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Synthesis of various lignans via the rearrangements of 1,4-diarylbutane-1,4-diols

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ABSTRACT

Selectively functionalised 1,4-diarylbutane-1,4-diols have been shown to undergo a number of different reactions upon treatment with methanesulfonyl chloride and triethylamine. These led to three different sub-classes of lignans, depending on the nature of the aryl groups. Rearrangement leading to the corresponding 4,4-diarylbutanals is the most common transformation and these butanals can be reduced to give analogues of *seco*-lignans.

Lignans are a large class of plant natural products formed by the oxidative dimerisation of two phenylpropanoid units (C_6–C_3) and are known to have a range of biological activities which include plant defence mechanisms, as well as antioxidant, antimicrobial and cytotoxic or anticancer activities.[1–3]

Lignans can be subdivided into a range of classes which are characterised by the dimer linkages between the phenylpropanoid units. Classical lignans (such as cyclogalgravin (**1**) and veraguensin (**2**)) are formed through 8–8′ linkages, neolignans (such as eusiderin A (**3**)) are formed through linkages other than 8–8′ linkages, and *seco*-lignans (such as *Schisandra* lignan (**4**) and kadangustin J (**5**)) are dimers in which one of the monomers has been reorganised (Fig. 1).[2,4–6]

Previous work by our group had shown that THF, aryltetralin and 4,4-diarylbutanol subclasses of lignans were all available from similar 1,4-diarylbutane-1,4-diols,[2] however the products obtained were dependent on the aromatic substitution patterns and alcohol protecting groups chosen. It was found that *para*-electron donating groups (e.g., 4-methoxy) promoted aryl migration to form 4,4-diarylbutanals, *meta*-electron donating groups promoted cyclisation to form aryl tetralins, whilst the presence of a MOM group on the alcohol at C-1 resulted in cyclisation to give THF lignans (Scheme 1).[2]

Based upon these initial findings, it was decided to further investigate the uncommon[2] 1,4-diaryl rearrangement in order to prepare 4,4-diarylbutanal products containing other aromatic substitution patterns. Previous work had shown this rearrangement occurred only in the case where both aromatic rings were *para*-methoxybenzene rings.

The proposed mechanism for this unusual 1,4- to 4,4-aryl migration is via a 5-membered cyclic intermediate which undergoes subsequent TBS elimination and ring opening to give the 4,4-diarylbutanal (Fig. 2). It was proposed that the aromatic ring at C-4 does not participate in the rearrangement and therefore was the first site examined for modifications to the rearrangement substrate.

Common aldehyde **6** was prepared in two steps, dihydroxylation followed by periodate cleavage, from alkene **7** which was prepared following literature procedures.[2,7] A range of aryl organometallic reagents were then added to aldehyde **6**, giving alcohols **8a–f** in moderate to good yields as single diastereoisomers, as predicted by the Felkin–Anh model (Scheme 2).[7,8]

As expected, upon treatment with triethylamine and methanesulfonyl chloride at 0 °C, butanols **8a–f** gave rise to 4,4-diarylbutanals **9a–f**. The aryl migration was found to be stereoselective with ^{1}H and ^{13}C NMR showing that for all aldehydes except **9d** (see below) a single diastereomer had formed. Whilst alcohol **8a** with bis-*para*-methoxyphenyl rings gave only aldehyde **9a**, in the cases of butanols **8b–f**, other products were also obtained. These were determined to be aryl tetralins **10b–d,f** for butanols **8b–d,f** and a 2,5-diaryl THF **10e** from butanol **8e**. The aryl tetralins **10b–d,f** were also obtained as single diastereoisomers and by comparison to literature compounds,[2,10,11] coupling constants between

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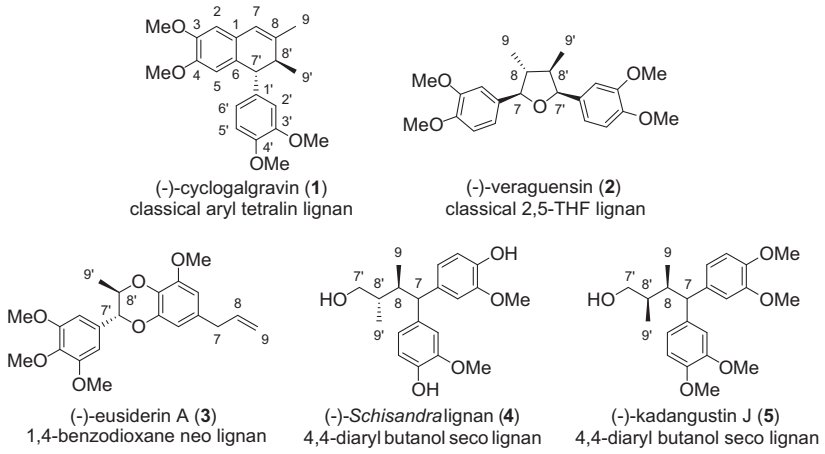
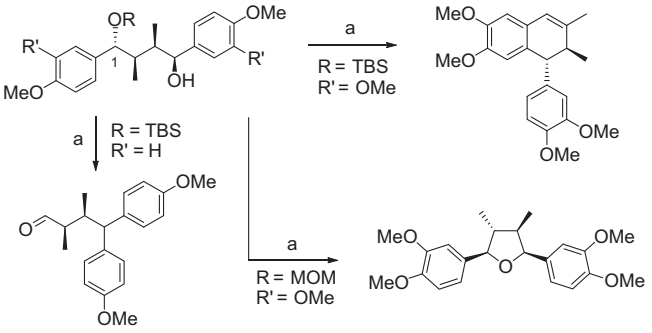


Figure 1. Representative examples of the four structural classes of lignans.



Scheme 1. Compounds prepared from 1,4-diarylbutane-1,4-diols. Reagents and conditions: (a) Et_3N, MsCl, DCM, 0 °C.

protons H-7′ and H-8′ determined a *trans*-relationship between these substituents.

The stereochemistry at the C-4 position of 4,4-diarylbutanals **9** was determined through cyclisation of butanal **9c**, using catalytic *p*-TsOH in toluene, which gave aryl tetralin **11** as a single isomer in 50% yield. Tetralin **11** had a coupling constant of 6.5 Hz between H-7′ and H-8′, suggesting a *cis*-relationship between the substituents at these positions, opposite to the tetralins formed from the rearrangement reaction (Scheme 3).

Based on this information a mechanism was proposed for the stereoselective formation of both the 4,4-diarylbutanals **9** and aryl tetralins **10**. It was proposed that the first step of the rearrangement is formation of a quinone-methide **12** which occurs via methane sulfonylation of the 8′-OH followed by elimination of methanesulfonate due to the electron donating properties of the adjacent aromatic ring (Fig. 2). The next step involves *ipso*-attack of C-1, via donation from the C-4 methoxy group, onto C-7′ giving two diastereomeric 5-membered intermediates **13a** and **13b**.

From here it is suggested that the *cis–trans–trans* intermediate **13a** would give rise to 4,4-diarylbutanal **9c** through elimination of TBSCl whereas the *cis–trans–cis* intermediate **13b** would give rise to aryl tetralin **10c**. The formation of the aryl tetralins is proposed to occur due to the pseudo-axial position of the C-1′–C-6′ aromatic ring, allowing attack of C-6′, due to donation from the oxygen at C-3′, at C-7 resulting in formation of the tetralin structure and re-aromatisation of the *para*-methoxyphenyl ring. A possible alternative pathway could proceed via breaking of the C-1–C-7 bond, resulting in a charged intermediate, followed by cyclisation from C-6′ onto C-7 to give the aryl tetralin. However, this non-cyclic alternative pathway would not account for the

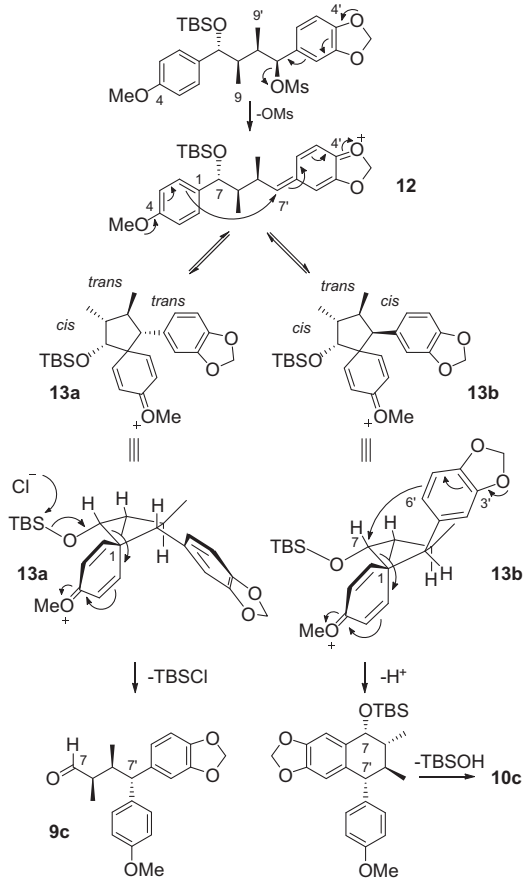


Figure 2. Proposed reaction mechanism for the 1,4-diaryl rearrangement.

stereospecific production of both aldehyde **9c** and tetralin **10c** and in particular would give rise to the diastereomers of aldehyde **9c**, which was not observed. Subsequent elimination of TBSOH gives the final aryl tetralin **10c**.

Interestingly, the tetralin product **10d** from the reaction of butanol **8d** which contained a trimethoxybenzene ring did not match the expected product (Fig. 3). The predicted product would have a proton at C-2 and a methoxy at C-5, and the isolated product **10d** had the reverse arrangement. Furthermore, analysis of the ^1H NMR spectrum of aldehyde **9d** showed that diastereomers had formed at C-4, which was not observed for any of the other aldehydes tested.