previously for the dimeric models. For example the phenylboronates (Nakatsubo and Higuchi 1975; Ralph and Young 1983; Ralph 1982) or the acetals (Ralph and Young 1983; Ralph 1982) can be resolved, and L-Selectride® reduction of ketones **14** or **22** would presumably favour the *threo* alcohol isomer by about 80:20 (Ralph and Young 1981). Stereoselectivity has also been observed using polymer-bound reducing agents (Brunow *et al.* 1981).

In the case of the phenylcoumaran trimers, the relative stereochemistry of the phenylcoumaran moiety is fixed. Although the coupling constant of approximately 9 Hz between the protons on the 5 membered ring of the phenylcoumaran would seem to indicate a dihedral angle of close to 0° and hence a *cisoid* configuration, there appears to be excellent chemical evidence for the ring being *transoid* (Aulin-Erdtman *et al.* 1963), i.e., for the RS/SR isomer. Simplistically, trimer **20** may be regarded as a single isomer. However, it must be recognised that there are 3 optical centres (implying 8 possible stereoisomers) and that even defining or fixing the phenylcoumaran moiety to be RS/SR leaves 4 possible stereoisomers, 2 pairs of

enantiomers. Analogously, the β -ether moiety in **23** has *erythro* and *threo* stereochemistry while the phenylcoumaran moiety has a fixed *transoid* stereochemistry, simplistically giving rise to only two isomeric forms, namely *erythro*-**23** and *threo*-**23**. This treatment is adequate for most purposes, and it is these two classes of isomers which are revealed by ^{13}C NMR (Table 1). Strictly there are four pairs of enantiomers, which may be designated *t*-RS, *t*-SR, *e*-RS, *e*-SR, where *t* and *e* represent the *threo* or *erythro* stereochemistry of the β -aryl ether unit and the RS/SR nomenclature refers to the two optical centers of the phenylcoumaran ring. Indeed, in the high field proton NMR spectrum, 3 of the 4 isomers of compound **24** (the triacetate of trimer **23**) are distinguishable (see below), and the spectra of compounds **16** (to be reported separately) showed similar complexity.

Spectra

Products were characterised primarily by low field ^1H NMR, ^{13}C NMR (Table 1) and mass spectrometry, and all spectra were consistent with the assigned structures. By far the most informative characterisation was by ^{13}C NMR which showed excellent (spectral) resolution of the isomers in at least one of the side-chain carbons (Table 1). The differences in the chemical shifts of the side-chain carbons are even greater in chloroform (Ralph 1982) but acetone was used predominantly here because acetone is the most widely used solvent for ^{13}C NMR of lignins and acetylated lignins and because of some solubility problems with these compounds in chloroform.

The ^{13}C NMR spectra did not show resolution of all of the possible stereoisomers. While the assignment of peaks in compounds **15** or **16** would have been extremely difficult from a mixture of all possible isomers, the synthesis of these compounds from stereochemically pure isomers of **2** (*via* compounds **9a** and **14**) considerably simplified the spectra. For example, Figure 1, compounds **15** prepared from *threo*-**2** (and therefore having *threo* stereochemistry in the second β -ether unit and approximately 60:40 *erythro*:*threo* stereochemistry in the first) can be conveniently described as a mixture of *tt* and *et* isomers, although this is a simplification. For each aliphatic carbon, the chemical shift of the carbons in the second moiety is not affected by the stereochemistry of the first (75.5, 80.7 and 63.7 for α' , β' and γ' respectively) and the SR/RS isomerism in the second moiety does not affect each resonance in the first moiety.

It is also worthy to note that, in the acetates **16**, the chemical shifts of the sidechain carbons are similar for each isomer, whether the unit is an end-group (and therefore has the phenol acetylated) or is an internal moiety (in which case the phenol is etherified by a β -carbon of the other unit). The difference between the *threo* and

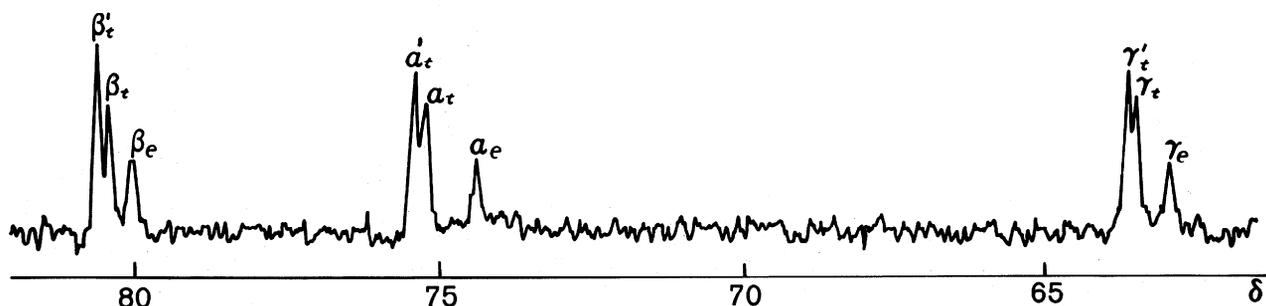


Fig. 1. Partial ^{13}C NMR spectrum of *tt*-**15** plus *et*-**15**

Table 1. ¹³C NMR data for selected aliphatic carbons

Compound	Isomer	Solvent	α	β	γ	α'	β'	γ'	α''	β''	γ''	Benzyl CH ₂
9a	t	A	193.8	72.3	—	73.5	87.6	61.7	—	—	—	71.1
9a	e	A	193.8	72.3	—	73.6	86.2	61.7	—	—	—	71.1
9b	e	A	193.9	72.2	—	74.5	83.6	170.3	—	—	—	71.1
10	—	A	193.6	72.0	—	192.7	71.3	—	—	—	—	71.0
13	—	A	?	83.9	64.0	?	83.4	64.0	—	—	—	71.2
14	t	A	196.1	83.9	64.0	73.6	87.7	61.8	—	—	—	71.2
14	e	A	196.1	83.9	64.0	73.6	86.3	61.8	—	—	—	71.2
15	tt	A	73.8	88.1	61.8	73.6	87.7	61.8	—	—	—	—
15	et	A	73.8	86.6	61.8	73.6	87.7	61.8	—	—	—	—
15	te	A	73.8*	88.2	61.8	73.7*	86.3	61.8	—	—	—	—
15	ee	A	73.8*	86.6	61.8	73.7*	86.3	61.8	—	—	—	—
16	tt	A	75.3	80.5	63.6	75.5	80.7	63.7	—	—	—	—
16	et	A	74.5	80.2	63.0	75.5	80.7	63.7	—	—	—	—
16	te	A	75.3	80.5	63.5	74.6	80.2	63.2	—	—	—	—
16	ee	A	74.5	80.1	63.0	74.6	80.2	63.2	—	—	—	—
2	t	A	73.9	88.2	61.9	—	—	—	—	—	—	—
2	e	A	73.8	86.5	61.8	—	—	—	—	—	—	—
2-(OAc) ₃	t	A	75.2	80.5	63.6	—	—	—	—	—	—	—
2-(OAc) ₃	e	A	73.9	80.1	62.6	—	—	—	—	—	—	—
18#	—	C	—	—	—	93.7	45.6	17.6	131.0	123.0	18.3	—
		A	—	—	—	93.9	46.0	17.7	131.9	123.2	18.4	—
19	—	C	193.5	72.2	—	93.4	45.6	17.7	130.9	123.5	18.3	—
20	—	C	72.1	76.1	—	93.5	45.7	17.7	130.9	123.5	18.4	—
		A	72.6	76.1	—	93.9	46.0	17.7	131.9	123.2	18.4	—
21	—	C	73.7	72.2	—	93.4	45.7	17.7	131.0	123.5	18.4	—
22	—	C	195.5	84.3	63.4	93.2	45.7	17.8	130.9	123.1	18.3	—
23	t	C	73.9	89.2	61.1	93.2	45.6	17.8	130.9	123.6	18.3	—
		A	73.7	88.0	61.7	93.5	46.2	18.0	131.9	123.3	18.4	—
23	e	C	72.8	87.1	61.0	93.2	45.6	17.8	130.9	123.6	18.3	—
		A	73.7	86.3	61.7	93.5	46.2	18.0	131.9	123.3	18.4	—
24	t	C	74.5	80.3	63.1	93.3	45.7	17.8	130.9	123.5	18.4	—
		A	75.2	80.6	63.4	93.4	46.3	18.0	131.9	123.3	18.4	—
24	e	C	73.7	80.3	62.5	93.3	45.7	17.8	130.9	123.5	18.4	—
		A	74.4	80.2	62.9	93.4	46.3	18.0	131.9	123.3	18.4	—

Chemical shifts referenced to TMS as 0.00 or the central d₆-acetone peak as 29.76

Solvents, A = acetone-d₆, C = CDCl₃

Spectra recorded at 22.5 MHz carbon.

Labelling of sidechain carbons to be consistent with those in trimers.

* assignments may be interchangeable.

the *erythro* isomer in each is, however, significant. Furthermore, these chemical shifts correspond exactly with peaks observed in the ¹³C NMR spectrum of acetylated milled wood lignin (Ralph 1982; Ralph et al. 1982) as shown in Table 2.

Table 2. Summary of ¹³C NMR chemical shifts of sidechain carbons in the acetylated trimers **16** and acetylated milled wood lignin (AMWL) from loblolly or radiata pine

	<i>Threo</i>		<i>Erythro</i>	
	16	AMWL	16	AMWL
αC's	75.3–75.5	75.4	74.5–74.6	74.7
βC's	80.5–80.7	80.7	80.1–80.2	80.2
γC's	63.5–63.7	63.6	63.0–63.2	63.2

Experimental

¹H NMR spectra, (available from the authors) were determined in CDCl₃ or acetone-d₆ on a Varian T60 CW spectrometer, a JEOL FX90Q FT multinuclear spectrometer or a Bruker WM250 FT spectrometer. ¹³C NMR spectra were determined in CDCl₃, or acetone-d₆ on a JEOL FX90Q spectrometer operating at 22.49 MHz in the ¹³C observation channel and 89.55 MHz in the proton decoupling channel. Spectra were recorded fully decoupled using broad-band proton decoupling. Assignment ambiguities were resolved where possible by broad-band decoupled ¹³C INEPT pulse sequencing using τ = 1/4J (= 1.7 ms) and a delay, Δ, of 3/4J (= 5.1 ms) leading to inversion of the methylene resonances and loss of the quaternary carbon resonances (Morris and Freeman 1979; Doddrell and Pegg 1980). Separate singlets-only spectra were recorded under normal conditions except with the broadband decoupler offset by 5 KHz (Wenkert et al. 1969).

Mass spectra were recorded using a direct insertion probe on a Hewlett-Packard HP5985 GC/MS operating under EI conditions.

Unless otherwise indicated, each product exhibited a single spot on analytical tlc (5–60% EtOAc/petroleum ether, visualised using iodine or phosphomolybdic acid).

General Methods

Lithium aluminium hydride (LAH) reduction

The compound was dissolved in anhydrous THF and added dropwise to a stirred solution containing an excess of LAH in anhydrous THF. The mixture was refluxed for three hours to reduce ketones and esters. Excess reducing agent was destroyed by dropwise addition of 50% THF/H₂O and the inorganic compounds dispersed with saturated aqueous ammonium chloride. The mixture was transferred to a separation funnel and extracted with ether, ethyl acetate or chloroform, and the organic phase washed several times with further ammonium chloride, then with saturated NaCl. The organic layer was dried over anhydrous MgSO₄, filtered, and the solvent removed under reduced pressure.

Acetylation

The compound was dissolved in 50% pyridine/acetic anhydride and a few crystals of 4-dimethylaminopyridine (Hofle et al. 1978) were added. The mixture was stirred for three hours and poured onto water in a separation funnel and extracted with ether or chloroform. The organic phase was washed with 5% H₂SO₄ (2X), water (2X) and finally with saturated aqueous NaHCO₃. The organic layer was dried over anhydrous MgSO₄, filtered and the solvent removed under reduced pressure.

Displacement of bromide in **6** by a phenol

Bromide **6a** or **6b** (1 eq), the phenol (1.02 eq), and powdered anhydrous potassium carbonate (1.05 eq) were refluxed in a small volume of acetone (ca. 4–5 ml for 100–1000 mg of **6**) for 15 h. The inorganic salts were filtered off and washed with acetone, and the filtrate evaporated to give the crude product.

Starting materials

Monomeric and dimeric precursors of the model trimers were prepared by standard literature methods with only minor modifications. Bromination of benzyl- or benzoyl-protected commercial acetovanillone to give **6** is best carried out by the method of Landucci et al. (1981). Guaiacol addition to **6** to give **7** was by the method of Landucci et al. (1981) as was the debenzoylation of **7** to **8** (except that only 1 atm H₂ was used). Alternatively **8** was prepared by hydrolysis of the benzoate protecting group of the benzoate analogue of **7**. *Threo* and *erythro* **2** were prepared as reported previously (Ralph and Young 1981) and **3** by Nakatsubo's (1975) method – the ester function was not reduced prior to debenzoylation. Dehydrodiisoeugenol **18** was prepared from commercial isoeugenol **17** (>90% trans) using Leopold's (1950) procedure.

Specific Methods

The β-ether-β-ether trimers

Compound *threo*-**9a**

Threo-guaiacylglycerol-β-guaiacyl ether, *threo*-**2**, (90.8 mg, 0.284 mmole) was reacted with bromide **6** as above to give *threo*-**9a** as a white foamy solid (159.6 mg, 100%), ¹³C NMR (Table 1): M/S (probe, EI, 70 eV) m/z 526 (M⁺–H₂CO–H₂O,3), 432(1), 406(7), 271(7), 241(18), 213(5), 165(6), 151(17), 150(28), 137(5), 124(12), 109(13), 91(100), 77(5).

Compound *erythro*-**9a**

Erythro-guaiacylglycerol-β-guaiacyl ether, *erythro* **2**, (108 mg, 0.338 mmole) was reacted with bromide **6** as above to give *erythro*-

9a as a white foamy solid (190 mg, 100%); ¹³C NMR (Table 1); M/S (probe, EI, 70 eV) m/z 526 (M⁺–H₂CO–H₂O,3), 432(1), 271(9), 241(17), 213(5), 165(6), 151(16), 150(30), 137(6), 124(12), 109(14), 91(100), 77(6).

Compound *erythro*-**9b**

Erythro-**3** (338.8 mg, 0.936 mmole) was reacted with bromide **6** as above to give *erythro*-**9b** as a white foamy solid. ¹³C NMR (Table 1); M/S (probe, EI, 70 eV) m/z 476(.1), 407(5), 406(6), 241(15), 210(15), 165(5), 151(6), 137(16), 123(11), 122(13), 91(100), 77(11).

Compound **10**

Phenolic ketone **8** (1.028 g, 3.52 mmole) was reacted with bromide **6** as above to give **10** as a pale yellow foamy solid (1.942 g, 104%). Recrystallisation from acetone-petroleum ether gave white crystals; mp 127–128°C; ¹³C NMR (Table 1); M/S (probe EI, 70 eV) m/z 542 (M⁺, 1), 405(6), 315(11), 241(6), 151(21), 137(8), 122(7), 91(100).

Compound **11**

Debenzoylation of **10** (234 mg, 0.432 mmole) with 5% Pd/C (23 mg), 1 atm H₂ (balloon method) at room temperature overnight in wet THF gave crude **11** (195 mg). Preparative thick layer chromatography gave pure **11** as a clear viscous oil (yield 51%, not optimized since this product was not critical).

Compound **12**

Reduction of **11** with LAH in refluxing THF for 1½ h using the standard procedure gave **12** in 72% yield after purification by preparative tlc.

Compound **12** was a colourless viscous oil; ¹³C NMR (Table 1); M/S (probe, EI, 70 eV) m/z 456 (M⁺, 1) 438(15), 420(3), 319(2), 314(2), 301(15), 272(17), 166(13), 163(18), 153(100), 151(18), 150(22), 149(28), 138(34), 137(42), 135(14), 133(16), 125(19), 124(40), 123(13), 122(16), 109(25), 107(13), 93(34), 77(27).

Compound **13**

Formaldehyde addition to **10** was carried out by a method analogous to that of Landucci et al. (1981), with a small modification. Thus, **10** (1.494 g, 2.75 mmole) was added to 95% ethanol (7 ml) and the mixture sonicated for 60 s to break up the particles. Powdered anhydrous potassium carbonate (95.5 mg, 0.69 mmoles) and 37% aqueous formaldehyde (900 mg, 11.10 mmoles) were added and the mixture stirred at 30–35°C for 26 h. The resulting thick gum was extracted into ethyl acetate and washed with saturated aqueous NaCl. The aqueous layer was extracted twice more with ethyl acetate and the combined fractions washed with NaCl solution, dried over MgSO₄ and the solvent evaporated to yield crude **14** (1.622 g). Flash chromatography on silica gel eluting with EtOAc followed by EtOAc/acetone yielded **13** (654 mg, 39%), and a mono-hydroxymethylated product (131 mg, 8%).

Compound **13** was a white foam; ¹³C NMR (Table 1); M/S (probe EI, 70 eV) m/z 354(1), 318(2), 288(2), 241(25), 151(36), 91(100).

Compounds **15**

95% ethanol (15 ml) was added to compound **13** (323 mg, 0.537 mmole – which did not dissolve) and 5% Pd/C (30 mg) added. The flask was flushed with hydrogen, and the mixture stirred under a balloon full of hydrogen for 46 h. The resulting mixture was filtered through celite to remove the Pd/C, which was washed with methanol. The solvent was evaporated leaving a white foamy oil (249 mg, 90%), which was only sparingly soluble in chloroform but readily soluble in acetone or methanol. ¹H NMR showed the presence of a small amount of α-keto products and all spectra were complex due to the presence of the four isomer groups. No attempt to separate the isomers was made. Spectral data; see below under separate isomers.

The pentaacetates **16** were prepared by reaction with 1:1 acetic anhydride:pyridine and worked up in the normal manner to give a colourless viscous oil (containing the four isomer groups). Spectral data; see below under separate isomers.

Compounds *threo*-14

Threo-**9a** (158 mg, 0.275 mmole) was dissolved in 95% ethanol (3 ml) and K_2CO_3 (5 mg, 0.036 mmole) and formaldehyde (9.1 mg, 0.303 mmole, in a 37% aq solution) added. The mixture was stirred for 15 hours at room temperature, then poured on water and extracted with ethyl acetate. The organic phase was washed with saturated NaCl (aq), separated, and the solvent removed under reduced pressure to give crude *threo*-**14**. This material was purified by multiple elution prep-*tlc* on silica gel using 80:20 ethyl acetate:petroleum ether as eluent. Yields of purified *threo*-**14** ranged from 50 to 65%. ^{13}C NMR (Table 1).

Compounds *erythro*-14

Erythro-**9a** (190 mg, 0.331 mmole), 95% ethanol (3 ml), K_2CO_3 (6 mg, 0.043 mmole) and formaldehyde (10.9 mg) were reacted as described above for *threo*-**14** and the product purified by *tlc* to give pure *erythro*-**14** (121.2 mg, 61%) as a pale yellow oil. Starting material, *erythro*-**9a** (58.6 mg) was also recovered so the conversion to **14** was 86%. ^{13}C NMR (Table 1).

Compounds *erythro*-*threo* 15 plus *threo*-*threo*-15

Debenzylation of *threo*-**14** in 95% ethanol by the method of Landucci et al. (1981) (or by using just 1 atm of H_2 , overnight) gave the free phenolic ketone as a white foamy solid in greater than 95% yield. This was immediately reduced using an excess of LAH (as above) to give a mixture of the *et* and *tt* isomers of **15** in a ratio of approximately 60:40. The yield of *et*-**15** + *tt*-**15** was 86%. ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z* 468 ($M^+ - H_2CO - H_2O$, 2), 420(1), 330(2), 300(9), 272(5), 211(3), 204(2), 180(9), 179(5), 178(18), 167(4), 166(4), 153(23), 151(26), 150(100), 137(22), 124(30), 121(16), 109(25), 93(16).

The penta-acetates, *et*-**16** + *tt*-**16** were prepared by acetylation in the normal manner, yield, 96%. ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z* 726 (M^+ , 2), 415(14), 355(27), 324(10), 323(57), 313(42), 285(9), 284(9), 283(11), 282(6), 281(30), 268(15), 263(14), 222(35), 221(92), 210(11), 209(84), 204(13), 203(11), 195(18), 180(12), 129(100), 178(49), 177(28), 167(12), 163(12), 162(20), 161(26), 153(74), 152(12), 151(30), 150(27), 149(32), 147(39), 137(23), 131(18), 125(13), 124(74), 123(24), 121(17), 119(20), 109(33), 93(11), 91(19), 81(11), 77(14), 43(76).

Compounds *erythro*-*erythro*-15 plus *threo*-*erythro*-15

Debenzylation of *erythro*-**14** as described above gave the ketone as a white foamy solid in about 95% yield. LAH reduction gave a mixture of *ee* and *te* isomers of **15** in a ratio of approx. 60:40 and a total yield of 84%. ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV): *m/z* 468 ($M^+ - H_2CO - H_2O$, 2), 420(1), 330(2), 300(11), 272(7), 211(4), 204(2), 180(10), 178(6), 178(22), 167(4), 166(5), 153(75), 151(27), 150(100), 137(25), 124(28), 121(17), 109(26), 93(14).

The penta-acetates, *ee*-**16** + *te*-**16** were prepared by acetylation in the normal manner, yield 96%. ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z* 726 (M^+ , 2) 415(10), 355(21), 324(10), 323(52), 313(32), 285(8), 284(10), 283(12), 282(6), 281(28), 268(14), 263(14), 222(39), 221(100), 209(58), 204(10), 195(15), 180(18), 179(98), 178(43), 177(31), 167(10), 163(12), 162(20), 161(25), 153(61), 152(12), 151(27), 150(21), 149(30), 147(40), 137(20), 131(21), 175(13), 124(67), 123(22), 121(15), 119(21), 109(39), 103(11), 95(12), 93(11), 91(12), 43(68).

The β -ether/phenylcoumaran trimer

Compound 19

The bromoketobenzoate **6b** (5.00 g, 14.3 mmole), dehydrodiisoeugenol **18** (4.80 g, 14.7 mmole) and powdered anhydrous potassium carbonate (12.16 g, 15.0 mmole) were refluxed in acetone (40 ml) for 18 h and worked up as above to give a creamy yellow foam (9.50 g). Attempts to crystallise this product were unsuccessful. Preparative *tlc* of a portion of the crude material (150 mg, ethyl acetate/pet. ether as eluant) gave **19** as a white foam (135 mg, 90% yield) which would not crystallise. ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z*: 594 (M^+ , 11), 490(11), 326(11), 325(10), 297(13), 151(32), 137(13), 105(100).

Compound 22

The ethylketobenzoate trimer **19** (1.00 g, 1.7 mmole) was dissolved in ethanol (25 ml). Powdered anhydrous potassium carbonate (0.028 g, 0.20 mmole) was added and 37% aqueous formaldehyde (0.30 g, 2.80 mmole) was slowly dropped into the solution. The reaction was left stirring at room temperature for 16 hours. The mixture was concentrated under reduced pressure and extracted twice with chloroform (100 ml). The organic extract was washed twice with water (100 ml), dried over anhydrous magnesium sulphate and the solvent removed to give a yellow oil (1.36 g). Analytical *tlc* using 60:40 ethyl acetate:pet. ether showed the presence of at least 4 components in the oil. Preparative *tlc* of a portion of this oil (94 mg) using 90:10 ethyl acetate:pet. ether gave starting material (31 mg) and the required product **22** (39 mg, 53% yield); ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV), *m/z* 606 ($M^+ - H_2O$, 1.0.), 594(8.0), 490(15.0), 326(25.0), 151(20.0), 105(100).

Guaiacylglycol- β -dehydrodiisoeugenyl ether (20)

The ethylketobenzoate **19** (1.00 g, 1.68 mmole) was reduced with LAH in the usual way. Workup yielded a light yellow oil (900 mg) containing the product **16** and benzyl alcohol. Flash column chromatography using 50:50 ethyl acetate:pet. ether separated **20** as a white foam (670 mg, 81%). ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z* 492 (M^+ , 13.9), 474(9.7), 326(100), 311(21.2), 153(14.9), 151(11.5), 137(11.3).

Guaiacylglycol- β -dehydrodiisoeugenyl ether **20** (50 mg, 0.102 mmole) was acetylated in the usual way to give the diacetate **21** as a light yellow oil (52 mg, 94% yield). ^{13}C NMR (Table 1).

Guaiacylglycerol- β -dehydrodiisoeugenyl ether (23)

The crude propylketobenzoate trimer reaction mixture (0.670 g, containing a maximum of 0.230 g, 0.44 mmole **22**) was reduced with LAH in the usual way. A yellow oil (0.675 g) was obtained. Preparative *tlc* of 124 mg of this oil using 60:40 ethyl acetate:pet. ether gave benzyl alcohol plus compound **20** (which resulted from reduction of **19** present in the starting material, 30 mg) plus the required products, *erythro*- and *threo*-guaiacylglycerol- β -dehydrodiisoeugenyl ether **23**, yield 83% (based on yield from **22** in the reactant); ^{13}C NMR (Table 1); M/S (probe, EI, 70 eV) *m/z* 522 (M^+ , 13.4), 504(1.2), 502(1.2), 474(8.0), 353(19.0), 352(100), 327(16.2), 326(71.4), 153 (29.1), 131(10.8), 125(30.4).

The guaiacylglycerol- β -dehydrodiisoeugenyl ethers **23** (40 mg, 0.077 mmole) were acetylated in the usual way to give the crude triacetates **24** as a light yellow oil (46 mg). Preparative *tlc* using 40:60 ethyl acetate:pet. ether gave a mixture of *erythro*- and *threo*-**24** in 63% yield. ^{13}C NMR (Table 1).

Additional Material Available

Proton NMR and mass spectra are available from the authors.

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