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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.

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-cyclolignan skeleton (Fig. 1), where the lactone structures are derived from dimethylconidendrin **1** and dimethylretrodendrin **6** (R = H), and the diol structures are derived from dimethylcyclolariciresinol **5** (R = H) (Scheme 2). The derivatization of the fundamental parental structures, that is, introduction of R-groups at carbons 9 and 9′ is

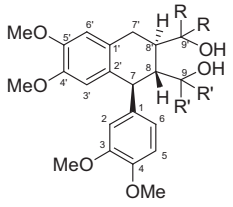

Figure 1. General structure and numbering of the sterically hindered 1,4-diol structures, represented by the 9 and 9′ substituted aryltetralin 2′,7-cyclolignan dimethylcyclolariciresinol.

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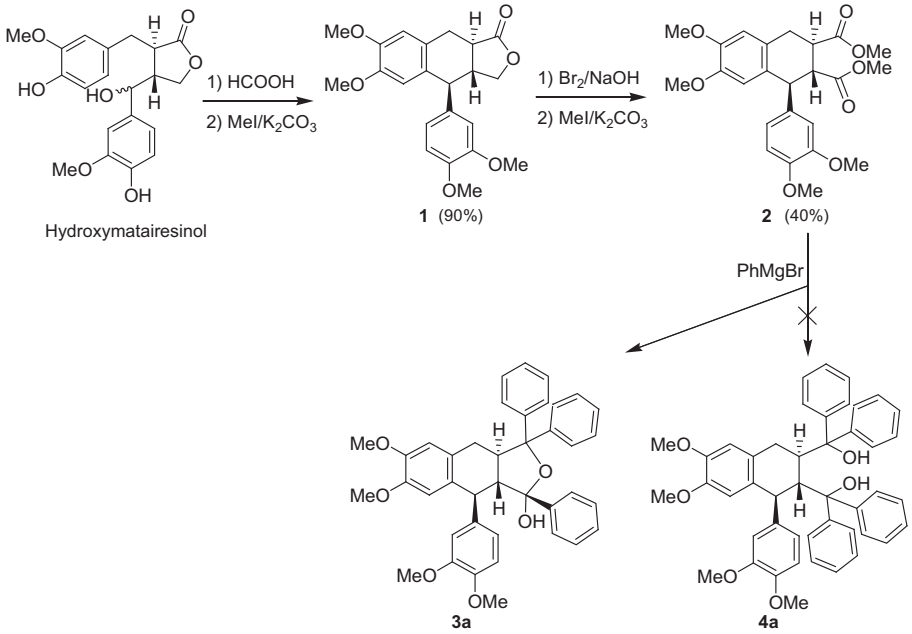
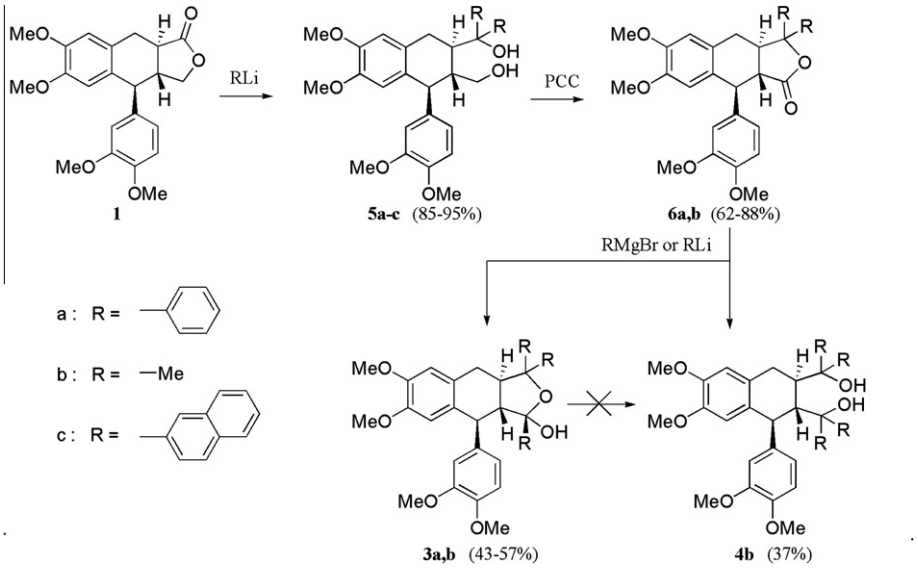


Scheme 1. The diester synthetic route applied on dimethylconidendrin (**13**).



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 TADDOL-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%).

The stereochemical configurations of the hemiketals were determined by NMR and assigned as 8*R*,8′*R*,7*S*,9*R* for **3a** and 8*R*,8′*R*,7*S*,9*S* for **3b**. No signals from the corresponding ketone or the tetrasubstituted diol were found in the NMR spectra. To explain this phenomena phenylation of 9′,9′-dimethyl-dimethylretrodendrin (**6b**) and methylation of 9′,9′-diphenyl-dimethylretrodendrin (**6a**) were performed. Both reactions led to the formation of hemiketal and no 1,4-diol was formed. Only the methylation of 9′,9′-dimethyl-dimethylretrodendrin (**6b**) gave a mixture of the target 9,9,9′,9′-tetramethyl-dimethylcyclolariciresinol (**4b**) and the trimethyl-hemiketal (**3b**). The mixture formed had a constant ratio of **3b** and **4b** (1:1.3), and only one diastereomer of the hemiketal was formed. According to these results, we assume that in this reaction the 9′,9′-disubstituted lactone structure (**6a**, **6b**) forms one diastereomer of the hemiketal, which is extremely stable and there is no equilibrium between this hemiketal and the ketone. The other hemiketal seemed to react further to give the diol product **4b**.

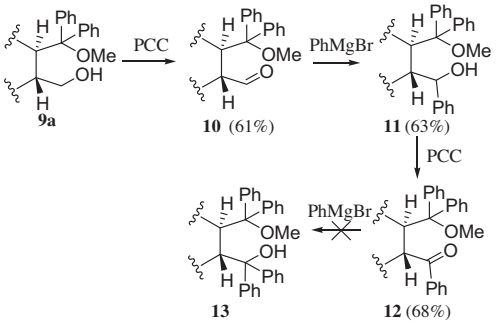
To study the possibility to further convert the intermediate hemiketals (**3a**, **3b**) into the diols, the hemiketals were isolated and treated under different nucleophilic and reductive conditions. However, in most cases, only the starting material was isolated and no desired reactivity was observed (see Supplementary data).

Computational analysis of the hemiketal **3** (see Supplementary data) supports the suggestion that the thermodynamically favored isomer should be 9*S*-isomer of **3b** (the Gibbs energy of the stable hemiketal isomer of **3b** was lower by 24–28 kJ/mol compared to the other diastereomer). Also information on the atomic charges showed that the reactivity of **3b** should be lower. However, a complete explanation for the lack of equilibrium with the corresponding ketone as well as the extremely poor reactivity would require additional studies.

To overcome the problem with the extreme stability of the hemiketals, we investigated a strategy in which no ring could be formed during the oxidation, that is, protection of the tertiary OH-group (PG^2, Scheme 3). We therefore set out to selectively protect the primary alcohol (PG^1) followed by the protection of the tertiary alcohol and then deprotection of PG^1 (Scheme 3). A number of different protecting groups and conditions were tested (see Supplementary data). Different PG^1 groups were successfully introduced but only a methyl group could be introduced as PG^2 (Scheme 3).

Since 9′*O*-methyl-9′,9′-diphenyl-dimethyl-cyclolariciresinol (**9a**) was obtained, the free hydroxymethyl group was oxidized to the aldehyde **10**, phenylated, and oxidized again to give the ketone **12** (Scheme 4). However, it turned out that this ketone did not react with phenylmagnesium bromide or with phenyllithium. This suggested that the desired tetraphenyl structure **13** was too sterically hindered to be prepared by the routes described.

The conformation of **4b** was studied computationally at molecular mechanics (MM), Hartree–Fock (HF)/6-31G*, and (DFT/B3LYP/TZVP) levels including entropy contributions. The computational results showed good correlation with the conformational studies by NMR spectroscopy.[7] For example, J_{H7-H8} was almost 0 Hz for



Scheme 4. Attempt to prepare a tetraphenyl substituted diol from the methyl protected compound **9a**.

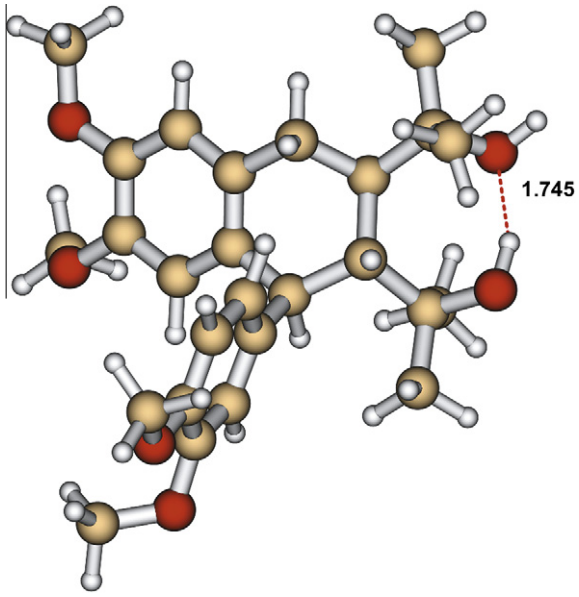
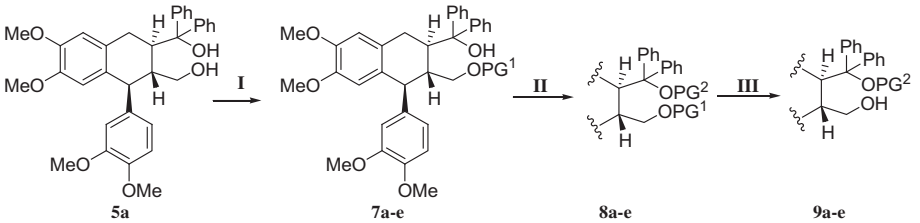
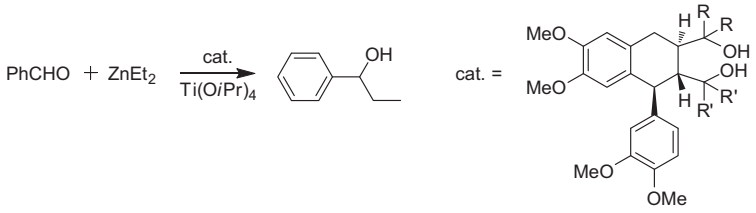


Figure 2. Energetically favored conformer of 9,9,9′,9′-tetramethyl-dimethyl-cyclolariciresinol (**4b**). The distance is given in Ångströms.

diol **4b** which corresponded to the calculated structures: in the four minimum energy conformers the torsion angle H7–C7–C8–H8 was close to 80°, which was in agreement with the small coupling constant. The most energetically favored conformers showed an H8–C8–C8′–H8′ torsion angle of around 115° and a coupling constant of $J_{H8-H8'}$ = 3.5 Hz in the NMR spectrum. The torsion angles H8′–C8′–C7′–H7′ were 39° and 154° and correlated with $J_{H8'-H7'}$ = 7 and 12 Hz. Both computational and NMR studies (see Supplementary data) showed that the most stable conformers adopted a half-boat conformation of the six-membered ring,[8] which was the major contribution to the overall conformation. In this conformation the hydroxy-containing arms are in a *trans*-equatorial



Scheme 3. Attempts to protect the more hindered OH group (O9′) (Experimental conditions in Table 2 in Supplementary data).



Scheme 5. Diethylzinc addition to benzaldehyde (test reaction).

conformation which is crucial for the formation of metal complexes and catalytic activity (Fig. 2).

To evaluate these novel 1,4-diol structures the well-known TADDOL-catalyzed diethylzinc addition to benzaldehyde[9] was employed as a preliminary model reaction.

However, diol **4b** showed reverse selectivity in comparison to the corresponding (−)-*R,R*-TADDOL (Scheme 5). The major isomer in the reaction catalyzed by our diols was shown to be *R* in contrast to the *S*-isomer formed in the (−)-TADDOL-catalyzed reaction.[9]

Despite the fact that the selectivity was only moderate, for example: ~20% ee with **4b** as the catalyst, the observed phenomena are of considerable interest.

The unsymmetrical structure of **4b** is, however, not directly comparable with TADDOLs and it can be assumed that the aromatic substituent at position seven has a major influence on the catalyst structure and hence on the induction of enantioselectivity. However, these results could be a good starting point for further investigation of lignan-based chiral ligands.

In conclusion, the TADDOL-like chiral 1,4-diols (**5a–c** and **4b**) were synthesized from the natural lignan hydroxymatairesinol. Furthermore, the addition reaction to the highly substituted lactones **6a** and **6b** was studied in detail. This showed that substituted butyrolactones form stable hemiketals, which has not been previously discussed in the literature. The steric hindrance and the formation of a stable hemiketal structure prevented the synthesis of the tetra-substituted 1,4-diol derivatives, unless a methyl was used as the alkyl group. The structures and the conformation of the diols were studied both by NMR spectroscopy and computational methods. The structural properties of these diols were mostly determined by the conformation of the six-membered non-aromatic ring and the 3,4-dimethoxyphenyl substituent at position seven.

The 1,4-diol **4b** was proven to work as a chiral ligand and therefore the study of these diols as well as the synthesis of other lignan-based diols, phosphines, and phosphoric acids is ongoing in our laboratory.

Acknowledgements

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Supplementary data

Supplementary data (full experimental and spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.066.

References and notes

1. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
2. Terada, M. *Synthesis* **2010**, *12*, 1929–1982.
3. Erdtman, H. *Liebigs Ann.* **1934**, *513*, 229–239.
4. Freudenberg, K.; Knof, L. *Chem. Ber.* **1957**, *90*, 2857–2869.
5. Holmbom, B.; Eckerman, Ch.; Eklund, P.; Hemming, J.; Nisula, L.; Reunanen, M.; Sjöholm, R.; Sundberg, A.; Willför, S. *Phytochem. Rev.* **2003**, *2*, 331–340.
6. Ito, Y. N.; Ariza, X.; Beck, A. K.; Boháč, A.; Ganter, C.; Gawley, R. E.; Kühnle, F. N. M.; Tuleja, J.; Wang, Y. M.; Seebach, D. *Helv. Chim. Acta* **1994**, *77*, 2071–2109.
7. Analytical data for compound **4b**: ^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 0.50 (s, 3H, 9Me), 0.65 (s, 3H, 9Me), 1.26 (s, 3H, 9Me), 1.58 (s, 3H, 9Me), 2.29 (ddd, *J* = 12.1, 6.8, 3.0 Hz, 1H, H8), 2.38 (dd, *J* = 14.0, 12.1 Hz, 1H, H7), 2.60 (dd, *J* = 14.0, 6.8 Hz, 1H, H7), 2.64 (d, *J* = 3.0 Hz, 1H, H8), 3.78 (s, 3H, 3OMe), 3.81 (s, 3H, 3OMe), 3.83 (s, 3H, 4OMe), 3.92 (s, 3H, 4OMe), 4.06 (s, 1H, H7), 6.40 (dd, *J* = 8.3, 1.9 Hz, 1H, H6), 6.56 (d, *J* = 1.9 Hz, 1H, H2), 6.59 (s, 1H, H6), 6.71 (d, *J* = 8.3 Hz, 1H, H5), 6.75 (s, 1H, H3). ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm 23.86 (9Me), 25.7 (9Me), 30.72 (C7), 30.78 (9Me), 31.62 (9Me), 44.96 (C8), 46.87 (C7), 52.69 (C8), 55.86 (OMe), 55.91 (OMe), 55.94 (OMe), 55.94 (OMe), 72.83 (C9), 73.8 (C9), 110.94 (C5), 111.02 (C3), 111.62 (C2), 112.38 (C6), 120.07 (C6), 130.32 (C1), 131 (C2), 136.84 (C1), 147.15 (C4), 147.69 (C5), 147.78 (C4), 148.9 (C3). HRMS (ESI): calcd for $C_{26}H_{36}NaO_6$ $[M+Na]^+$ 467.2410; found 467.2430. $[\alpha]_D^{20}$ +67° (*c* = 1, $CHCl_3$).
Values for the H–H coupling constants for **4b** were calculated from the ^{1}H NMR spectral data using the PERCH software.
8. Sandberg, T.; Brusentsev, Y.; Eklund, P.; Hotokka, M. *Int. J. Quantum Chem.* **2011**, *111*, 4309–4317.
9. Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323.