Synthesis of (1R,2S)-2-(4′-allyl-2′,6′-dimethoxyphenoxyl)-1-(4′′-hydroxy-3′′,5′′-dimethoxyphenyl)propan-1-ol

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The asymmetric synthesis of the natural neolignan (1*R*,2*S*)-2-(4′-allyl-2′,6′-dimethoxyphenoxyl)-1-(4′′-hydroxy-3′′,5′′-dimethoxyphenyl)propan-1-ol based on an asymmetric dihydroxylation as a key reaction using AD-mix-β to preparing the chiral *threo*-(1*R*,2*R*)-glycerol. The reaction, *threo*-alcohols were inverted by an S_N2 reaction into *erythro*-(1*R*,2*S*)-isomers.

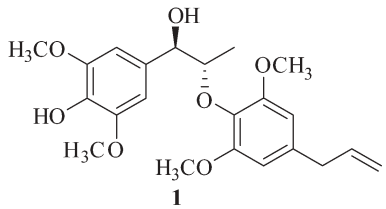
Keywords: synthesis, enantioselectivity, neolignan

The aril of *Myristica fragrans* Houtt. (Myristicaceae) has been widely used as a spice and a valuable remedy in Ayurvedic medicine for the treatment of low levels of fever, in consumptive complaints, asthma, and when mixed with aromatics, in wasting and long-term bowel complaints.[1–4] In 1987, a new *erythro*-bisphenylpropanoid 2-(4′-allyl-2′,6′-dimethoxyphenoxyl)-1-(4″-hydroxy-3″,5″-dimethoxyphenyl)propan-1-ol (**1**) was obtained from the aril of *Myristica fragrans*, and shown to be a 8-*O*-4′-neolignan.[5] 8-O-4′-neolignans are a very interesting class of natural products because of their pharmacological properties, and they have been shown to have antioxidant, antimalarial and antileishmanial activities.[6–8] The synthesis of 8-*O*-4′-neolignans has been accomplished by several methods, the majority of which have given racemic mixtures of *threo*- and *erythro*-isomers.[9–12] Zacchino reported the stereoselective synthesis of *threo*-8-O-4′-neolignan, by selecting the appropriate starting materials, and using the mould *Rhizopus nigricans* to obtain the natural product Virolin and to establish its configuration.[13] Recently, the development of a truly general and modular asymmetric route to *threo*- and *erythro*-8-*O*-4′-neolignans compound class was outlined in a nine-step sequence.[14]

An effective approach is described here for the synthesis of *erythro*-8-*O*-4′-neolignans based on a key reaction using AD-mix-β to prepare chiral *threo*-(1*R*,2*R*)-glycerols and then by an S_N2 reaction, to invert the *threo*-alcohols to the *erythro*-isomers. (1*R*,2*S*)-2-(4′-Allyl-2′,6′-dimethoxyphenoxyl)-1-(4″-hydroxy-3″,5″-dimethoxyphenyl)propan-1-ol (**1**) was obtained using this product.

Results and discussion

As shown in Scheme 2, synthesis of the first part began from compound **2**. Demethylation of 3,4,5-trimethoxybenzaldehyde(**2**) by treatment with piperidine and H_2O yielded compound **3**. This method was effective to cleave the 4-O-methyl group of 3,4,5-trimethoxybenzaldehyde(**2**), whilst the 3-O-methyl ether and 5-O-methyl ethers were stable under these conditions.[15] Protection of **3** with benzyl chloride afforded compound **4**. A Wittig reaction was carried out between compound **4** and $(Ph)_3PCHCOOEt$, to give the unsaturated ester (E)-**5**. Reduction of (E)-**5** with AlH_3 which was prepared from LAH/$AlCl_3$ gave the corresponding unsaturated alcohol (E)-**6** in good yield. AlH_3 can selectively reduce esters without reducing alkenes. Asymmetric dihydroxylation of **6** with AD-mix-β formed two chiral centres and gave threo-(1R,2R)-7.[16] Treatment of **7** with TsCl in pyridine provided threo-(1R,2R)-**8**. Because of steric hindrance, this reaction only occurred at the primary hydroxyl of **7** with Tscl.[17] Epoxide formation by treatment with base yielded threo-(1R,2R)-**9**. The hydroxy group of **9** was protected by DHP, and then ring opening by $LiAlH_4$ in THF gave threo-(1R, 2R)-**10**. The benzyl group of compound **10** was removed, and then the hydroxyl group was protected with MOMCl to give the key intermediate threo-(1R, 2R)-**11**.



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Scheme 1

As shown in Scheme 3, 4-allyl-2,6-dimethoxyphenol (**15**) was obtained, following a procedure which has been described previously.[17]

As shown in Scheme 4, a Mitsunobu reaction between *threo*-(1*R*,2*R*)-**11** and compound **15** gave the *erythro*-configuration, and the absolute configuration at the C-8 chiral centre was inverted completely from *R*- to *S*-configuration.[18] Then, the THP and MOM group were cleaved by HCl in MeOH and the natural product (−)-(1*R*,2*S*)-2-(4′-Allyl-2′,6′-dimethoxyphenoxyl)-1-(4-hydroxy-3,5-dimethoxyphenyl) propan-1-ol (**1**) was obtained.

In conclusion, we have demonstrated the validity of our methodology for the preparation of *erythro*-8-*O*-4′-neolignans by the synthesis of (−)-(1*R*,2*S*)-2-(4′-allyl-2′,6′-dimethoxyphenoxyl)-1-(4″-hydroxy-3″,5″-dimethoxyphenyl)propan-1-ol (**1**).

Experimental

Melting points were taken on Gallenkamp melting point apparatus and are uncorrected. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. Chrial analysis was performed on Varian Dynamax SD-300 using chiralcel column CDMPC (150 × 4.6 mm D) with hexane/isopropyl alcohol as eluant. IR spectra were recorded on a Nicolet NEXUS 670 FT−IR. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Mercury Plus−300 MHz and Bruker–500 MHz spectrometers. Mass spectra were recorded on a ZAB−HS spectrometer. HRMS were obtained on a Bruker Daltonics APEXII47e spectrometer. Flash column chromatography was performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF254 plates.

4-Hydroxy-3,5-dimethoxybenzaldehyde (**3**): A solution of 3,4,5-trimethoxy benzaldehyde(**2**) (15.6 g, 80 mmol) in piperidine/H_2O (1:1, 100 mL) was heated under reflux for 48 h and the cooled mixture was poured into 4 N HCl. The mixture was extracted with AcOEt. The organic layer was dried over $MgSO_4$, filtered, then concentrated *in vacuo*. Flash column chromatography of residue gave compound **3** as a white crystal (10.5 g, 72%). M.p. 111−112 °C. ^{1}H NMR (200 MHz, $CDCl_3$), δ: 3.97 (s, 6H, 2 × OCH_3), 7.16 (s, 2H, ArH), 9.82 (s, 1H, CHO). EI-MS, *m/z*: 182 (M^+, 12.3), 167 (2.8), 139 (14.7), 91 (5.7), 65 (100).

4-Benzyloxy-3,5-dimethoxybenzaldehyde (**4**): To a well-stirred solution of K_2CO_3 (7.0 g, 50 mmol) and compound **3** (9.0 g, 50 mmol) in ethanol was added dropwise benzyl chloride (5.0 g, 50 mmol).The mixture was stirred and warmed to reflux for 4 h, then concentrated *in vacuo*. The residue was dissolved in AcOEt (100 mL), filtered, and

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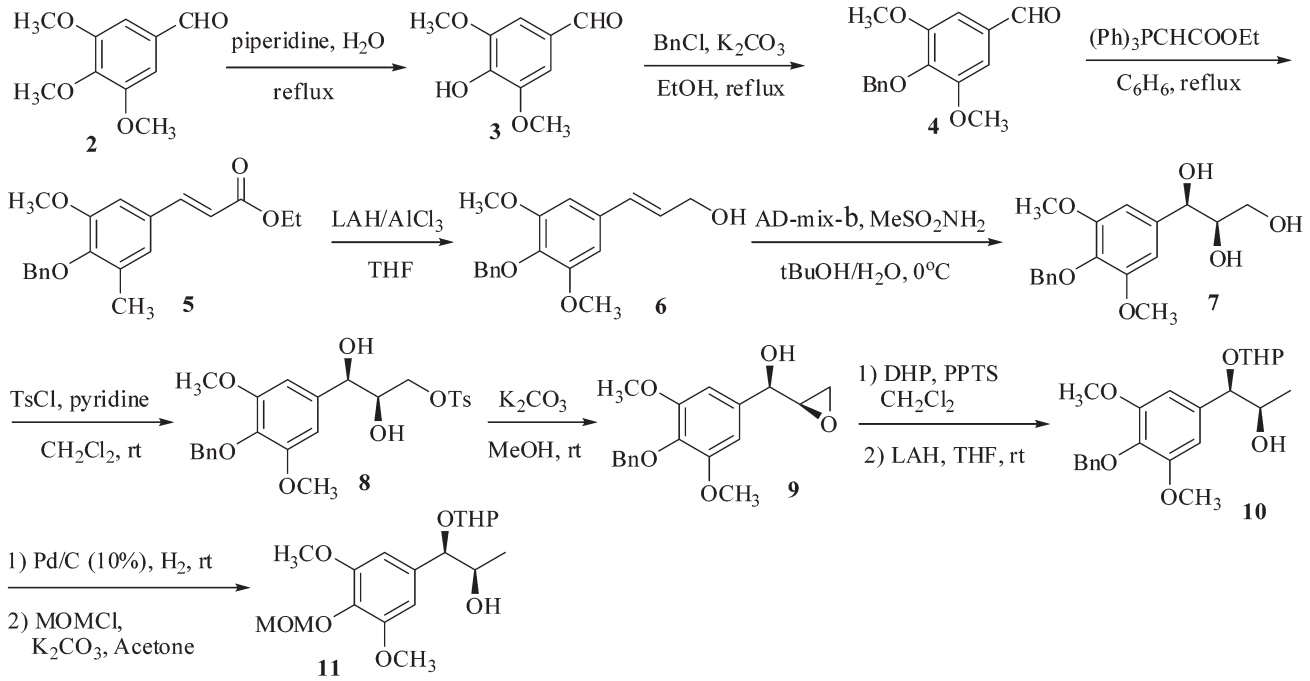
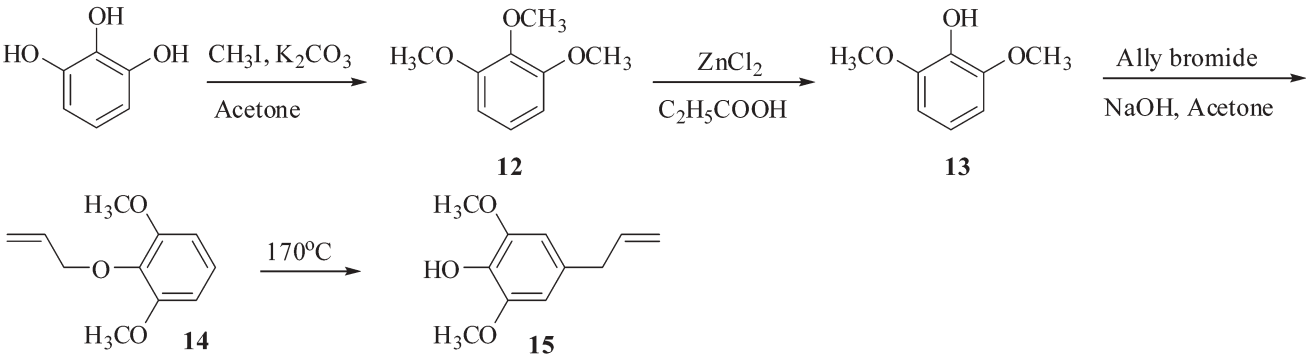
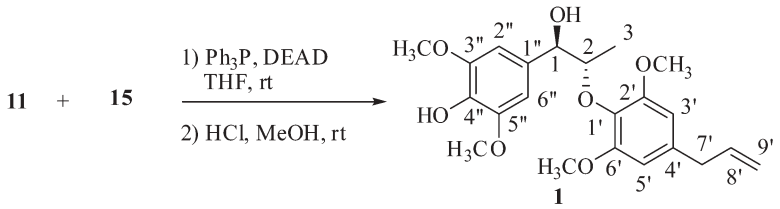


Scheme 2



Scheme 3



Scheme 4

washed with 10% aqueous NaOH and NaCl saturated solution for 3 times respectively. The extract was dried over $MgSO_4$, filtered, then concentrated *in vacuo* to remove AcOEt. The solids were recrystallised in C_2H_5OH to yield the compound **4** as a colourless crystal (12.2 g, 90%). M.p. 89–91 °C. ^{1}H NMR (200 MHz, DMSO-d_6), δ: 3.94 (s, 6H, 2 × OCH_3), 5.17 (s, 2H, $ArCH_2O$), 7.18 (s, 2H, ArH), 7.23–7.64 (m, 5H, Ar-H), 9.84 (s, 1H, CHO). EI-MS, *m/z*: 272 (M^+, 5.2), 257 (12.7), 229 (2.8), 91 (100), 51 (28.2).

*Ethyl (*E*)-4-benzyloxy-3,5-dimethoxyphenylcinnamate* (**5**): The compound **4** (10.9 g, 40 mmol) and $(Ph)_3PCHCOOEt$ (13.9 g, 40 mmol) in dry benzene was refluxed for 10 h, and then concentrated *in vacuo*. Flash column chromatography of the residue gave compound **5** as a white crystal (10.3 g, 75%). M.p. 71–72 °C (lit.[19] m.p. 69 °C.). ^{1}H NMR (200 MHz, $CDCl_3$), δ: 1.35 (t, 3H, *J* = 7.5 Hz, $COCH_2CH_3$), 3.85 (s, 6H, 2 × OCH_3), 4.26 (q, 2H, *J* = 7.5 Hz, $COCH_2CH_3$), 5.05 (s, 2H, $ArCH_2O$), 6.35 (d, 1H, *J* = 16.0 Hz, ArCH=C*H*), 6.74 (s, 2H, ArH), 7.30–7.52 (m, 5H, ArH), 7.60 (d, 1H, *J* = 16.0 Hz, ArC*H*=CH). EI-MS, *m/z*: 342 (M^+, 11.4), 297 (19.7), 251 (4.5), 91 (100).

*(*E*)-4-benzyloxy-3,5-dimethoxyphenylcinnamyl alcohol* (**6**): Dry $AlCl_3$ (3.4 g, 25 mmol) was added at 0 °C, to a suspension of $LiAlH_4$ (1.0 g, 25 mmol) in dry THF (40 mL), the and stirred for 20 min to obtain the reagent AlH_3. Then compound **5** (8.6 g, 25 mmol) was added. The mixture was stirred for 10 h at room temperature, and then quenched with H_2O, filtered, and concentrated *in vacuo*. Flash column chromatography of residue gave **6** as a colourless oil (6.5 g, 86%). ^{1}H NMR (200 MHz, $CDCl_3$): 3.81 (s, 6H, 2 × OCH_3), 4.28 (d, 2H, *J* = 5.5 Hz, CH_2OH), 5.01 (s, 2H, $ArCH_2O$), 6.25 (dt, 1H, *J* = 5.5, 15.5 Hz, ArCH=C*H*), 6.51 (d, 1H, *J* = 15.5 Hz, ArC*H*=CH), 6.60 (s, 2H, ArH), 7.27–7.52 (m, 5H, ArH). EI-MS, *m/z*: 300 (M^+, 8.3), 209 (12.1), 177 (4.7), 121 (15.3), 91 (100).

threo-*(1R,2R)-1-(4′-Benzyloxy-3′,5′-dimethoxyphenyl)-1,2,3-glycerol* (**7**): AD-mix-β (27.8 g), $MeSO_2NH_2$ (2.0 g) were added to a stirred solution of t-BuOH (40 mL) and H_2O (40 mL), the mixture was stirred at room temperature until both phases were clear, and then cooled to 0 °C. Compound **6** (6.0 g, 20 mmol) was added at once, and the mixture was stirred vigorously at 0 °C until TLC revealed the absence of **6**. The reaction was quenched at 0 °C by addition of Na_2SO_3 (30 g),

then warmed to room temperature and stirred for 0.5 h. The reaction mixture was extracted with AcOEt (3 × 50 mL) and dried over $MgSO_4$, then the AcOEt was distilled off. Flash chromatography of the residue over silica gel gave compound **7** (6.0 g, 90%) as a white crystal in 93% e.e.. M.p. 77–78 °C. $[\alpha]_D^{20} = -18$ (c 1.6, $CHCl_3$) (lit.[20] m.p. 78 °C. $[\alpha]_D^{20} = -18$.). IR (KBr/cm^{-1}): 3440, 2943, 2835, 1645, 1515, 1462, 1150. ^{1}H NMR (300 MHz, $CDCl_3$): 3.45–3.52 (m, 2H, CH_2OH), 3.74–3.76 (m, 1H, C*H*OHCH$_2$OH), 3.77 (s, 6H, 2 × OCH$_3$), 4.55 (d, *J* = 6.5 Hz, 1H, ArC*H*OH), 4.96 (s, 2H, ArCH$_2$OAr), 6.55 (s, 2H, ArH), 7.30–7.52 (m, 5H, ArH). EI-MS, *m/z*: 334 (M$^+$, 1.8), 273 (3.9), 183 (15.7), 123 (4.8), 91 (100).

threo-*(1R,2R)-1-(4′-Benzyloxy-3′3′,5′-dimethoxyphenyl)-3-O-tosyl-1,2-glycol* (**8**): Compound **7** (5.0 g, 15 mmol) and pyridine (15 mL) were added at room temperature to a solution of TsCl (2.9 g, 15 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred vigorously until TLC revealed the absence of **7**. The mixture was quenched with HCl solution, and then extracted with AcOEt. The organic layer was washed with $NaHCO_3$ and NaCl saturated solution respectively, then was dried over $MgSO_4$ and concentrated *in vacuo*. Flash chromatography of the residue over silica gel gave compound **8** (6.4 g, 87%) as a white powder. M.p. 122–124 °C. $[\alpha]_D^{20} = -10$ (c 1.5, $CHCl_3$) (lit.[20] m.p. 123 °C. $[\alpha]_D^{20} = -10$.). IR (KBr/cm^{-1}): 3438, 2927, 2835, 1640, 1521, 1420, 1318, 1235, 1106, 1025. ^{1}H NMR (300 MHz, $CDCl_3$): 2.44 (s, 3H, ArCH$_3$), 3.79 (s, 6H, 2 × OCH$_3$), 3.84–3.90 (m, 1H, C*H*OHCH$_2$OTs), 3.95–4.03 (m, 2H, CH_2OTs), 4.60 (d, 1H, *J* = 6.0 Hz, ArC*H*OH), 4.98 (s, 2H, ArCH$_2$OAr), 6.55 (s, 2H, ArH), 7.30–7.76 (m, 9H, ArH). EI-MS, *m/z*: 488 (M$^+$, 2.1), 470 (5.3), 424 (1.5), 334 (13.2), 172 (25.8), 91 (100).

threo-*(1R,2R)-1-(4′-Benzyloxy-3′,5′-dimethoxyphenyl)-2,3-epoxy-1-propanol* (**9**): Compound **8** (4.9 g, 10 mmol) was added to a solution of K_2CO_3 (2.1 g, 15 mmol) in methanol. The mixture was stirred at room temperature for 5 h, and then the reaction mixture was concentrated *in vacuo*. The residue was dissolved in AcOEt and washed with water and NaCl saturated solution for 3 times respectively.The extract was dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue over silica gel gave compound **9** (2.8 g, 88%). M.p. 98–100 °C. $[\alpha]_D^{20} = -8$ (c 1.0, $CHCl_3$) (lit.[20] M.p. 100 °C. $[\alpha]_D^{20} = -8$.). IR (KBr/cm^{-1}): 3448, 2940, 2836, 1735, 1604, 1592, 1515, 1459, 1250, 1137, 1024. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.81–2.88 (m, 2H, CHOCH_2), 3.18–3.25 (m, 1H, C*H*CH$_2$O), 3.81 (s, 6H, 2 × OCH$_3$), 4.43 (d, 1H, *J* = 5.5 Hz, ArC*H*OHCH), 5.00 (s, 2H, ArCH$_2$OAr), 6.65 (s, 2H, ArH), 7.32–7.54 (m, 5H, ArH). EI-MS, *m/z*: 316 (M$^+$, 7.2), 225 (1.5), 153 (12.6), 91 (100).

threo-*(1R,2R)-1-(4′-Benzyloxy-3′,5′-dimethoxyphenyl)-1-O-2″-tetrahydropyrane-2-propanol* (**10**): DHP(0.7 g, 7 mmol), and a catalytic amount of PPTS were added to a solution of compound **9** (2.2 g, 7 mmol) in dry CH_2Cl_2. The mixture was stirred at room temperature until TLC revealed the absence of **9**. Then the mixture was concentrated *in vacuo*. The residue was added to a solution of $LiAlH_4$ (0.4 g, 10 mmol) in dry THF. The mixture was stirred at room temperature for 24 h. The mixture was quenched with H_2O, filtered and concentrated *in vacuo*. Flash column chromatography of the residue over silica gel gave compound **10** (2.1 g, 75%) as colourless oil. IR (KBr/cm^{-1}): 3420, 2938, 2846, 1598, 1515, 1448, 1409, 1380, 1257, 1135, 1065, 1028. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 1.05 (d, 3H, *J* = 6.8 Hz, OHCHCH_3), 1.45–1.75 (m, 6H, CH$_2$), 3.16–3.24 (m, 1H, CH$_2$CH_2O), 3.41–3.49 (m, 1H, CH$_2$CH_2O), 3.83 (s, 6H, 2 × OCH$_3$), 3.86–4.03 (m, 1H, C*H*OHCH$_3$), 4.16 (d, 1H, *J* = 7.0 Hz, ArCHOTHP), 4.84– 4.93 (m, 1H, OCHO), 5.01 (s, 2H, ArCH$_2$OAr), 6.58 (s, 2H, ArH), 7.30–7.65 (m, 5H, ArH). EI-MS, *m/z*: 402 (M$^+$, 1.5), 358 (2.4), 312 (8.3), 151 (4.2), 91 (100). HRMS Calcd for $C_{23}H_{31}O_6$ (M + H$^+$): 403.2116. Found: 403.2118.

threo-*(1R,2R)-1-(3′,5′-Dimethoxy-4′-methoxymethoxyphenyl)-1-O-2″-tetrahydropyrane-2-propanol* (**11**): 10% palladised charcoal (80 mg) was added to a stirred solution of compound **10** (2.0 g, 5 mmol) in methanol (20 mL). After stirring for 4 h at room temperature under atmospheric pressure of hydrogen, the solvent was filtered and concentrated under reduced pressure. A solution of MOMCl (0.5 g, 5 mmol) was added all at once to a rapidly stirred mixture of the residue and K_2CO_3 (0.9 g, 6 mmol) in 20 mL acetone under N_2 at room temperature. This was allowed to stir for 3 h and quenched with H_2O. The aqueous layer was extracted with ethyl acetate. The extracts were washed (brine), dried with Na_2SO_4, the solvent was removed *in vacuo* and flash column chromatography of the residue over silica gel gave compound **11** (1.2 g, 70%) as a gum. IR (KBr/cm^{-1}): 3448, 2935, 2836, 1595, 1515, 1460, 1382, 1257, 1130, 1024. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.06 (d, 3H, *J* = 7.0 Hz, OHCHCH_3), 1.44–1.75 (m, 6H, CH$_2$), 3.12–3.20 (m, 1H, CH$_2$CH_2O), 3.39–3.45 (m, 1H, CH$_2$CH_2O), 3.50 (s, 3H, OCH$_3$), 3.83–4.05 (m, 7H, C*H*OHCH$_3$, 2 × OCH$_3$), 4.14 (d, 1H, *J* = 7.5 z, ArCHOTHP), 4.86–4.92 (m, 1H, OCHO), 5.23 (s, 2H, CH$_3$OCH_2OAr), 6.56 (s, 2H, ArH). EI-MS, *m/z*: 356 (M$^+$, 0.8), 338 (1.6), 310 (10.7), 293 (5.2), 91 (100). HRMS Calcd for $C_{18}H_{32}NO_7$ (M + NH$_4^+$): 374.2174. Found: 374.2170.

(1R,2S)-2-(4′-Allyl-2′,6′-dimethoxyphenoxyl)-1-(4″-hydroxyl-3″, 5″-dimethoxyphenyl) propan-1-ol (**1**): A mixture of (1*R*,2*R*)-**11** (0.7 g, 2 mmol), compound **15** (0.4 g, 2 mmol), triphenylphosphine (0.6 g, 2 mmol) and diethylazodicarboxylate (0.3 mL, 2 mmol) was stirred in dry THF (30 mL) at room temperature for 24 h under nitrogen. The mixture was concentrated under reduced pressure. The residue was added to a solution of HCl in MeOH (1 N, 30 mL), and the mixture was stirred at room temperature for 8 h. The solution was neutralised with $NaHCO_3$ saturated solution. Subsequently the solvent was concentrated *in vacuo* and the residue was taken up in AcOEt. The organic phase was washed with H_2O, dried with $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography of the residue over silica gel gave product **1** (0.30 g, 38%) as gum. $[\alpha]_D^{20} = -12.5$ (c 0.1, $CHCI_3$). IR (KBr/cm^{-1}): 3450, 2936, 2840, 1615, 1540, 1525, 1250, 1026. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 1.12 (d, 3H, *J* = 6.5 Hz, H-3), 3.37 (d, 2H, *J* = 6.5 Hz, H-7′), 3.86 (s, 6H, 2 × OCH$_3$), 3.87 (s, 6H, 2 × OCH$_3$), 4.27–4.35 (m, 1H, H-2), 4.78 (d, 1H, *J* = 3.0 Hz, H-1), 5.10–5.18 (m, 2H, H-9′), 5.92–6.08 (m, 1H, H-8′), 6.46 (s, 2H, H-3′, H-5′), 6.55 (s, 2H, H-2″, H-6″). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 12.6 (C-3), 40.5 (C-7′), 56.1 (2 × OCH$_3$), 56.3 (2 × OCH$_3$), 73.2 (C-2), 82.4 (C-1), 103.1 (C-2″, C-6″), 105.7 (C-3′, C-5′), 116.1 (C-9′), 131.2 (C-4′), 133.7 (C-1″), 136.2 (C-1′), 137.0 (C-8′), 140.1 (C-4″), 147.1 (C-3″, C-5″), 153.5 (C-2′, C-6′). EI-MS, *m/z*: 404 (M$^+$, 4.6), 386 (10.5), 221 (17.8), 194 (100). HRMS Calcd for $C_{22}H_{29}O_7$ (M + H$^+$): 405.1908. Found: 405.1911. The data were agreement with those reported in the literature.[5]

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