Synthetic transformation of hydroxymatairesinol from Norway spruce (*Picea abies*) to 7-hydroxysecoisolariciresinol, (+)-lariciresinol and (+)-cyclolariciresinol

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We have developed a method for the transformation of hydroxymatairesinol to optically pure (+)-lariciresinol and (+)-cyclolariciresinol *via* the hitherto unreported lignan 7-hydroxysecoisolariciresinol. The two naturally occurring isomers of hydroxymatairesinol were reduced with $LiAlH_4$ to a mixture of two epimers of 7-hydroxysecoisolariciresinol, which were further selectively transformed to (+)-lariciresinol and (+)-cyclolariciresinol by an acid catalysed intramolecular cyclisation reaction. The structure of the major isomer of 7-hydroxysecoisolariciresinol was confirmed by X-ray crystallography and thereby also the absolute configurations of the two isomers of hydroxymatairesinol were unambiguously proven. Optical purities were determined by chiral HPLC-MS/MS and optical rotation measurements.

Introduction

Hydroxymatairesinol is the most abundant lignan in Norway spruce (*Picea abies*) and can be readily isolated as a mixture of two isomers in the ratio of ~1 : 3. The isomers were first isolated by Freudenberg and Knof in 1957 and later the lignan components of Norway spruce were re-examined by Ekman.[1,2] The two isomers were shown to be diastereomers, differing in the relative stereochemistry at position C-7 (Scheme 1). According to the literature, the minor isomer has the relative configuration 7*S**,8*R**,8′*R** and is named (−)-*allo*-hydroxymatairesinol (**1a**) and the major isomer has the configuration 7*R**,8*R**,8′*R** and is named (−)-hydroxymatairesinol (**1b**).[1,3] The stereochemistry of the hydroxymatairesinol isomers has been studied by NMR spectroscopy,[3,4] but the absolute configurations have never been unambiguously proven.

Despite several attempts to achieve suitable crystals for X-ray analysis of hydroxymatairesinol, crystallisation was unsuccessful. However, the corresponding triol obtained by reduction of the lactone ring of hydroxymatairesinol afforded crystals suitable for X-ray studies, and the absolute configuration of hydroxymatairesinol was thereby indirectly determined in this work.

In 1979 Ekman reported high concentrations of hydroxymatairesinol in the heartwood of branches of Norway spruce (4–6% of dry wood weight) and recently, Willför *et al.* showed that even larger amounts can be found in knots (~10% w/w) from where it can be easily isolated on a large scale.[5]

Like many other lignans, hydroxymatairesinol has beneficial biological and physiological properties. It has been shown to be metabolised into enterolactone by intestinal bacteria and hence to have antitumourigenic properties.[6] Hydroxymatairesinol has also been shown to have antioxidant properties and is thereby able to decrease the oxidation of LDL particles.[7]

Various routes for the total synthesis of racemic as well as of optically pure lignans have been employed.[8,9] However, the synthetic transformation of lignans obtained from natural sources by isolation may provide a more convenient way to produce other, less abundant, optically pure lignans. Hydroxymatairesinol has not been the subject of such studies and therefore we here report the transformation of hydroxymatairesinol to (7*S*,8*R*,8′*R*)-(+)-lariciresinol (**3**) and (7*S*,8*R*,8′*R*)-(+)-cyclolariciresinol [(+)-isolariciresinol] (**4**) *via* the hitherto unreported semisynthetic lignan 7-hydroxysecoisolariciresinol [(8*R*,8′*R*)-3,3′-dimethoxyligna-4,4′,7,9,9′-pentaol] (**2**) (Scheme 1).

(+)-Lariciresinol is a common plant lignan and has been isolated from several plant species including Norway spruce.[2,8,10–13] It has also been obtained by catalytic hydrogenation from pinoresinol and thereby the absolute stereostructure was determined.[14] Racemic (±)-lariciresinol has been fully synthesised *via* different routes.[15,16] Lariciresinol was recently shown to be an excellent precursor for conversion to enterolactone by intestinal bacteria in humans, and it has also shown activity against promyelocytic leukaemia (HL-60) cells.[17–19] Lariciresinol could therefore be a potential chemopreventive agent for different cancer forms. (+)-Cyclolariciresinol, also named as isolariciresinol, has been found in numerous plant species and is believed to possess antiinflammatory as well as antioxidant properties.[20,21]

Compared to lariciresinol (**3**) and cyclolariciresinol (**4**), hydroxymatairesinol (**1**) is a far more abundant lignan in spruce wood. The potential large-scale isolation from Norway spruce knots makes **1** a readily available starting material for synthetic transformations to **3** and **4**. This semi-synthetic preparation of **3** and **4** may thereby be advantageous to their isolation from natural sources.

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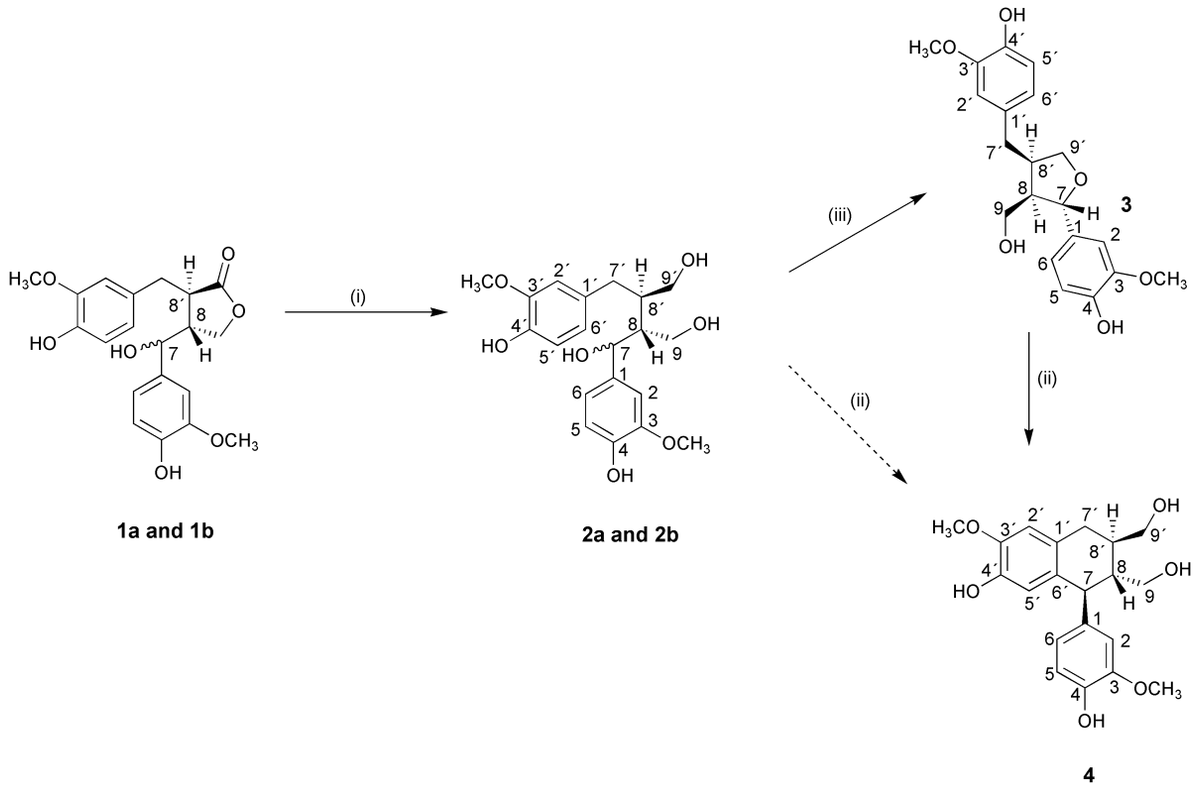

Scheme 1 *Reagents and conditions*: (i) $LiAlH_4$, THF, 50 °C, 5 h. (ii) and (iii) 5% H_2SO_4 in MeOH, THF, 20 °C, 4 h or $BF_3{\cdot}Et_2O$ in CH_2Cl_2, THF, 50 °C.

Results and discussion

Reduction of butyrolactone lignans to the corresponding bis-primary diols, without isomerisation of the configuration at the α-position, has been performed with $LiAlH_4$ and is a well-known transformation in lignan chemistry.[8] When a mixture of **1a** and **1b** was reduced with $LiAlH_4$ in anhydrous THF under an atmosphere of argon, a mixture of 7-hydroxy-secoisolariciresinol stereoisomers was obtained in good yields (Scheme 1). The obtained mixture showed the same isomeric ratio as the starting material and it seemed obvious that **1a** and **1b** yielded the hitherto unknown semisynthetic lignans *allo*-hydroxy- and hydroxy-secoisolariciresinol **2a** and **2b**, respectively. The major isomer (**2b**), which was formed from **1b**, was crystallised from MeOH : H_2O (1 : 1 v/v) to afford colourless plates, which were analysed by X-ray crystallography. The plates were methanol adducts of **2b** with the formula **2b·MeOH**. The stereo structure of **2b** represents the 7*S*,8*R*,8′*R* configuration (Fig. 1).

The assignments of the absolute configurations 8*R* and 8′*R* are based on the following arguments. **1a** and **1b** form (−)-α-conidendrin when treated with formic acid.[1] (−)-α-Conidendrin has been enantioselectively synthesised and thereby proven to have the 8*R*,8′*R* configuration.[22] Comparison of NMR spectroscopic data and optical rotation data of the product obtained, when **1a** and **1b** were treated with formic acid, confirmed the formation of (−)-α-conidendrin.† Since the lactone ring in hydroxymatairesinol is not affected during the formation of (−)-α-conidendrin, the same 8*R*,8*R*′ configuration is expected in both epimers of hydroxymatairesinol. Following this, the *R*,*R* configurations were assigned to C-8 and C-8′ in **2b**. Based on the X-ray analysis C-7 then has the *S*-configuration.

The bonding parameters of **2b** are normal. The structure of the adduct is stabilised by extensive intermolecular hydrogen bonding. It is interesting to notice that the aromatic rings in **2b** are quite close to each other (in a stacking position). For example the C3 ··· C4′ and C4 ··· C3′ distances are 3.581(3) and 3.524(3) Å, respectively.

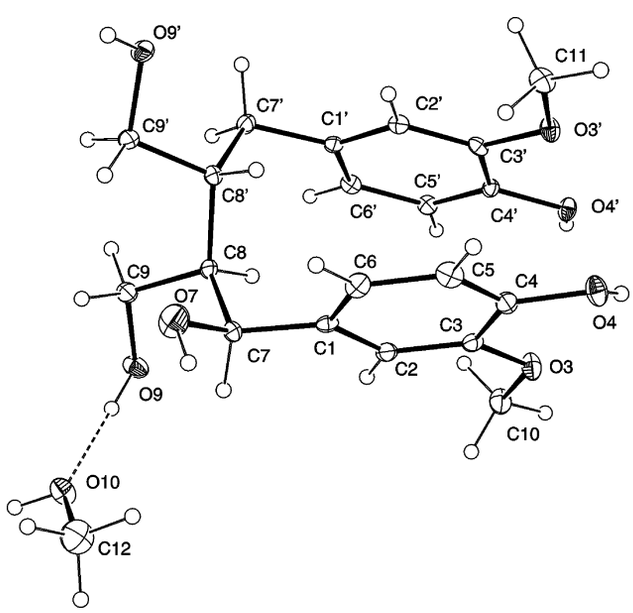

Fig. 1 An ORTEP plot (ellipsoids at 30% probability) of the major isomer of 7-hydroxysecoisolariciresinol (**2b**), epimer 7*S*.

In addition to X-ray crystallographic analysis of **2b**, the structures of both isomers of **2** were elucidated by homo- and hetero-nuclear chemical shift correlation NMR spectroscopy and mass spectrometry. The ^1H NMR spectrum of **2b** revealed aromatic signals expected for the 3-methoxy-4-hydroxyphenyl (guaiacyl) substitution pattern. The proton H-7 showed a signal at 4.91 ppm as a triplet, which emerged as a doublet ($J = 6.0$ Hz) on addition of D_2O to the sample. The signal was correlated to a multiplet at 1.98 ppm (H-8) in the ^1H–^1H COSY spectra.

† (−)-α-Conidendrin $[a]_D^{22}$ −52.2 (*c* 10 mg ml^{-1} in acetone), $[a]_D$ −52.5 (*c* 1 in acetone),[22] −54.5 (4% in acetone).[1] NMR spectroscopic data were in accordance with previously reported.[22]

The H-8 signal showed further correlation to a multiplet at 2.21 ppm (H-8′) and to two methylene protons mutually coupled at 3.56–3.62 and 3.78 ppm (H-9a, H-9b; a broadening of these signals indicated coupling to a OH proton). The coupling between H-8 and H-8′ was 2.3 Hz, which indicated that the H-8–H-8′-*syn* conformation is preferred in solution. The H-8′ signal correlated both to OH coupled broadened signals of two protons mutually coupled at 3.5–3.6 ppm (H-9a′, H-9b′) and to similar signals at 2.47 and 2.66 (H-7′a, H-7′b), which showed no coupling to OH. Upon addition of D_2O to the sample the OH couplings vanished and well-resolved signals of H-9 and H-9′ were observed. Long-range correlation allowed the distinction between unprimed and primed aromatic rings by the correlation of H-7 and H-7′ to the aromatic signals H-2 and H-2′, respectively. The assignments of the carbon signals were established by heteronuclear COSY spectra and multiple bond connectivity spectroscopy (HMBC) made the assignments of the quaternary carbon (C-1, C-1′, C-3, C-3′, C-4 and C-4′) signals possible.

As the reduction of **1** to **2** can be expected to proceed without isomerisation of stereocenters, the structural determination of **2** also proved that the structure of the major isomer of hydroxymatairesinol (**1b**) in Norway spruce (*Picea abies*), namely (−)-hydroxymatairesinol, is (7*S*,8*R*,8′*R*)-(−)-7-hydroxymatairesinol. To further confirm this we isolated the two isomers of hydroxymatairesinol by chromatography and compared NMR spectroscopic and optical rotation data with previously published data.[1,3,4] The comparison of these data confirmed the major isomer in Norway spruce to be (−)-hydroxymatairesinol (**1b**) and the minor isomer to be (−)-*allo*-hydroxymatairesinol (**1a**).‡ In conclusion, the absolute stereochemistry and the identity of the two isomers of **1** in Norway spruce were unambiguously proven to be (7*R*,8*R*,8′*R*)-(−)-7-*allo*-hydroxymatairesinol (minor isomer) and (7*S*,8*R*,8′*R*)-(−)-7-hydroxymatairesinol (major isomer).

The complete IUPAC name of the minor isomer of hydroxymatairesinol from Norway spruce is then (−)-(7*R*,8*R*,8′*R*)-4,4′,7-trihydroxy-3,3′-dimethoxylignano-9,9′-lactone and the major isomer is (−)-(7*S*,8*R*,8′*R*)-4,4′7-trihydroxy-3,3′-dimethoxylignano-9,9′-lactone.

Transformation of **2** to (+)-lariciresinol (**3**) was accomplished by a mild acid-catalysed cyclisation with $BF_3{\cdot}Et_2O$ in CH_2Cl_2–THF or with methanolic H_2SO_4 and also observed in aqueous HCl (see Experimental). Both isomers of **2** gave **3**. However, the 7*R* isomer (**2a**) was more easily transformed to **3** as compared to the 7*S* isomer (**2b**). The latter could not be transformed into **3** without the formation of **4** as a by-product (*ca.* 5–10%). Treatment of both **2** and **3** under stronger acidic conditions ($BF_3{\cdot}Et_2O$, H_2SO_4, aqueous HCl or TFA) led to complete transformation to **4** (see Experimental).

Cyclisation of **2** to **3** may be explained by an initial protonation/complexation of the secondary alcohol group at C-7. The protonated alcohol group may then be substituted by the 9′-OH group, or alternatively form a carbonium ion by loss of water. The formation of **3** from both **2a** and **2b** would indicate a sterically favoured nucleophilic attack on the carbonium ion (S_N1). However, the fact that the *S* isomer (**1b**) does not form **3** as easily as the *R* isomer (**1a**) supports a nucleophilic substitution mechanism with an inversion of configuration at C-7 (S_N2). The primary formation of a mixture of 7*R* and 7*S* lariciresinols would then be followed by an acid catalysed epimerisation (S_N1) of the 7*R* epimer (a, Fig. 2) *via* a carbonium ion intermediate (b, Fig. 2) to yield the most stable epimer. The 7*S* epimer, which is the natural (+)-lariciresinol and the isomer formed in our case, should be energetically more favoured by the *trans* positions of the substituents at C-7 and C-8. Similar acid catalysed epimerisation at benzyl ether linkages has been reported for (+)-pinoresinol and (+)-*epi*-pinoresinol.[14]

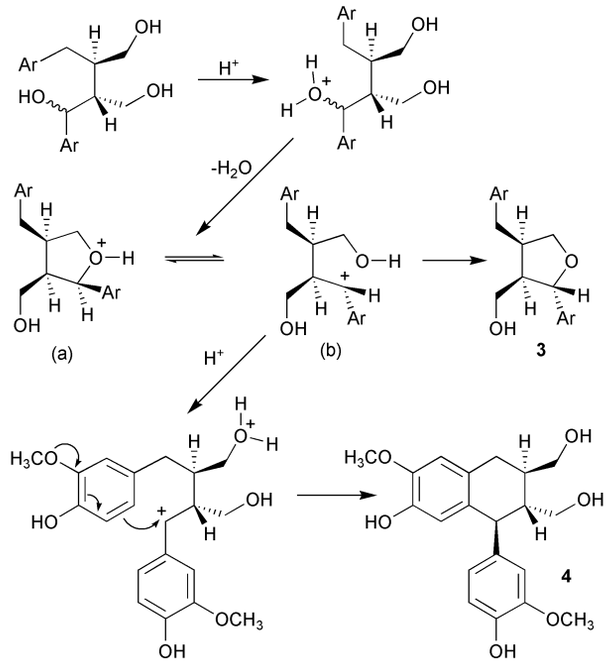

Fig. 2 Acid catalysed epimerisation of 7*R*-lariciresinol (a) to 7*S*-lariciresinol (**3**) *via* a carbonium ion intermediate (b). Further protonation yields **4** by the indicated electron transfer route.

At higher acidic concentrations, the hydroxy groups at C-9 and C-9′ are partly protonated and the formation of **3** is hindered. Compound **2** and/or **3** therefore undergo a rearrangement to afford **4** (Fig. 2).

The structures of compounds **3** and **4** were confirmed by mass spectrometry and NMR spectroscopy. The NMR data for **3** were in accordance with previously published data for **3**.[12] Chiral HPLC-MS/MS and optical rotation measurements confirmed the structure of **3** to be optically pure (+)-lariciresinol, $[a]_D^{24}$ = +26.2 (*c* 0.01 g ml^{-1} in MeOH), lit. +19.8 (*c* 1 g ml^{-1} in MeOH).[12] The ^{1}H and ^{13}C NMR data of compound **4** agreed with those reported in the literature,[20,21] although we wish to reassign the signals of the quaternary carbon atoms C-1 and C-6′. Optical rotation and chiral HPLC-MS/MS confirmed the compound to be (+)-cyclolariciresinol, $[a]_D^{24}$ = +65 (*c* 0.01 g ml^{-1} in acetone), lit. +68 (*c* 1 g ml^{-1} in acetone).[23]

Conclusions

The naturally occurring lignans (+)-lariciresinol, (+)-cyclolariciresinol and a new lignan, 7-hydroxysecoisolariciresinol were obtained by a simple high-yielding method starting from the readily available lignan hydroxymatairesinol as described above. The absolute configuration of 7-hydroxysecoisolariciresinol was determined based on X-ray crystallography and by comparison of existing data on related lignans. As a consequence, the absolute configurations of (−)-*allo*-hydroxymatairesinol and (−)-hydroxymatairesinol from Norway spruce were unambiguously determined.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-A500 spectrometer at 500 and 125 MHz, respectively. Chemical shifts are reported in ppm (δ) downfield from TMS. 2D experiments (COSY, HMQC, and HMBC) were recorded using standard

‡ The minor isomer of hydroxymatairesinol in Norway spruce showed $[a]_D^{22}$ −5.8 (*c* 4 mg ml^{-1} in THF), $[a]_D^{22}$ +10 (*c* 4 mg ml^{-1} in EtOH) and the major isomer $[a]_D^{22}$ −11.5 (*c* 4 mg ml^{-1} in THF), $[a]_D^{22}$ −5.5 (*c* 4 mg ml^{-1} in EtOH), −7.6 (*c* 1 mg ml^{-1} in EtOH). According to the literature (−)-*allo*-hydroxymatairesinol showed $[a]_D^{25}$ −9.8 (*c* 4 mg ml^{-1} in THF), $[a]_D^{25}$ +4.9 (*c* 4 mg ml^{-1} in alcohol), (−)-hydroxymatairesinol showed $[a]_D^{25}$ −11.0 (*c* 4 mg ml^{-1} in THF), $[a]_D^{25}$ −6.3(*c* 4 mg ml^{-1} in alcohol).[1]

JEOL pulse sequences. Some coupling constants in the dddd signals were not resolved and are calculated from the total J value of the signals. HRMS were recorded on a ZabSpec-TOF system. GC analyses (TMS-ether derivatives) were performed on a standard HP-5890 gas chromatograph equipped with a HP-5 capillary column and a FI detector.

Optical rotations were measured with a Perkin Elmer 241 digital polarimeter with a 1 dm, 1 ml cell. Chiral HPLC-MS/MS-MRM (multiple reaction monitoring) was performed on a PE-Sciex API 3000 instrument equipped with a CHIRALCEL OD-R analytical column (0.46 × 25 cm) using isocratic elution (MeOH : 0.1% HOAc, 85 : 15 v/v for lariciresinol and 60 : 40 for cyclolariciresinol) with a flow rate of 0.5 ml min^{-1}.

Silica gel column chromatography was done on Kieselgel 60 (Merck). Melting points were measured with a Stuart Scientific melting point apparatus and are uncorrected. THF was freshly distilled from benzophenone ketyl and sodium metal prior to use. All other commercially available chemicals were used as supplied by the manufacturers. Hydroxymatairesinol was isolated from Norway spruce as described by Ekman.[2]

X-Ray crystallographic analysis §

The crystallographic data for **2b·MeOH** were collected at 173 K on a Nonius Kappa CCD area-detector diffractometer using graphite monochromatised MoKα radiation (λ = 0.71073 Å). Lattice parameters were determined from 10 images recorded with 1° ϕ scans and subsequently refined on all data. The data collection was performed using ϕ and ω scans with 2° steps using an exposure time of 40 s per frame for **2b**. The crystal-to-detector distance was 30 mm. The data were processed using DENZO-SMN v0.93.0.[24]

The structure was solved by direct methods using the *SIR92* program[25] and full matrix least squares refinements on F^2 were performed using the *SHELXL-97* program.[26] All heavy atoms were refined anisotropically and the OH isotropically with the fixed displacement parameter. The CH hydrogen atoms were included at the calculated distances from their host atoms with the fixed displacement parameters. It was not possible to determine the absolute configuration of compound **2b** from the data using the Flack parameter, which gave the values 0.4(10) and 0.6(10) for different enantiomers. The figure was drawn with *Ortep-3 for Windows*.[27]

Crystal data for **2b**. $C_{21}H_{30}O_8$, M_r = 410.45, orthorhombic, space group $P2_12_12_1$ (No 19), lattice parameters: a = 8.9956(2), b = 12.2107(2), c = 18.5397(5) Å, $\alpha = \beta = \gamma = 90°$, V = 2036.45(8) $Å^3$, T = 173 K, Z = 4, D_c = 1.339 g cm^{-3}, μ(MoKα) = 0.102 mm^{-1}, colourless plates, crystal dimension 0.12 × 0.22 × 0.24 mm, 12147 reflections measured, 3585 unique (R_{int} = 0.041) were used in calculations. The final $wR(F^2)$ was 0.100 (all data).

3.1 Synthesis of 7-hydroxysecoisolariciresinols (2)

A mixture of (−)-*allo*-hydroxymatairesinol (4.5%) and (−)-hydroxymatairesinol (95.5%) (1.5 g, 4.017 mmol) was dissolved in dry THF (50 ml, freshly distilled over benzophenone and sodium metal). To the mixture was added portionwise $LiAlH_4$ (0.91 g, 24.021 mmol) over a period of 30 min at room temperature. The mixture was then slowly heated to 50 °C and stirred for 5 h under Ar. The reaction mixture was poured onto a NaCl solution (200 ml) and neutralised with 10% HCl solution. The product was extracted with ethyl acetate (2 × 150 ml) and after addition of more NaCl to the aqueous phase, the mixture was further extracted with 100 ml EtOAc. The EtOAc fractions were combined and the solvent removed under reduced pressure. The product was crystallised from a mixture of EtOH and $CHCl_3$ (1 : 1), filtered and air-dried. Yield 1.18 g, 78%, isomeric ratio 4 : 96, 7*R* : 7*S* (**2a**, **2b**). Purity by GC 95% of **2**, 2.4% of **4** and 1% of **3**. The product was then crystallised from MeOH : H_2O to yield **2b**. Mp 149–151 °C (MeOH); $[\alpha]_D^{24}$ = −56.2 (c 0.01 g ml^{-1} in THF).

(7*S*,8*R*,8′*R*)-(−)-7-Hydroxysecoisolariciresinol (2b). δ_H (500 MHz, acetone-d_6, 30 °C) 1.98 (1H, dddd, J = 2.3, 6.0, 6.0, 5.3 Hz, H-8), 2.20 (1H, m, H-8′), 2.47 (1H, dd, J = 13.6, 7.6 Hz, H-7′a), 2.66 (1H, dd, J = 13.6, 7.9 Hz, H-7′b), 3.52 (1H, dd, J = 7.2, 11.0 Hz, H-9′b), 3.56–3.62 (2H, two double doublets overlapping, H-9′a, H-9b), 3.72 (3H, s, MeO′), 3.76 (3H, s, MeO), 3.78 (1H, dd, J = 6.0, 11.0 Hz, H-9a), 4.91 (1H, d, J = 6.0 Hz, H-7) 6.51 (1H, dd, J = 7.9, 2.0 Hz, H-6′), 6.56 (1H, d, J = 2.0 Hz, H-2′), 6.66 (1H, d, J = 7.9 Hz, H-5′), 6.73 (1H, d, J = 8.1 Hz, H-5), 6.75 (1H, dd, J = 8.1, 1.6 Hz, H-6), 6.80 (1H, d, J = 1.6 Hz, H-2); δ_C (125 MHz, acetone-d_6, 30 °C) 37.28 (C-7′), 41.11 (C-8′), 50.56 (C-8), 56.03, 56.07 (2 × OMe), 60.49 (C-9), 62.08 (C-9′), 73.87 (C-7), 110.54 (C-2), 113.13 (C-2′),115.03 (C-5), 115.22 (C-5′), 119.65 (C-6), 122.41(C-6′), 133.32 (C-1′), 137.40 (C-1), 145.45 (C-4′), 145.99 (C-4), 147.90 (C-3′), 148.07 (C-3). HRMS; m/z calculated for $C_{20}H_{26}O_7$ (M^+) 378.16785, found 378.16790.

(7*R* 8*R*,8′*R*)-7-Hydroxysecoisolariciresinol (2a). δ_H (500 MHz, acetone-d_6, 30 °C) 1.83 (1H, m, H-8′), 1.86 (1H, m, H-8), 2.59 (1H, dd, J = 13.7, 8.1 Hz, H-7′b), 2.70 (1H, dd, J = 13.7, 6.6 Hz, H-7′a), 3.50–3.65 (2H, m, coupled to OH, H-9′a, H-9′b), 3.73 (3H, s, OMe′), 3.74 (3H, s, OMe), 3.83 (1H, m, coupled to OH, H-9a), 3.95 (1H, m, coupled to OH, H-9b), 4.87 (1H, broad dd, H-7), 6.54 (1H, dd, J = 2.0, 8.0 Hz, H-6′), 6.61 (1H, d, J = 2.0 Hz, H-2′), 6.69 (1H, d, J = 8.0 Hz, H-5′), 6.70 (1H, dd, J = 1.8, 8.0 Hz, H-6), 6.73 (1H, d, J = 8.0 Hz, H-5), 6.75 (1H, d, J = 1.8 Hz, H-2); δ_C (125 MHz, acetone-d_6, 30 °C) 36.97 (C-7′), 43.70 (C-8′), 48.81 (C-8), 55.87 (OMe), 55.92 (OMe), 60.48 (C-9), 62.60 (C-9′), 76.23 (C-7), 110.63 (C-2), 113.29 (C-2′), 114.97 (C-5), 115.31 (C-5′), 120.40 (C-6), 122.52 (C-6′), 133.39 (C-1′), 137.16 (C-1), 145.50 (C-4′), 146.39 (C-4), 148.07–148.1 (C-3, C-3′).

3.2 Synthesis of (7*S*,8*R*,8′*R*)-(+)-lariciresinol (3)

To a stirred solution of **2** (500 mg, 1.32 mmol, isomeric ratio 12 : 88 *R* : *S*) in dry THF (50 ml), was added $BF_3{\cdot}Et_2O$ (50 µl, (47% BF_3) in 5 ml dry CH_2Cl_2) as 100 µl portions every half an hour, in total 1.2 ml. The mixture was heated to 50 °C and stirred under Ar for 60 h. The reaction was then quenched by adding 3 ml triethylamine and the mixture was poured into a saturated NaCl solution (150 ml). The product was extracted with EtOAc (3 × 50 ml) and the EtOAc fractions were combined, washed with 50 ml water and dried over $NaSO_4$. The solvent was removed under reduced pressure and the residue chromatographed on a silica column ($CHCl_3$: MeOH, 99 : 1 v/v) yielding **2** (400 mg, 84%, purity by GC 98%) which was further crystallised from $CHCl_3$ as white small needles; mp 169–171 °C ($CHCl_3$); $[\alpha]_D^{24}$ = +26.2 (c 1.0 in MeOH); δ_H (500 MHz, $CDCl_3$, 30 °C) 2.40 (1H, dddd, J = 6.5, 6.6, 7.2, 7.3 Hz, H-8), 2.54 (1H, dd, J = 13.7, 10.7 Hz, H-7′b), 2.73 (1H, m, H-8′), 2.91 (1H, dd, J = 13.7, 5.2 Hz, H-7′a), 3.74 (1H, dd, J = 8.6, 6.3 Hz, H-9′a), 3.77 (1H, dd, J = 10.5, 6.5 Hz, H-9a), 3.86 (3H, s, OMe′), 3.87 (3H, s, OMe), 3.90 (1H, dd, J = 10.5, 7.3 Hz, H-9b), 4.05 (1H, dd, J = 8.6, 6.5 Hz, H-9′b), 4.78 (1H, d, J = 6.6 Hz, H-7), 5.55 (1H, s, 4-OH), 5.63 (1H, s, 4′-OH), 6.68 (1H, d, J = 2.0 Hz, H-2′), 6.69 (1H, dd, J = 2.0, 8.5 Hz, H-6′), 6.80 (1H, dd, J = 2.0, 8.1 Hz, H-6), 6.83 (1H, d, J = 8.5 Hz, H-5′), 6.86 (1H, d, J = 2.0 Hz, H-2), 6.86 (1H, dd, J = 8.1 Hz, H-5); δ_C (125 MHz, $CDCl_3$, 30 °C) 33.35 (C-7′), 42.44 (C-8′), 52.61 (C-8), 55.95 (OMe), 55.97 (OMe), 60.95 (C-9), 72.92 (C-9′), 82.86 (C-7), 108.37 (C-2), 111.25 (C-2′), 114.22 (C-5), 114.45 (C-5′), 118.78 (C-6), 121.22 (C-6′), 132.30 (C-1′), 134.82 (C-1), 144.05 (C-4′), 145.08 (C-4), 146.57 (C-3′), 146.67 (C-3); EIMS;

§ CCDC reference number 181809. See http://www.rsc.org/suppdata/p1/b2/b202493d/ for crystallographic files in .cif format.

m/z 360 (100%, M^+), 194 (24), 180 (16), 151 (29), 137 (76). HRMS; *m/z* calculated for $C_{20}H_{24}O_6$ (M^+) 360.157289, found 360.157600.

3.3 Synthesis of (7*S*,8*R*,8′*R*)-(+)-cyclolariciresinol (4)

Compound **2** (150 mg, 0.397 mmol, isomeric ratio 12 : 88 7*R* : 7*S*) was dissolved in 20 ml THF and 100 µl $BF_3{\cdot}Et_2O$ (47% BF_3) was added. The mixture was stirred under Ar and heated to 50 °C and an additional 100 µl $BF_3{\cdot}Et_2O$ was added after one hour and again after two hours. After 6 hours in total, 50 ml EtOAc followed by 3 ml triethylamine was added. The mixture was then poured into 50 ml NaCl solution and extracted with 50 ml EtOAc. The EtOAc fraction was washed with 50 ml water, dried over $NaSO_4$ and the solvent was removed under reduced pressure. The residue was precipitated from CH_2Cl_2 yielding **4** as a white powder (110 mg, 77%); mp 151–153 °C (CH_2Cl_2); $[\alpha]_D^{24}$ = + 65 (*c* 1.0 in acetone); δ_H (500 MHz, acetone-d_6, 30 °C) 1.78–1.85 (1H, m, H-8), 1.95–2.02 (1H, m, H-8′), 2.73 (1H, dd, *J* = 15.8, 5.1 Hz, H-7′a), 2.79 (1H, dd, *J* = 15.8, 10.8 Hz, H-7′b), 3.41 (1H, dd, *J* = 11.0, 4.4 Hz, H-9a), 3.67–3.73 (3H, dd,dd,dd, overlapping, H-9′a, H-9′b, H-9b), 3.77 (3H, s, OMe), 3.79 (3H, s, OMe′), 3.82 (1H, d, *J* = 10.1 Hz, H-7), 6.19 (1H, s, H-5′), 6.62 (1H, dd, *J* = 7.9, 2.0 Hz, H-6), 6.66 (1H, s, H-2′), 6.75 (1H, d, *J* = 2.0 Hz, H-2), 6.77 (1H, d, *J* = 7.9 Hz, H-5); δ_C (125 MHz, $CDCl_3$–acetone-d_6, 30 °C) 33.28 (C-7′), 40.15 (C-8′), 47.86 (C-7), 48.13 (C-8) 55.79, 55.85 (2 × MeO), 62.43 (C-9), 66.09 (C-9′), 110.59 (C-2′), 112.04 (C-2), 114.43 (C-5), 115.90 (C-5′), 122.28 (C-6), 127.57 (C-1′), 132.96 (C-6′), 137.34 (C-1), 143.87 (C-4′), 144.41 (C-4), 145.23 (C-3′), 147.02 (C-3). EIMS; *m/z* (TMS-ethers) 648 (7%, M^+), 633 (4), 558 (12), 527 (22), 468 (18), 455 (50), 437 (25), 209 (26).

3.4 Synthesis of (+)-lariciresinol (3) with methanolic H_2SO_4 in THF

To a stirred solution of **2** in 25 ml THF (233 mg, 0.616 mmol isomeric ratio 12 : 88 7*R* : 7*S*) was added 200 µl 5% H_2SO_4 in MeOH at room temperature. One hour later, additional 5% H_2SO_4 in MeOH (200 µl) was added and the reaction was stirred for 1 h more. Then 2 ml triethylamine was added, the mixture was poured into a saturated NaCl solution (50 ml) and extracted with EtOAc (3 × 50 ml). The EtOAc fractions were combined, dried over $NaSO_4$ and the solvent was removed under reduced pressure. The residue was chromatographed on a silica column ($CHCl_3$: MeOH, 99 : 1 v/v) yielding **3** (185 mg, 83.4%). Purity by GC 98%.

3.5 Transformation of (+)-lariciresinol (3) to (+)-cyclolariciresinol (4)

Lariciresinol (**3**) (120 mg, 0.333 mmol) was dissolved in 15 ml dry THF. To the solution was added MeOH–H_2SO_4 (5% H_2SO_4 in MeOH, 1.5 ml) portionwise under stirring at room temperature. The mixture was then heated to 45 °C and stirred for 4 h. The reaction was quenched with triethylamine (3 ml) and the mixture was poured into a saturated NaCl solution. The mixture was extracted with EtOAc (3 × 50 ml), the organic phase was dried over $NaSO_4$ and the solvent removed under reduced pressure. The residue was crystallised from $CHCl_3$ yielding **4** (112 mg, 93%). Purity by GC 98.6%.

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