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Synthesis of (–)-Matairesinol, (–)-Enterolactone, and (–)-Enterodiol from the Natural Lignan Hydroxymatairesinol

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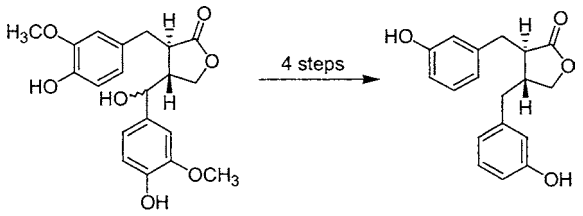
ABSTRACT



Hydroxymatairesinol (-)-Enterolactone

We describe here a four-step semisynthetic method for the preparation of enantiomerically pure (–)-enterolactone starting from the readily available lignan hydroxymatairesinol from Norway spruce (*Picea abies*). Hydroxymatairesinol was first hydrogenated to matairesinol. Matairesinol was esterified to afford the matairesinyl 4,4′-bistriflate, which was deoxygenated by palladium-catalyzed reduction to 3,3′-dimethylenterolactone. Demethylation of 3,3′-dimethylenterolactone and reduction with $LiAlH_4$ yielded (–)-enterolactone and (–)-enterodiol, respectively.

Lignans have attracted much interest over the years because of their widespread occurrence in various plant species[1] and their broad range of biological activity.[1b,2] Two lignans, unique in lacking *para* substitution in the benzylic groups, enterolactone (ENL) [2,3-bis(3-hydroxybenzyl)-γ-butyrolactone] (**5**) and enterodiol (END) [2,3-bis(3-hydroxybenzyl)-butane-1,4-diol] (**6**), have been found in human and animal urine.[2,3] Enterolactone is a mammalian lignan, which has recently been shown to form by the metabolization of plant lignans such as matairesinol (**2**), secoisolariciresinol, 7-hydroxymatairesinol (HMR) (**1**), and lariciresinol by intestinal bacteria.[4] The detection of the mammalian lignans ENL and END in human urine has led to much discussion about their biological function.[2,3,5] They have been suggested to have a role as antiestrogens and anticarcinogens among other possible biological activities.[6] In recent studies, HMR, the

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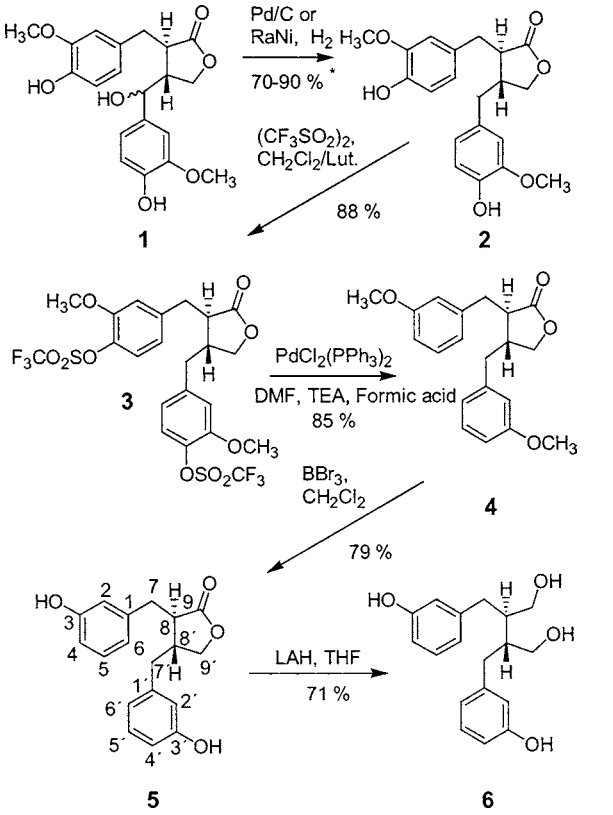
most abundant lignan in Norway spruce (*Picea Abies*) wood, was shown to metabolize mainly to ENL in rats.[7] Also, both HMR and ENL have been shown to inhibit the growth of 7,12-dimethylbenz[*a*]anthracene-induced mammary carcinoma in rats.[7−9] Numerous metabolites of ENL have been characterized, but little is known about their possible biological effects.[5c,e] According to some older sources, ENL and END found in humans and in vervet monkeys are essentially racemic.[3,5a] However, in more recent papers, it seems accepted that the metabolically formed ENL is mainly (−)-(8*R*,8′*R*)-enterolactone (**5**, Scheme 1).[10,11]

Scheme 1



*Yields depend on the starting material used (HMR or HMR−KAc) and the purity thereof.

Because of the significant biological activity of this compound, it has been an interesting target for synthetic chemists and several synthetic routes to enantiomerically pure ENL have been reported.[10,11] We here report an alternative semisynthesis of (−)-ENL starting from the readily available natural lignan HMR.

HMR is found in exceptionally high concentrations (>10% of the dry weight) in knots of Norway spruce (Picea abies).[12] Methods for the separation of knots and isolation of HMR in large scale have been developed, making HMR the first butyrolactone lignan available in large scale.[13] Knots are dried, ground, and extracted with acetone−water. The raw extract is purified by flash chromatography to yield pure HMR. Alternatively, the formation of a K-acetate adduct of (−)-HMR described by Freudenberg et al.[14] is used to isolate HMR. Knots are extracted with ethanol and K-acetate is added to the extract to yield a HMR−K-acetate adduct, which is separated by precipitation and filtration. Undoubtedly, this method is superior in large-scale isolation.

Natural HMR comprises of two diastereomers, namely, (7*S*,8*R*,8′*R*)-(−)-7-hydroxymatairesinol (major isomer) and (7*R*,8*R*,8′*R*)-(−)-7-*allo*-hydroxymatairesinol (minor isomer), whose absolute configurations were determined recently.[15] The stereochemical structure and the good availability of HMR make it an excellent precursor for synthesis of (−)-matairesinol, (−)-ENL, and (−)-END.

In this work, HMR was first submitted to pressurized hydrogenolysis over Pd/C in dichloroethane or the K-acetate adduct of HMR was hydrogenolyzed with RaNi or Pd/C in ethanol to afford (8*R*,8′*R*)-(−)-matairesinol (**2**) in almost quantitative yields. In a typical experiment, 15 g of adduct was dissolved in ethanol; catalyst was added, and the mixture was hydrogenated under pressure for 200 min (Figure 1). Matairesinol was then deoxygenated to 3,3′-dimethylenterolactone (**4**) according to a procedure that has been described for hindered phenols but, to our knowledge, never been applied to natural lignans.[16,17]

Two different methods for palladium-catalyzed phenolic reduction/deoxygenation of **2** under mild conditions were studied, deoxygenation via triflate derivatives and deoxygenation via 1-phenyl-tetrazyl ether derivatives. The latter method showed promising results for the first step; etherification of the phenolic hydroxyl groups was successful, and the product was obtained by crystallization. However, deoxygenation of the 1-phenyl-tetrazyl derivatives was unsuccessful. Despite several attempts by catalytic deoxy-

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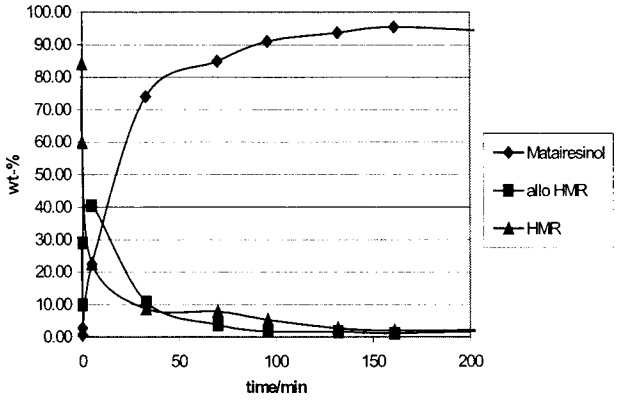

Figure 1. Conversion of HMR−KAc adduct to matairesinol using RaNi as a catalyst in EtOH, 130 °C, 700 PSI.

genation using Pd/C and PtO with H_2, satisfactory yields could not be obtained. The former method was undoubtedly favorable to the latter and could be used for the phenolic deoxygenation.

Matairesinol (**2**) was esterified with triflic anhydride in lutidine to afford matairesinyl 4,4′-bistriflate (**3**) in good yields. Compound **3** was then converted to **4** with 1,3-bis-(diphenylphosphino)propane and $PdCl_2(PPh_3)_2$ in DMF/TEA using formic acid as a hydrogen donor. Demethylation of **4** was carried out using BBr_3 in dichloromethane to yield **5** (overall yield ∼55%, calculated from HMR), which was reduced with $LiAlH_4$ to **6** (overall yield ∼40%, calculated from HMR) (Scheme 1). The products were identified using NMR spectroscopy, HRMS, and chiral HPLC-MS.

Although several works identifying ENL in mammalian body fluids have been published, the enantiomeric composition has not been discussed. Preliminary results based on optical rotation and circular dichroism showed that mammalian ENL is essentially racemic.[3,5a] However, Saarinen et al. recently showed (by using our semisynthetic (−)-ENL as reference) that the excretion of the two enantiomeric forms of ENL in rats after administration of a single dose of lignan precursors depends on the enantiomeric compositions of the precursors.[18]

To study the enantiomeric composition of ENL in humans, human serum and urine were analyzed by chiral HPLC-ESI-MS/MS using multiple reaction monitoring techniques (MRM). Three blood serum samples, one being an average sample of three persons (Serum 3), and one urine sample were analyzed, using the semisynthetic (−)-ENL as a reference compound. The enantiomeric composition shown in Table 1 showed some differences between samples.

Table 1. Enantiomeric Composition of ENL in Human Serum and Urine

sample	(−)-ENL (%)	(+)-ENL (%)
serum 1	49	51
serum 2	46	54
serum 3	78	22
urine	67	33

According to our results and the results of Saarinen et al., it seems reasonable to assume that ENL in mammalian samples is neither racemic nor enantiomerically pure but that its stereochemistry correlates with the dietary intake of enantiomerically different precursors. Variations in the enantiomeric composition in humans are therefore to be expected. It may vary between individuals and populations and/or be geographically related. It also seems most probable that no configurational changes are introduced during the microbial metabolism. However, to finally establish the enantiomeric variations in humans, as well as possible different biological properties for the two enantiomers of ENL, a more comprehensive study is necessary.

In summary, we have developed a new approach for the synthesis of enentiopure (−)-ENL and (−)-END. The method of synthesis described in this work may also be used for other lignans as well as for other phenolic natural compounds. The simplicity of the reactions and the good yields give an efficient semisynthetic route to enantiomerially pure deoxygenated lignan derivatives, also in large scale. These derivatives may be well suited for metabolization studies of plant lignans.

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Supporting Information Available: Experimental procedures and complete analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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