



Synthesis and structural analysis of sterically hindered chiral 1,4-diol ligands derived from the lignan hydroxymatairesinol

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ABSTRACT

The readily available natural lignan hydroxymatairesinol was transformed into sterically hindered and optically pure diphenyl, di-2-naphthyl, and tetramethyl 1,4-diol derivatives via arylation/alkylation of the aryltetralinbutyrolactone lignan (–)-conidendrin. In addition, the diastereoselective formation of stable hemiketals from the highly substituted butyrolactone was studied in detail. The conformations of the molecules prepared were studied computationally at molecular mechanics (MM), Hartree–Fock (HF)/6-31G*, and (DFT/B3LYP/TZVP) levels including entropy contributions and by NMR-spectroscopy. The conformations adopted showed that these novel chiral 1,4-diols may be suitable as chiral ligands for the development of new chiral transition metal and organo catalysts.

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Chiral 1,4-diols have been shown to be useful starting materials for the preparation of chiral catalysts, chiral reagents, resolving agents, etc.¹ The numerous reports of TADDOLs or BINOLs in the literature show the versatility of this type of chiral diol. Traditionally, TADDOLs or BINOLs have been used as ligands for transition metal based asymmetric catalysts, but more recently and in particular phosphoric acid derivatives have shown excellent results as chiral Brønsted acids in the field of organocatalysis.² We herein report the synthesis and conformational study of chiral 1,4-diols derived from the lignan (–)-conidendrin, obtained from 7-hydroxymatairesinol.

(–)-Conidendrin is a natural product of the lignan family. In the early reports of Erdtman et al.³ it was referred to as ‘sulfitlaugen lacton’. Later it was shown that (–)-conidendrin could be easily obtained in quantitative yields from the lignan hydroxymatairesinol.⁴ Large-scale methods for the isolation of hydroxymatairesinol from spruce knotwood have been developed.⁵ Today, a mixture of hydroxymatairesinol diastereomers can be produced on a kilogram scale, which after treatment with acid and recrystallization gives access to optically pure (–)-conidendrin in quantitative yield.⁴

The enantiomerically pure butyrolactone ring of (–)-conidendrin prompted us to perform alkylation (arylation), oxidation, and a second alkylation (arylation) in order to obtain sterically hindered 1,4-diol structures resembling those of TADDOLs (Fig. 1). We wanted to evaluate both the synthetic pathways and the possibility

to utilize the backbone of conidendrin as a chiral ligand. The choice of substituents for the target diols was based on simple TADDOL derivatives (phenyl, naphthyl, and methyl). The target diols were considered as suitable lead compounds for further investigation of their structural properties by NMR spectroscopy and by computational molecular modeling, as well as for evaluation of their properties as chiral ligands in asymmetric catalysis (proof of principle).

The compounds presented, are semisystematically named according to the trivial names of the parental-lignan structure. The structures are based on the aryltetralin 2',7'-cyclo lignan skeleton (Fig. 1), where the lactone structures are derived from dimethylconidendrin **1** and dimethylretrodendrin **6** (R = H), and the diol structures are derived from dimethylcycloariciresinol **5** (R = H) (Scheme 2). The derivatization of the fundamental parental structures, that is, introduction of R-groups at carbons 9 and 9' is

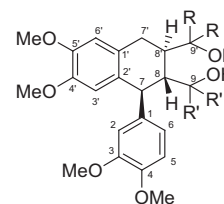
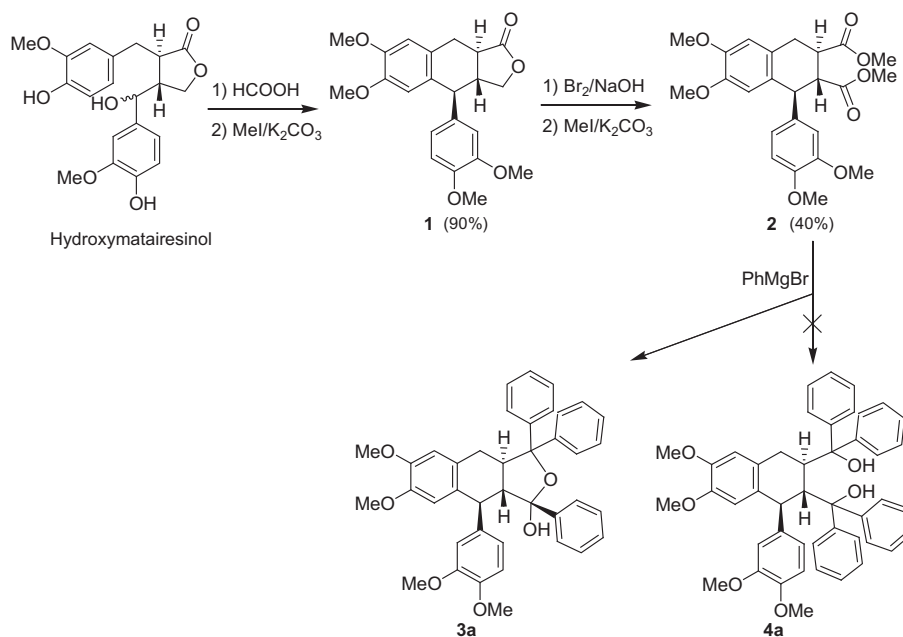


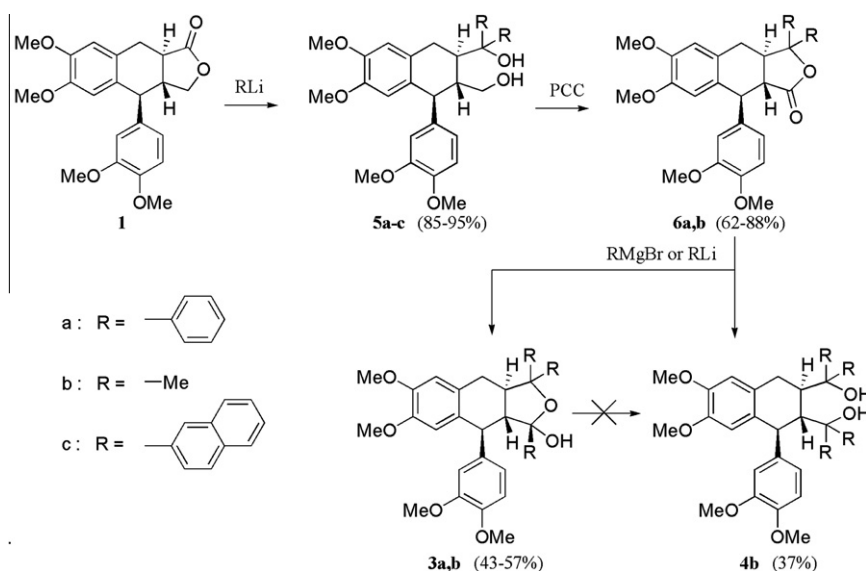
Figure 1. General structure and numbering of the sterically hindered 1,4-diol structures, represented by the 9 and 9' substituted aryltetralin 2',7'-cyclo lignan dimethylcycloariciresinol.

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Scheme 1. The diester synthetic route applied on dimethylconidendrin (**13**).



Scheme 2. Stepwise synthesis of the diols.

indicated in the prefix. The carbons are numbered as depicted in Figure 1.

In the literature, only a few methods for the synthesis of TAD-DOL-like structures are described. Usually, the synthesis is based upon the one-pot addition of four alkyl or aryl groups with an appropriate Grignard reagent to the diester of a 1,4-dicarboxylic acid. To evaluate this methodology on the conidendrin structure, we prepared the diester **2** (see the Supplementary data).

However, the Grignard reaction of the diester with excess of phenylmagnesium bromide gave only the undesired hemiketal **3a** (Scheme 1). This problem has not been previously reported for TADDOLs or similar structures, although the reported yield of the target diol in most cases seldom exceeded 50%.⁶

In other attempts to obtain the target structures, stepwise Grignard reactions and oxidations (Scheme 2) were performed. In this study the arylation and alkylation with organolithium reagents

worked better than the corresponding Grignard reagents. In the reactions of **1** with Grignard reagent, the yields of **5a-c** were usually around 65%, and with alkyl- or aryllithium yields of 85% or higher were obtained.

The oxidation of the primary alcohols **5a-c** with pyridinium chlorochromate (PCC) proceeded smoothly as a stepwise process. In reactions performed with 1 equiv of PCC the hemiacetal was the major product and could be isolated in 60% yield. This hemiacetal was shown to be very stable and the corresponding aldehyde could not be detected in aqueous solutions of the hemiacetal. When an excess of PCC was used the oxidation gave excellent yields (~90%) of the lactone **6a** or **6b**.

Phenylation of 9',9'-diphenyl-dimethylretrodendrin (**6a**) with either phenylmagnesium bromide or with phenyllithium gave only the hemiketal **3a** as the major product and the other diastereomer as a minor product (less than 15%).

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