Synthesis of Sterically Hindered Chiral 1,4-Diols from Different Lignan-Based Backbones

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Abstract: Methods for synthetic modifications of the natural dibenzylbutyrolactone lignan hydroxymatairesinol into chiral 1,4-diols with different lignan-derived backbones have been developed. A stepwise procedure, involving alkylation and oxidation, was shown to be successful and several highly substituted 1,4-diols were prepared. Some substituted butyrolactones resisted alkylation and led to the formation unusually stable hemiketals (butyrolactols). The formation of stable hemiketals was investigated in detail, showing that different backbone structures influence the formation and reactivity of the hemiketals.

Key words: hydroxymatairesinol, chiral 1,4-diols, TADDOL, lignans, burtyrolactol

Utilizing wood-derived compounds as high-value chemicals has become increasingly important due to the development of biorefinery processes. Norway spruce (*Picea abies*) is highly abundant and one of the most economically important coniferous species in Europe. The knotwood of Norway spruce has been shown to be rich in polyphenolic compounds with up to 20% of its dry weight consisting of the lignan hydroxymatairesinol.[1] The synthetic modification of hydroxymatairesinol to high-value compounds has been of interest to us for several years.

We have recently investigated the possibility of transforming hydroxymatairesinol into sterically hindered ligands (similar to TADDOL). Several chiral 1,4-diol structures based on the aryltetralin skeleton of dimethylconidendrin (**1**, Scheme 1) have been synthesized and their potential application as ligands in asymmetric catalysis investigated.[2] When converting an intermediate substituted butyrolactone **3**, by addition of Grignard or alkyl lithium reagents, stable hemiketals **4** were predominantly formed. Only the methyl-substituted lactone formed the diol **5** (Scheme 1). It was shown that one reason for this problem was the steric bulk of the lignan backbone, but even in case of the less bulky methyl groups the main product was still the hemiketal. Surprisingly, the formation of hemiketals for TADDOL-like structures has only rarely been reported in the literature. However, recent papers on TADDOL derivatives have addressed similar problems.[3,4]

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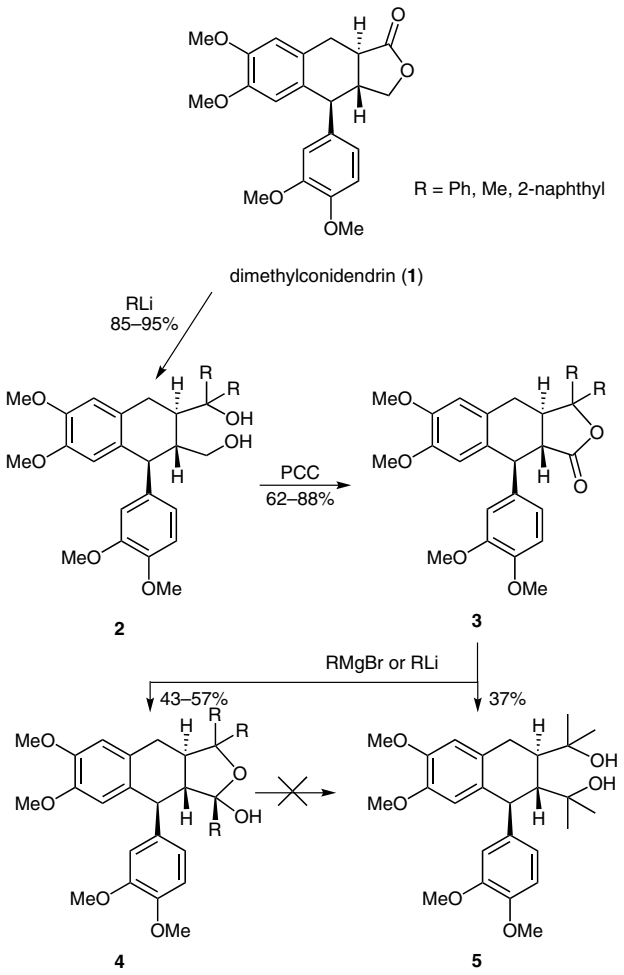
Patrik Eklund (left) obtained his master degree in chemistry from Åbo Akademi University in 2000. Following this he worked for Hormos Medical Ltd. for a short period. In 2002 he started his PhD studies under the supervision of Prof. Rainer Sjöholm at Åbo Akademi University. He completed his PhD in 2005 in the field of synthetic modification of the natural products and continued as a research fellow and lecturer until 2006 when he was appointed as a senior lecturer in organic chemistry at the Laboratory of Organic Chemistry, Åbo Akademi University. In 2009 he was appointed as an adjunct professor in organic synthesis and natural product chemistry. His current research is focused on natural product synthesis, semisynthesis of anticancer agents, drug discovery, and structural determination and chemical modification of noncellulosic natural polysaccharides.

To overcome this problem and to study the stability of the hemiketals, we decided to investigate the reactivity of other lignan-derived backbones, with the hypothesis that more flexible and accessible backbones would react to give the target 1,4-diols. For this purpose, three new lignan backbones were selected: dimethylmatairesinol (**6a**), a fully flexible structure, the macrocycle **6c** with a slightly more fixed conformation, and a cyclooctadiene structure **6b** with a more rigid structure (Scheme 2).

The use of hydroxymatairesinol as a starting material gave access to the enantiopure butyrolactone with the 8*R*,8*R*′ configuration, the configuration of these stereocentres being preserved during the synthetic modifications.

Hydroxymatairesinol was first converted into matairesinol by catalytic hydrogenolysis on Pd/C (Scheme 2).[5] Compound **6a** was then prepared in almost quantitative yield from matairesinol by methylation with methyl io-



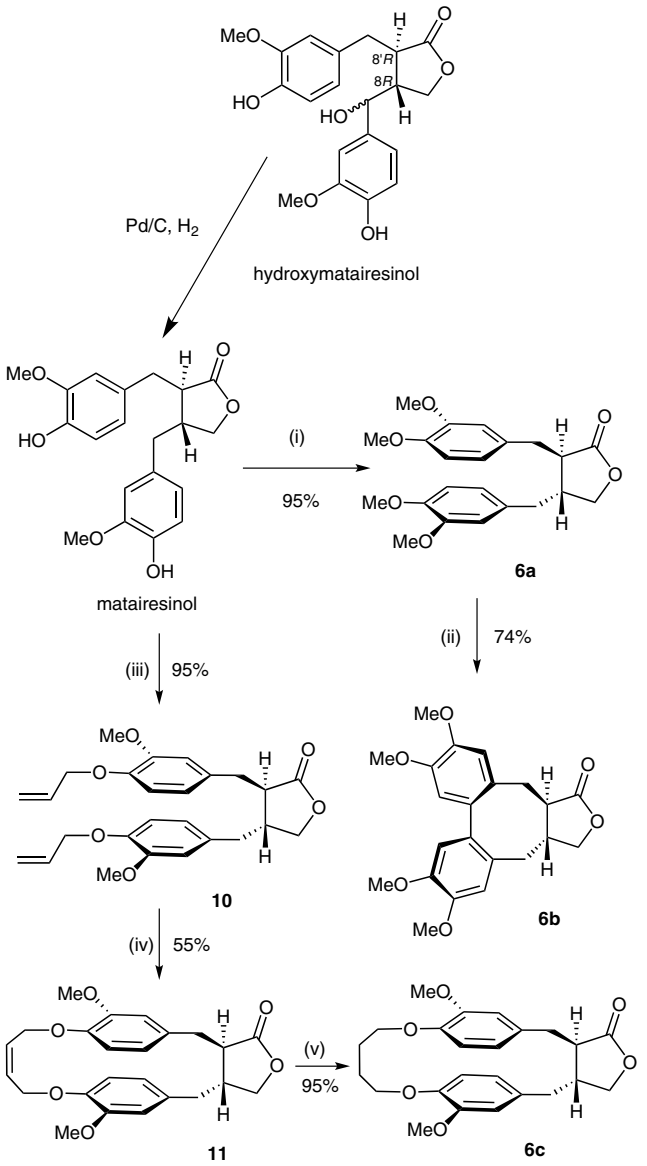
Scheme 1 Transformation of dimethylconidendrin (**1**) into chiral diols[2]

dide. Compound **6b** was prepared from **6a** by intramolecular oxidative coupling mediated by vanadium oxyfluoride in good yield.[6] For preparation of the macrocyclic compound **6c**, the phenolic groups of matairesinol were first allylated to give **10** and then cyclized by ring-closing metathesis to give **11**, followed by hydrogenation of the double bond (for details see Supporting Information).

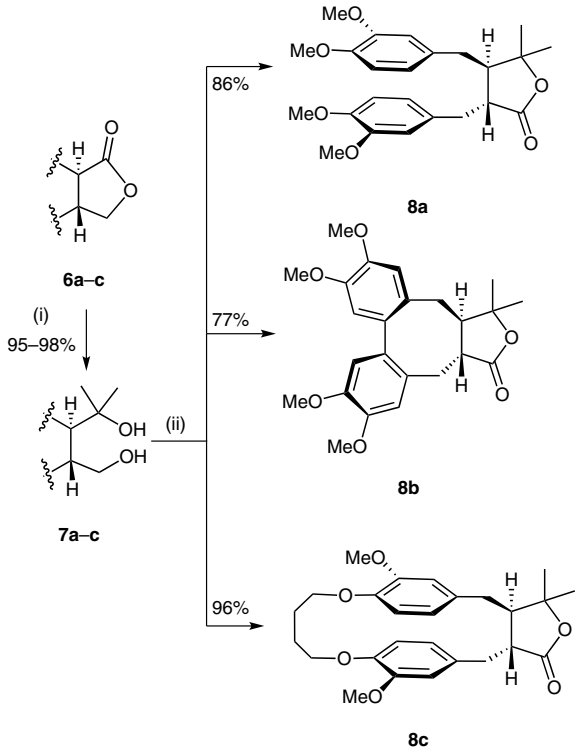
The lactones **6a**–**c** were then methylated with methylmagnesium bromide to afford compounds **7a**–**c** in excellent yields. The diols **7a**–**c** were further oxidized with pyridinium chlorochromate (PCC) in good to excellent yields to the lactones **8a**–**c** (Scheme 3).

When the substituted lactones **8a** and **8c** were reacted with methylmagnesium bromide, a mixture of hemiketals (diastereomers) was first formed, but with excess of methylmagnesium bromide the diols **9a** and **9c** were slowly obtained (Scheme 4). In case of the lactone **8b**, the mixture of hemiketals (*S*)- and (*R*)-**9b** was stable and did not undergo any further reactions regardless of the reaction conditions. Experimental details for methylation of the lactones **8a**–**c** as well as some analytical data for compounds **9a**–**c** are presented in the references.[7] For more detailed experimental information see Supporting Information.

These results are in good agreement with the observations by Budragchaa et al.[3] In a similar synthesis of TADDOL-like structures, stable substituted hemiketals were formed and the introduction of the fourth substituent took up to 48 hours. In the case of lactones **8a** and **8c**, formation of a close to 50:50 mixture of the hemiketal (one diastereomer) and the tetramethyl diol was observed in one hour, and by addition of more methylmagnesium bromide very slow conversion of the hemiketal into tetramethyl diol (several days) was observed. A more detailed study of the reaction mixture (by NMR) indicated that predominatly one of the hemiketals reacted with a moderate rate, whereas the other reacted slowly.



Scheme 2 Synthesis of different lactone backbones. *Reagents and conditions*: (i) MeI (5 equiv), K_2CO_3, DMF, r.t. 3 h; (ii) VOF_3 (3 equiv), TFA–CH_2Cl_2, –45 °C; (iii) allyl bromide (5 equiv), K_2CO_3, DMF, r.t.; (iv) Grubbs I catalyst 5%, CH_2Cl_2, r.t.; (v) 5% Pd/C, MeOH, r.t.



Scheme 3 Alkylation and oxidation of the different lactones **6a–c**. *Reagents and conditions*: (i) MeMgBr (3 equiv), THF, r.t.; (ii) PCC (3 equiv), CH_2Cl_2, r.t.

These observations, as well as the fact that compound **3** led to the formation of the unreactive butyrolactol **4** upon alkylation, clearly showed that in a flexible backbone both diastereomers of the hemiketals react further to furnish the diols, but with considerable difference in reaction rate. In a more rigid structure with a certain configuration and conformation of the butyrolactol ring [compounds (*S*)-**9b**, (*R*)-**9b**, and **4**], further reaction to the diol was prevented. For these stable hemiketals no equilibrium between the ketone and the hemiketal was observed. Whatever the configuration at the hemiketal carbon, the torsion angle between OH and the oxygen in the butyrolactol ring were of equal magnitude in (*S*)- and (*R*)-**9b** and similar to that of compound **4**. The bond angles and the flexibility in the butyrolactol ring clearly determined the reactivity of this intermediate.

The tetramethyl diol **9c** was crystallized from benzene to give single crystals suitable for X-ray diffraction. The resulting molecular structure is shown in Figure 1. A strong intramolecular hydrogen bond between the hydroxyl groups [O···O′ distance 2.674(2) Å] induces a nonsymmetrical structure in the solid state, and the parallel alignment of the aromatic rings is distorted by about 15°. Furthermore, intermolecular hydrogen bonds link the diols together forming molecular chains (Figure S1 in Supporting Information). However, the NMR spectrum shows the molecule to be completely symmetrical, which indicates that the hydrogen bonding does not distort the structure in solution.

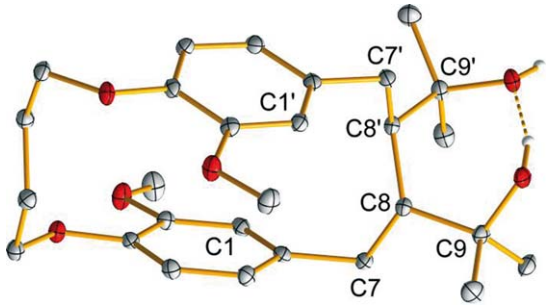
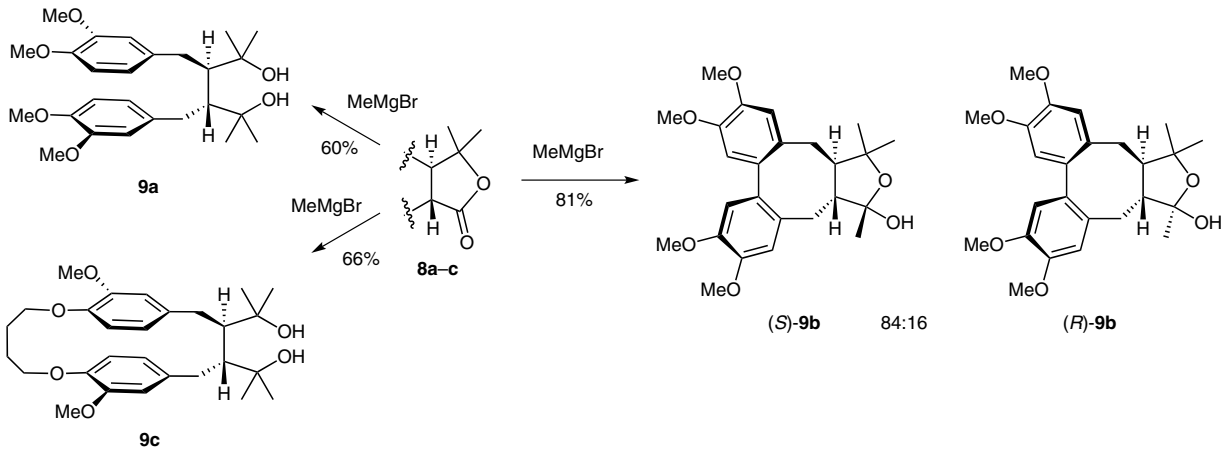


Figure 1 X-ray structure of diol **9c**. Thermal ellipsoids have been drawn at 30% probability level and CH hydrogens are omitted for clarity.

In conclusion, we have developed methods for diverse synthetic modifications of the lignan skeleton of hydroxymatairesinol. The preparation of highly substituted 1,4-diols was not straightforward due to formation of stable hemiketals. This problem has recently been recognized and has now been investigated in more detail by modification of the backbone structure. According to our results, the formation and further reactivity of highly substituted butyrolactol (hemiketal) structures is only partially dependent on the flexibility and bulkiness of the molecule.



Scheme 4 Reaction of the dimethyl lactones **8a–c** with methylmagnesium bromide. *Reagents and conditions*: MeMgBr (3–5 equiv), THF, r.t.

A more important feature is the configuration and conformation of the butyrolactol. The prepared sterically hindered chiral diols could potentially be used as ligands in transition-metal-mediated asymmetric catalysis.[8,9] Further transformation of 1,4-diols into chiral phosphine ligands is ongoing in our laboratory.

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(7) The dimethyl lactone **8a**, **8b**, or **8c** (1 mmol) was dissolved in THF (30 mL), the solution was cooled to 0 °C, and MeMgBr (3 mL of 3 M solution in Et_2O, 9 mmol) was added dropwise during 30 min. The solution was allowed to warm to r.t. and stirred for 20–72 h. Saturated NH_4Cl (10 mL) and H_2O (10 mL) were added to the reaction mixture, and the organic phase was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and the solvent evaporated. The residue was purified by column chromatography using $CHCl_3$–MeOH (70:1) as eluent, to give products **9a**–**c**.
Analytical Data for Compounds **9a**–**c**
Compound **9a** (reaction time 72 h, yield 265 mg, 60%): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.06 (s, 6 H), 1.23 (s, 6 H), 2.58 (dd, *J* = 7.1, 5.1 Hz, 2 H), 2.65 (dd, *J* = 14.9, 7.1 Hz, 2 H), 2.96 (dd, *J* = 14.9, 5.1 Hz, 2 H), 3.88 (s, 6 H), 3.90 (s, 6 H), 6.82 (d, *J* = 7.9 Hz, 2 H), 6.85 (d, *J* = 1.5 Hz, 2 H), 6.87 (dd, *J* = 7.9, 1.5 Hz, 2 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 26.3, 30.9, 33.9, 48.3, 55.9, 74.3, 111.2, 112.1, 120.5, 135.3, 147.2, 148.9 ppm.
Compound **9b** (reaction time 20h, yield 350 mg, 0.81 mmol, 81%)
(*S*)-**9b**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.01 (s, 3 H), 1.44 (s, 3 H), 1.57 (s, 3 H), 1.77 (dd, *J* = 12.3, 10.0 Hz, 1 H), 2.07 (dd, *J* = 12.1, 10.2 Hz, 1 H), 2.13 (br s, 1 H), 2.20 (dd, *J* = 13.0, 10.2 Hz, 1 H), 2.31 (dd, *J* = 13.6, 10.0 Hz, 1 H), 2.47 (d, *J* = 13.0 Hz, 1 H), 2.64 (d, *J* = 13.6 Hz, 1 H), 3.87 (s, 3 H), 3.89 (s, 3 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 6.68 (s, 1 H), 6.71 (s, 1 H), 6.72 (s, 1 H), 6.74 (s, 1 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 22.9, 26.4, 28.9, 32.8, 33.3, 54.5, 55.2, 56.0, 56.06, 56.1, 56.2, 81.7, 102.9, 112.0, 112.1, 113.4, 113.6, 132.5, 132.6, 133.0, 133.2, 147.0, 147.1, 148.6, 148.7 ppm.
(*R*)-**9b**: ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.28 (s, 3 H), 1.35 (s, 3 H), 1.69 (dd, *J* = 12.6, 10.6 Hz, 1 H), 2.08 (dd, *J* = 12.6, 10.0 Hz, 1 H), 2.13 (br. s., 1 H), 2.20 (dd, *J* = 12.8, 10.0 Hz, 1 H), 2.22 (dd, *J* = 13.2, 10.6 Hz, 1 H), 2.42 (d, *J* = 13.2 Hz, 1 H), 2.73 (d, *J* = 12.8 Hz, 1 H), 3.88 (s, 3 H), 3.89 (s, 3 H), 3.94 (s, 3 H), 3.95 (s, 3 H), 6.66 (s, 1 H), 6.71 (s, 1 H), 6.74 (s, 1 H), 6.80 (s, 1 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 23.6, 24.4, 28.1, 32.9, 33.1, 55.9, 56.0, 56.1, 56.1, 56.1, 56.3, 80.5, 104.5, 111.9, 112.2, 113.3, 113.4, 132.3, 132.8, 132.9, 132.9, 147.0, 147.1, 148.6, 148.7 ppm.
Compound **9c** (reaction time 48 h, yield 310 mg, 0.66 mmol, 66%): ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.56 (s, 6 H), 1.65 (s, 6 H), 1.65–1.71 (m, 2 H), 1.87 (d, *J* = 10.6 Hz, 2 H), 2.06–2.14 (m, 2 H), 2.62 (dd, *J* = 13.6, 10.6 Hz, 2 H), 2.76 (d, *J* = 13.6 Hz, 2 H), 3.70 (br s, 2 H), 3.81 (s, 6 H), 4.17–4.23 (m, 2 H), 4.29–4.34 (m, 2 H), 6.26 (dd, *J* = 8.1, 1.9 Hz, 2 H), 6.44 (d, *J* = 1.9 Hz, 2 H), 6.50 (d, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 23.5, 30.9, 32.9, 37.7, 53.5, 55.9, 67.5, 74.4, 113.3, 113.5, 120.4, 134.5, 144.5, 148.1 ppm.
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