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ORIGINAL PAPER

Asymmetric synthesis of the natural *erythro*-(1*R*,2*S*)-8-*O*-4′-neolignan myrislignan

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Abstract An efficient and practical asymmetric synthesis of *erythro*-(1*R*,2*S*)-8-*O*-4′-neolignan myrislignan was achieved by using vanillin and pyrogallic acid as the starting materials. Two key steps are involved: preparation of an enantiopure *threo* alcohol of predictable stereochemistry by dihydroxylation with AD-mix-β, and inversion of the absolute configuration from the *threo* to the *erythro* isomer using a Mitsunobu reaction. The route illustrates a new methodology for the synthesis of *erythro*-8-*O*-4′-neolignan.

Keywords Asymmetric dihydroxylation · Myrislignan · Neolignan · Mitsunobu reaction

Introduction

Myrislignan is found in the seeds (nutmeg) or aril (mace) of *Myristica fragrans* Houtt (Myristicaceae) used as traditional Chinese medicine in China and Japan owing to its carminative, anxiogenic, and anti-ulcerogenic activities [1, 2]. Since *erythro*-(1*R*,2*S*)-myrislignan was discovered in 1973, it has attracted increasing interest because of its biological activities. Various studies suggest that it may affect hepatic mixed-function oxidase enzyme activity and have antifungal properties [3–5]. In 2006, Yang reported the biotransformation of myrislignan by rat liver microsomes in vitro [6].

erythro-(1*R*,2*S*)-Myrislignan belongs to the very interesting class of 8-*O*-4′-neolignans, and nature offers an extensive library of representatives of the class [7]. However, obtaining supplies from nature is an arduous task because of the low quantity of isolable compounds and the fact that most of the isolated neolignans reported are racemic mixtures [8]. On the other hand, the alternative of obtaining useful quantities of enantiopure materials via synthesis has not been carefully pursued. Most of the pioneering synthetic studies afforded racemic mixtures of *threo*- and *erythro*-configured products, while existing enantioselective routes appear limited by low overall efficiency and poorly enantioselective processes; most of asymmetric synthesis gave *threo*-8-*O*-4′-neolignans [9–13].

Herein, an efficient asymmetric synthesis of *erythro*-8-*O*-4′-neolignans is presented. The synthetic route involved two key steps: preparation of an enantiopure *threo* alcohol of predictable stereochemistry by dihydroxylation with AD-mix-β, and inversion of the absolute configuration from *threo* to *erythro* using a Mitsunobu reaction. By this method the *erythro*-(1*R*,2*S*)-8-*O*-4′-neolignan myrislignan was obtained for the first time.

Results and discussion

As shown in Scheme 1, synthesis of the target compound started from vanillin. Protection of the hydroxyl group with benzyl chloride afforded compound **2** [14]. A Wittig reaction between compound **2** and $Ph_3PCHCOOEt$ gave the unsaturated ester (*E*)-**3** [15]. Reduction of (*E*)-**3** with $LiAlH_4$ afforded the corresponding unsaturated alcohol (*E*)-**4** in high yields. Asymmetric dihydroxylation of compound **4** with AD-mix-β directly afforded *threo*-(1*R*,2*R*)-**5** in 93% ee [16], i.e., with creation of two adjacent stereocenters with *threo* configuration [17]. Treatment of *threo*-(1*R*,2*R*)-**5** with *p*-toluenesulfonyl chloride in

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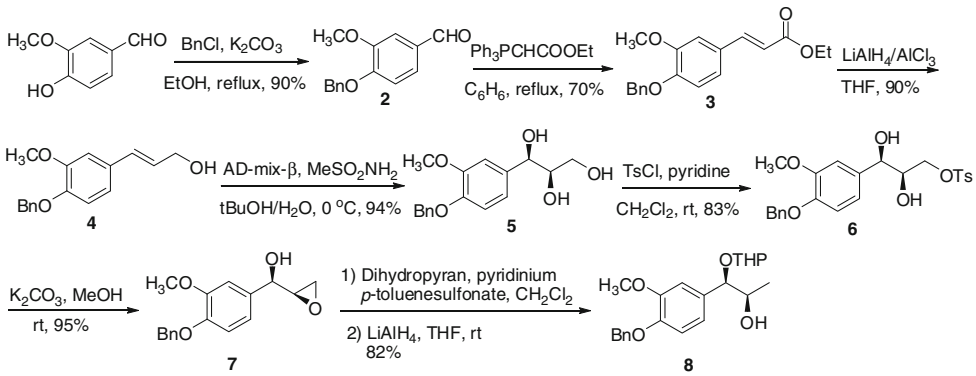
Scheme 1



pyridine provided the primary tosylate *threo*-(1*R*,2*R*)-**6**. As a result of steric hindrance, only the primary hydroxyl group of *threo*-(1*R*,2*R*)-**5** was tosylated. Ring closure of (1*R*,2*R*)-**6** was promoted by K_2CO_3 in methanol, generating the oxirane (1*R*,2*R*)-**7**. The hydroxyl group of **7** was protected with dihydropyran to afford the corresponding tetrahydropyran (THP) ether, followed by oxirane reduction using $LiAlH_4$ to give *threo*-(1*R*,2*R*)-**8** in 82% yield.

As shown in Scheme 2, trimethylation of pyrogallic acid with CH_3I afforded compound **9**. Selective cleavage of the 2-*O*-methyl ether in compound **9** by $ZnCl_2$ in propionic acid gave compound **10**; the 1-*O*- and 3-*O*-methyl ethers were stable under these reaction conditions. The reaction of **10** and allyl bromide afforded compound **11**. The Claisen rearrangement of allyl phenyl ether **11** at 170 °C produced *p*-allylphenol **12** [18]. This reaction was also accelerated by pressure.

The benzyl group of compound **8** was removed by hydrogenolysis, then the resulting phenol was protected with methoxymethyl chloride (MOMCl) to afford *threo*-(1*R*,2*R*)-**13**. Mitsunobu reaction between *threo*-(1*R*,2*R*)-**13** and compound **12** gave a product with *erythro* configuration, where the absolute configuration at the C-8 stereogenic center was inverted completely by the S_N2-type nucleophilic displacement by **12** (>92% ee) [19]. Then, the MOM and THP groups were cleaved by HCl in MeOH and (1*R*,2*S*)-myrislignan **1** was obtained as a single *erythro* isomer in 62% yield. The total yield of compound **1** is 9.7%. The data of **1** were in agreement with those reported in the literature [5, 20].

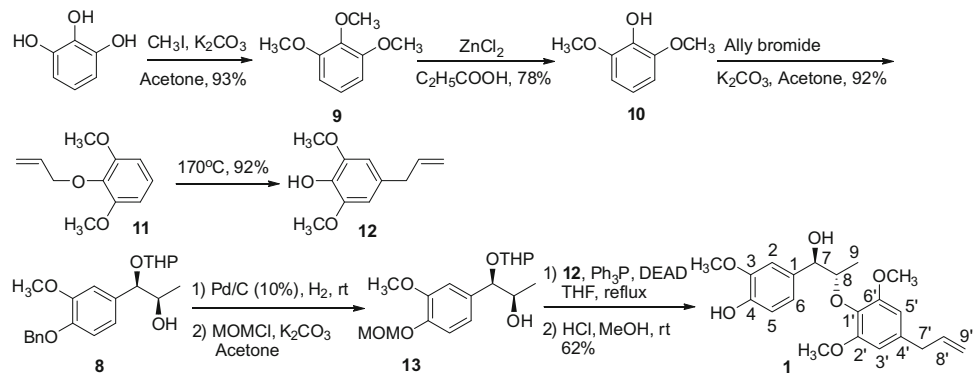
Experimental

Melting points were taken on a Gallenkamp melting point apparatus. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. Chiral analysis was performed on a Varian Dynamax SD-300 using chiralcel column CDMPC (150 × 4.6 mm ID) with hexane/isopropyl alcohol as eluent. Infrared spectra were recorded on a Nicolet NEXUS 670 FT-IR. The ^1H NMR and ^{13}C NMR spectra were recorded on 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 plates (GF_{254}).

threo-(1R,2R)-1-(4-Benzyloxy-3-methoxyphenyl)-3-O-tosyl-1,2,3-propanetriol (**6**, $C_{24}H_{26}O_7S$)

Compound **5** (6.1 g, 20 mmol) and 20 cm^3 pyridine were added to a solution of 3.8 g *p*-toluenesulfonyl chloride (20 mmol) in 70 cm^3 CH_2Cl_2 at room temperature. The mixture was stirred vigorously until TLC revealed the absence of **5**, then quenched with HCl solution and

Scheme 2



extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and NaCl solution, dried over $MgSO_4$, and concentrated in vacuo. Flash chromatography of the residue over silica gel afforded 7.6 g (83%) **6** as amorphous powder with 95% ee. Mp: 130–132 °C; $[\alpha]_D^{20} = +42.3°$ cm^3 g^{-1} dm^{-1} ($c = 0.5$, $CHCl_3$); IR (KBr): $\bar{\nu} =$ 3,420, 2,941, 2,845, 1,641, 1,520, 1,422, 1,318, 1,235, 1,102, 1,023 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.44$ (s, 3H, $ArCH_3$), 3.90 (s, 3H, $ArOCH_3$), 3.84–3.96 (m, 1H, C*H*OHCH$_2$OTs), 3.98–4.11 (m, 2H, CH_2OTs), 4.60 (d, 1H, $J = 6.0$ Hz, ArC*H*OH), 5.14 (s, 2H, $ArCH_2OAr$), 6.72–7.76 (m, 12H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.6$ ($ArCH_3$), 56.0 (OCH_3), 70.3 (CH_2OTs), 70.9 (*C*HOHCH$_2$OTs), 73.4 ($ArCH_2OAr$), 73.7 (Ar*C*HOHCH), 109.9, 113.7, 118.8, 127.2, 127.2, 127.9, 127.9, 128.6, 128.6, 129.9, 129.9, 132.5, 132.5, 136.9, 136.9, 146.1, 148.1, 149.8 ppm; EI-MS: $m/z = 458$ (M^+, 2.4), 286 (1.2), 268 (0.7), 243 (4.8), 123 (7.8), 91 (100); HRMS: calcd for $C_{24}H_{30}NO_7S$ ($M + NH_4^+$) 476.1738, found 476.1732.

threo-(1R,2R)-1-(4-Benzyloxy-3-methoxyphenyl)-2,3-epoxy-1-propanol (**7**, $C_{17}H_{18}O_4$)

Compound **6** (6.9 g, 15 mmol) was added to a solution of 2.1 g K_2CO_3 (15 mmol) in methanol. The mixture was stirred at room temperature for 5 h and concentrated in vacuo. The residue was dissolved in EtOAc, then washed with water and saturated NaCl aqueous solution for three times. The extract was dried over $MgSO_4$ and concentrated in vacuo. Flash column chromatography of the residue over silica gel afforded 4.1 g (95%) **7** as a colorless liquid in 92% ee. $[\alpha]_D^{20} = +36.2°$ cm^3 g^{-1} dm^{-1} ($c = 0.6$, $CHCl_3$); IR (KBr): $\bar{\nu} =$ 3,450, 2,983, 2,936, 2,840, 1,732, 1,604, 1,592, 1,512, 1,465, 1,262, 1,140, 1,027, 916 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.80$–2.89 (m, 2H, CHOCH_2), 3.16–3.25 (m, 1H, C*H*CH$_2$O), 3.97 (s, 3H, OCH_3), 4.43 (d, 1H, $J = 5.8$ Hz, ArC*H*OHCH), 5.17 (s, 2H, $ArCH_2OAr$), 6.87–7.45 (m, 8H, ArH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 45.6$ (CH*C*H$_2$O), 56.2 (OMe-3), 56.7 (*C*HCH$_2$O), 71.3 ($ArCH_2OAr$), 74.8 (Ar*C*HOHCH), 109.3, 113.9, 121.5, 126.7, 127.2, 127.2, 127.9, 128.5, 128.5, 137.1, 147.3, 149.6 ppm; EI-MS: $m/z = 286$ (M^+, 5), 243 (0.7), 165 (0.4), 123 (0.2), 91 (100); HRMS: calcd for $C_{17}H_{22}NO_4$ ($M + NH_4^+$) 304.1544, found 304.1547.

threo-(1R,2R)-1-(4-Benzyloxy-3-methoxyphenyl)-1-(tetrahydropyran-2-yloxy)-2-propanol (**8**, $C_{22}H_{28}O_5$)

Dihydropyran (0.9 g, 10 mmol) and a catalytic amount of pyridinium *p*-toluenesulfonate were added to a solution of 2.9 g **7** (10 mmol) in dry CH_2Cl_2 and the mixture was stirred at room temperature until TLC revealed the absence of **7**. Then the solvent was evaporated under reduced pressure and the residue was added to a solution of 0.6 g $LiAlH_4$ (15 mmol) in an appropriate amount of dry THF. The mixture was stirred at room temperature for 24 h, quenched with water, filtered, and concentrated in vacuo. Flash column chromatography of the residue over silica gel gave 3.1 g (82%) **8** as a colorless liquid in 93% ee. $[\alpha]_D^{20} = +31.8°$ cm^3 g^{-1} dm^{-1} ($c = 0.3$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3{,}418$, 2,936, 2,869, 1,593, 1,513, 1,457, 1,418, 1,380, 1,263, 1,226, 1,137, 1,075, 1,028, 809 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (d, 3H, $J = 7.0$ Hz, OHCHCH_3), 1.44–1.72 (m, 6H, CH_2), 3.20 (m, 1H, CH_2CH_2O), 3.45 (m, 1H, CH_2CH_2O), 3.89 (s, 3H, OCH_3), 3.84–4.05 (m, 1H, C*H*OHCH$_3$), 4.16 (d, 1H, $J = 7.5$ Hz, ArCHOTHP), 4.84 (s, 1H, OCHO), 5.14 (s, 2H, $ArCH_2OAr$), 6.82–6.90 (m, 3H, Ar), 7.30–7.44 (m, 5H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 18.2$ (CH_2CH_2), 19.3 (HOCH*C*H$_3$), 25.2 (CH_2CH_2), 30.5 (*C*H$_2$CH$_2$), 55.9 (CH_3O), 62.4 (*C*H$_2$OCH), 71.0 (CH$_3$*C*HOH), 71.1 ($ArCH_2O$), 85.7 (ArCHOTHP), 100.0 (OCHO), 110.8, 113.4, 119.7, 127.3, 127.3, 127.8, 128.5, 128.5, 133.3, 137.1, 147.6, 149.3 ppm; EI-MS: $m/z = 372$ (M^+, 0.4), 328 (1.6), 288 (0.3), 271 (0.6), 243 (37), 91 (98), 85 (100); HRMS: calcd for $C_{22}H_{32}NO_5$ ($M + NH_4^+$) 390.2273, found 390.2275.

threo-(1R,2R)-1-[3-Methoxy-4-(methoxymethoxy)phenyl]-1-(tetrahydropyran-2-yloxy)-2-propanol (**13**, $C_{17}H_{26}O_6$)

Palladized charcoal (10%, 80 mg) was added to a stirred solution of 2.2 g **8** (6 mmol) in 20 cm^3 methanol. 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 0.6 g MOMCl (6 mmol) was added (in one go) to a rapidly stirred mixture of the resulting residue and 1.2 g K_2CO_3 (8 mmol) in 40 cm^3 acetone under N_2 at room temperature. The mixture was stirred for 3 h and quenched with water. The aqueous layer was extracted with ethyl acetate and the extracts were washed with brine and dried with Na_2SO_4. Then the solvent was removed in vacuo and flash column chromatography of the residue over silica gel afforded 1.8 g (90%) **13** as a colorless liquid. $[\alpha]_D^{20} = +28.7°$ cm^3 g^{-1} dm^{-1} ($c = 0.2$, $CHCl_3$); IR (KBr): $\bar{\nu} = 3{,}452$, 2,943, 2,852, 1,602, 1,513, 1,467, 1,382, 1,263, 1,135, 1,028, 902 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.06$ (d, 3H, $J =$ 7.0 Hz, OHCHCH_3), 1.47–1.78 (m, 6H, CH_2), 3.20 (m, 1H, CH_2CH_2O), 3.43 (m, 1H, CH_2CH_2O), 3.52 (s, 3H, OCH_3), 3.85–4.02 (m, 4H, C*H*OHCH$_3$, OCH_3), 4.15 (d, 1H, $J = 8.0$ Hz, ArCHOTHP), 4.87 (s, 1H, OCHO), 5.29 (s, 2H, CH_3OCH_2OAr), 6.85–7.10 (m, 3H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 17.8$ (CH_2CH_2), 19.5 (HOCH*C*H$_3$), 24.9 (CH_2CH_2), 31.2 (CH_2CH_2), 55.7 (CH_3O), 56.9 (*C*H$_3$OCH$_2$Ar), 62.4 (*C*H$_2$OCH), 71.8 (CH$_3$*C*HOH), 82.7 (ArCHOTHP), 95.8 (CH$_3$O*C*H$_2$Ar), 100.2 (OCHO), 111.8, 116.5, 120.2, 123.8, 144.3, 149.7 ppm; EI-MS: $m/z = 326$ (M^+, 3.8), 294 (12.3),

280 (4.5), 263 (23.1), 91 (100); HRMS: calcd for $C_{17}H_{30}NO_6$ ($M + NH_4^+$) 344.2068, found 344.2073.

erythro-(1R,2S)-Myrislignan (**1**, $C_{21}H_{26}O_6$)
A mixture of 0.7 g (1*R*,2*R*)-**13** (2 mmol), 0.4 g **12** (2 mmol), 0.6 g triphenylphosphine (2 mmol), and 0.3 cm^3 diethyl azodicarboxylate (2 mmol) in 20 cm^3 anhydrous THF was heated to reflux for 24 h under nitrogen. The mixture was concentrated under reduced pressure. A solution of HCl in MeOH (1 N, 20 cm^3) was added to the residue and the mixture was stirred at room temperature for 8 h. The solution was neutralized with saturated $NaHCO_3$ solution and concentrated in vacuo. The residue was taken up in EtOAc, washed with water, dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Flash column chromatography of the residue over silica gel gave 0.5 g (62%) (1*R*,2*S*)-myrislignan (**1**) as amorphous powder in 91% ee. The data of **1** were in agreement with those reported in the literature [5, 20].

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