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Authors: Nicholas James Westwood, James Montgomery, Karl Kempf, Daniel Miles-Barrett, Oxana Kempf, and Tomas Lebl

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Preparation and Reactivity of Biomass-derived dihydro-Dioxins

James R. D. Montgomery,[a] Karl Kempf,[a] Daniel M. Miles-Barrett,[a] Oxana Kempf,[a] Tomas Lebl and Nicholas J. Westwood*[a]

Abstract: The depolymerisation of the biopolymer lignin can give pure aromatic monomers but selective catalytic approaches remain scarce. Here, an approach was re-routed to deliver an unusual phenolic monomer. This monomer's instability proved challenging but a degradation study identified strategies to overcome this. Heterocycles and a useful synthetic intermediate were prepared. The range of aromatics available from the β-O-4 unit in lignin was extended.

As the second most abundant natural polymer, lignin will contribute to a sustainable future.[1] Whilst lignin has a complex structure, its construction from arylpropene units[2] means it can deliver aromatics.[3] Pure aromatic monomers can be prepared from lignin[4], but alternative monomers continue to be targeted. This is because a focus on just a few compounds, such as vanillin[5], limits opportunities and creates a strong dependence on the market price of a few monomers.[6] Diverse processing of lignin remains a major challenge.

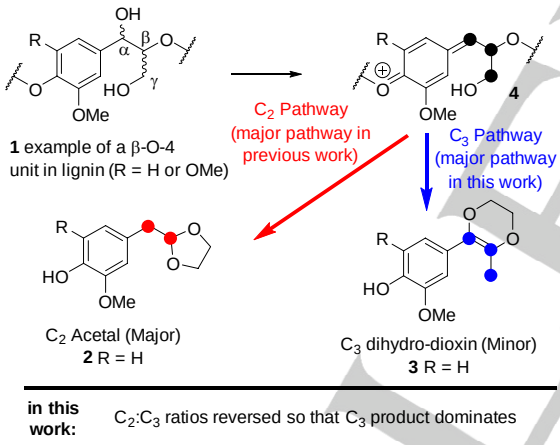
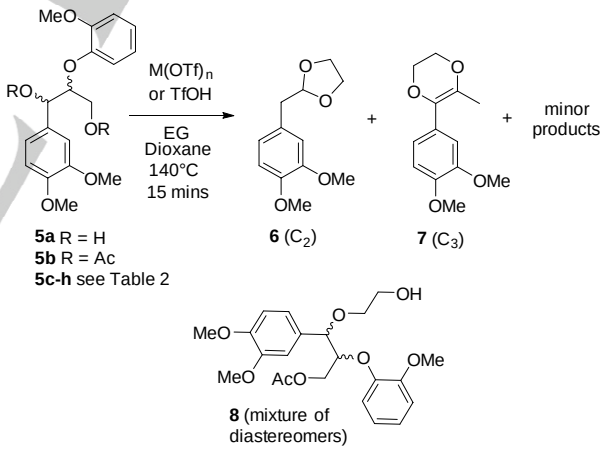


Figure 1. Processing the β-O-4 linkage in lignin to generate phenolic monomers using metal triflates/TfOH and ethylene glycol. The literature[7] reports C_2-products. Here the C_2:C_3 ratio is reversed to give C_3-products.

For lignin to function as a source of aromatics, selective depolymerisation strategies are needed. Barta *et al.* have used metal triflates or triflic acid with ethylene glycol (EG) to target the β-O-4 linkage **1** (Figure 1).[7] This approach generates C_2 products[7] including **2** with trace amounts of C_3 products (*e.g.* **3**).[7b] Recently, the reaction of a dioxasolv pinewood lignin with $Fe(OTf)_3$ and EG gave **2** in 16 wt% yield.[7b]

The C_2:C_3 ratio is determined by the fate of intermediate **4**. Deformylation of **4** gives the C_2 acetal **2** whereas a range of mechanisms can be considered for formation of the C_3 product **3** from **4** (Scheme S1). Here we describe the re-routing of this reaction to favour the C_3 pathway, delivering an additional aromatic monomer from the β-O-4 unit in lignin. Our strategy is based on acylation of the γ-alcohol (and coincidentally the α-alcohol) in the β-O-4 unit. This substrate modification blocks the C_2 pathway by stopping deformylation of **4**. Initial studies were focused on the reaction of lignin models **5**a and **5b** (Scheme 1, Tables 1 and S1). Overall the results demonstrated that an almost complete selectivity switch could be achieved both in the models and with lignin.



Scheme 1. Overview of study on lignin models **5a-5h**.

Reaction of **5a** and its acetylated derivative **5b** with EG and $Fe(OTf)_3$ at 140 °C for 15 minutes led to a significant difference in the C_3:C_2 product ratios (Table 1, entries 1 and 2). In line with the literature,[7a, 7c] **5a** was fully converted to the C_2 acetal **6** (entry 1, Figure S1) with trace amounts of C_3 dioxene **7** also formed. In contrast, **5b** was fully converted to **6** and **7** in a C_3 **7**:C_2 **6** ratio of 1:1 (entry 2). The reaction of **5a** and **5b** with alternative metal triflates was carried out. For **5b** with $Bi(OTf)_3$, $Al(OTf)_3$, $Hf(OTf)_4$ or $Cu(OTf)_2$, the same reversal of selectivity was seen as with $Fe(OTf)_3$ with **7** being the dominant product (entries 3-6). When $Cu(OTf)_2$ was used, a third product was identified (diastereomeric mixture **8**, entry 6, Figure S2).[8] In all the reactions and especially when triflic acid or $Fe(OTf)_3$ were used (entries 7 and 2), the C_2

[a] J. R. D. Montgomery, Dr K. Kempf, D. M. Miles-Barrett, O. Kempf, Dr T. Lebl, Prof. N. J. Westwood
School of Chemistry and Biomedical Sciences Research Complex
University of St Andrews and EaStCHEM
St Andrews, Fife, KY16 9ST, UK
E-mail: njw3@st-andrews.ac.uk

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acetal **6** was still formed from **5b**. One possible explanation was that hydrolysis or transesterification with EG of the γ-ester in **5b** had occurred re-opening the C_2 pathway. When the reaction of **5b** with TfOH was repeated at a two-fold dilution (*c.f.* entries 7 and 8), full conversion of **5b** was still observed but the C_3 **7**:C_2 **6** ratio increased to 1.7 (Figure S3), potentially consistent with a decreased conversion of **5b** to **5a**.

Table 1. Metal triflate screen: ratio of products **6**-**8** (Scheme 1), determined by ^{1}H NMR expressed in form that gives a total of 100 molecules.

Entry	Substrate	Catalyst	Products **6**-**8** (rel. amounts) [c]	C_3:C_2 for **5b** (for **5a**)
1	**5a**	$Fe(OTf)_3$	**6** (96), **7** (4)	(<0.1) [a]
2	**5b**	$Fe(OTf)_3$	**6** (50); **7** (50)	1 [b] (<0.1)
3	**5b**	$Bi(OTf)_3$	**6** (28); **7** (72)	2.6 (< 0.1)
4	**5b**	$Al(OTf)_3$	**6** (42); **7** (58))	1.4 (< 0.1)
5	**5b**	$Hf(OTf)_4$	**6** (33); **7** (67)	2.0 (<0.1)
6	**5b**	$Cu(OTf)_2$	**6** (18), **7** (72), **8** (10)	4.0 (<0.1)
7	**5b**	TfOH	**6** (59); **7** (41)	0.7 (<0.1)
8	**5b**	TfOH [d]	**6** (37); **7** (63)	1.7

[a] reaction conditions based on ref.[7a] $Fe(OTf)_3$ (3 mol%), EG (2.7 eq), 140°C, 1,4-dioxane, 15 mins.; [b] repeated and products isolated to give a C_3 **7**:C_2 **6** ratio of 1.4; [c] In all cases in Tables 1 and 2, only trace quantites of degradation products of **7** were observed (Figure S4); [d] Reaction diluted. C_2:C_3 NMR yield increased to 64% *c.f.* original concentration (entry 7, 28%).

It was decided to vary the structure of the γ-ester in **5b**. Increasing the size of the ester substituent from Me (**5b**, Table 2 entry 1 and Table S2) to Et in **5c** and *iso*-propyl in **5d** led to C_3 **7**:C_2 **6** ratios of 2.9 and 6.3 respectively (entries 2 and 3 and Figure S4). Although the C_3:C_2 ratio had increased, trace amounts of **6** were observed even when **5e** was used (entry 4). Next, benzoylated derivatives **5f-h** were prepared and, under analogous conditions, gave exclusively the C_3 product **7** with full conversion (entries 5-7). These conditions achieved both the desired switch in reaction outcome and yields that were in line with literature reports.[7c] Studies continued with a benzoylated lignin.

A softwood Douglas fir lignin (DFL) was prepared[9] and converted to benzoylated lignin (Bz-DFL) using *N*-methyl-imidazole and benzoic anhydride. 2D HSQC NMR analysis was consistent with full conversion of all the β-O-4 units (Figures S5-S8). Reaction of Bz-DFL with TfOH and EG using an extended reaction time of 1 hour proved successful with C_3 product **3** (Figure 1) being isolated after chromatographic purification (Table S3 and Figure S9). It also proved possible to recover significant quanties of benzoic acid from this reaction when it was run on a larger scale (Figure S10). Analysis of the remaining lignin indicated that full conversion of the benzoylated β-O-4 units had occured (Figure S10C). Interestingly, a small quantity of the C_2 product **2** was also generated from this Bz-DFL. One possible explanation may be an inability to detect incomplete benzoylation of the β-O-4 γ-alcohols in lignin using 2D HSQC analysis. Whilst this approach enabled the isolation of the C_3-product **3** from lignin for the first time, concerns about product stability were raised.

Table 2. TfOH-catalysed reaction of β-O-4 derivatives. Yields and ratios of C_2 **6** and C_3 **7** determined by ^{1}H NMR. Reactions run in triplicate (Table S2).

Entry	lignin model	R	Average NMR Yield of **6**, **7**	C3:C2 ratio (yield)
1	**5b**	MeCO	24 ± 0.36, 40 ± 2.9	1.7 (64)
2	**5c**	EtCO	14 ± 0.32, 40 ± 2.7	2.9 (54)
3	**5d**	*iso*-propylCO	7 ± 0.36, 44 ± 2.0	6.3 (51)
4	**5e**	*tert*-butylCO	1 ± 0.04, 47 ± 0.7	47 (48)
5	**5f**	PhCO	0, 41 ± 3.7	only C3 (41)
6	**5g**	*p*-F-PhCO	0, 45 ± 1.9	only C3 (45)
7	**5h**	*p*-MeO-PhCO	0, 49 ± 4.8	only C3 (49)

A detailed study of the stability of **3** was carried out (Scheme S2). Previous literature reports on related but not identical compounds[10] suggested that formation of either diester **9** or diketone **10** was likely. **3** was found to degrade on storage in $CDCl_3$ (in air) to a mixture of compounds including the predicted **9** and **10** (*c.f.* Figures 2Ai-2Aiii). The reaction of **3** with *m*CPBA was interesting and the outcome variable. For example, an authentic sample of **9** was prepared for comparison by reaction of **3** with two equivalents of *m*CPBA via a Grob-fragmentation (Figures 2Aiv and 2B).[11] When **3** was reacted with one equivalent of *m*CPBA, an authentic sample of diketone **10** was obtained.

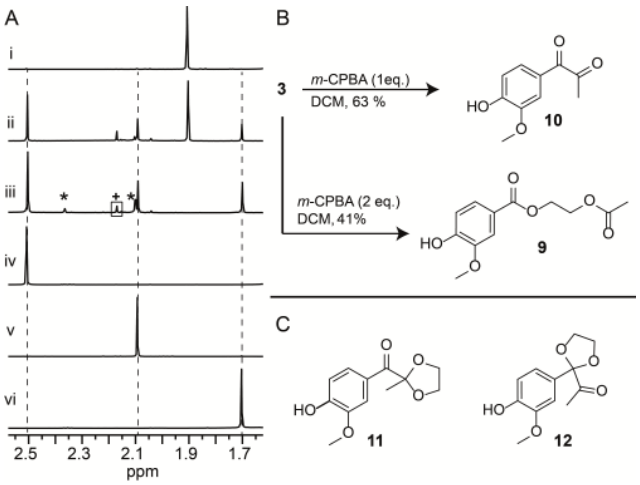
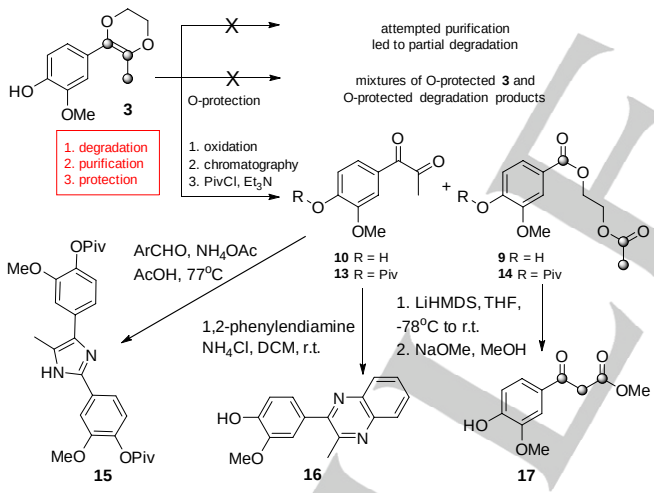


Figure 2. A. Selected region of the ^{1}H NMR analysis of: (i) purified **3**; **3** stored in $CDCl_3$ for (ii) 7 and (iii) 29 days; (iv) **10**; (v) **9**; (vi) **11**; B. Reaction conditions used for selective conversion of **3** to **9** or **10**; C. Structures of novel compounds **11** and **12**. * signals corresponding to additional unidentified degradation products. + signal assigned to methyl group adjacent to carbonyl in **12**.

Addition of one equivalent of water and a catalytic amount of TfOH in addition to the *m*CPBA lead to the formation of **10** as the exclusive product (Figures 2Av and 2B, Figure S10). More detailed inspection of the degradation of **3** in $CDCl_3$, showed the presence of two additional products which contained a methyl signal at either 1.70 or 2.17 ppm respectively (Figures 2Aii-iii). The structures of these novel compounds **11** and **12** were assigned as isomeric mono-acetals of diketone **10** (Figures 2Avi, 2B and Figure S11). One possible mechanism for formation of **11** and **12** from **3** involves acid-catalysed opening of an initially formed epoxide followed by subsequent ether-oxygen migration.[12]

With a more detailed understanding of the degradation of **3** in hand, a reanalysis of the reactions reported in Tables 1 and 2 was carried out. It was confirmed that no significant degradation of **7** had occurred under the 15 minute TfOH reaction conditions (*e.g.* Figure S12). However, the reactions of the lignin models **5b-h** did not involve extended heating times or purification of **7** by column chromatography, as was required to generate **3** from lignin (Bz-DFL). Given (i) the relative instability of **3**, (ii) the observation of degradation products of **3** in the mixture of lignin-derived monomers (Figure S14) and (iii) the number of reactive groups (*e.g.* alcohols) present in lignin that **3** or degradation products of **3** could react with, it seems reasonable to assume that degradation of **3** has an impact on the observed yields from lignin. Rather than fight against instability of **3**, it was decided to embrace its reactivity as a means of preparing more stable products.[7a-c]



Scheme 2. Summary of studies carried out on **3** culminating in preferred approach to processing of **3** en route to exemplar heterocycles and the synthetically useful β-ketoester **17**. The three carbon units present in the tail of **3** and **9**/**10** are highlighted to show how they are separated and then rejoined via the intramolecular Claisen reaction. **15** prepared from **13** and **16** from **10**. Use of protection step to give **13** and **14** was optional.

It was decided to force the conversion of **3** under oxidative conditions (using *m*CPBA), purify the degradation products **9** and **10** and then, in an optional step, protect the phenolic oxygen with a pivaloyl protecting group. This process proved reproducible and delivered pure samples of diketones **10** and **13** as well as diesters **9** and **14** (Scheme 2). It is clear that both the diketones **10** and **13** and the diesters **9** and **14** are potentially very useful building blocks. For example, conversion of diketone **13** to the corresponding imidazole **15** was readily achieved. Imidazole **15** was prepared using two biomass-derived aromatic monomers and related imidazoles are known to possess interesting biological activity.[13] In parallel, diketone **10** was converted to pyrazine **16**. The degradation of **3** to the corresponding diester **9** is, in some ways, disappointing as the hard-earned C_3 tail in **3** would lose two of the three carbons if hydrolysis or reduction of the esters was carried out. In an attempt to retain the two carbon atoms, it was decided to submit **14** to an intramolecular Claisen-type ester condensation reaction. Gratifyingly, this resulted in the formation of β-ketoester **17** after transesterification using NaOMe. To the best of our knowledge this is the first time that a synthetically useful structure of this type has been prepared from lignin.

In conclusion, we have described the controlled depolymerisation of the β-O-4 unit in the biopolymer lignin to deliver a phenolic dioxene monomer **3**. This was achieved *via* a strategic re-routing of a metal triflate/TfOH-catalysed depolymerisation protocol through an accessible modification (benzolyation) of the substrate. Interestingly, a number of natural lignins contain significant amounts of γ-acylation/acetylation (*e.g.* grasses) so the C_3-pathway described here could well be relevant if these are used as the source of lignin. Despite the fact that a significant amount of benzoic anhydride was used to protect the α- and γ-alcohols of the β-O-4 linkage in lignin, benzoic acid was easily recovered at the end of the depolymerisation reaction. This could in theory be recycled back into benzoic anhydride and used in the next round of a process (see Figure S10 for more details). A detailed study of the stability of **3** guided alternative strategies for generating useful heterocycles and synthetic intermediates from lignin. Continued efforts to deliver a wider range of aromatics from lignin may well prove important as the biorefinery concept continues to develop.

Experimental Section

Triflic acid cleavage of protected G-G β-O-4 models **5b**-**h**.Reactions were performed in triplicate. Stock solutions of **5b-h** in 1,4-dioxane (33.3 mg mL^{-1}) and triflic acid in 1,4-dioxane (1.73 mg mL^{-1}) were prepared. Reaction solutions were prepared by mixing the two stock solutions (1.5 mL of each) and ethylene glycol (25 mg) in a sealed tube. The reaction mixture was then heated to 140 °C for 15 mins in a preheated oil bath and allowed to cool to room temperature in a water bath. The solution was diluted with ethyl acetate (20 mL) and washed with water (20 mL) and brine (20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Once dry and as quickly as possible, the crude product mixture was dissolved in $CDCl_3$ (0.7 mL) and analysed by quantitative ^1H NMR methods.

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Keywords: dihydro-dioxin • hetereocycles • renewable monomers • depolymerisation • lignin

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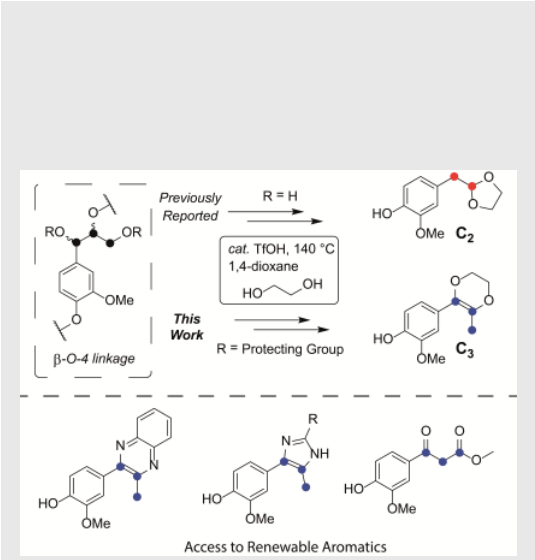

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Page No. – Page No.

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