First Enantioselective Synthesis of the Neolignans Rhaphidecursinol A and Virolongin B

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The enantioselective synthesis of the neolignans Rhaphidecursinol A and Virolongin B is reported for the first time. The key reactions in the synthesis were Sharpless asymmetric dihydroxylation and Mitsunobu reaction. The absolute configuration of Rhaphidecursinol A was confirmed.

Keywords: Enantioselective; Synthesis; Neolignan; Rhaphidecursinol A; Virolongin B.

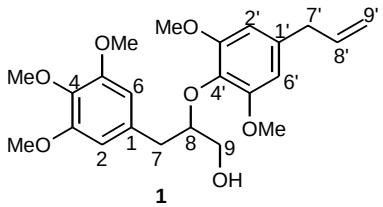
INTRODUCTION

Lignans and neolignans are an important group of natural products consisting of two phenylpropane monomers linked through carbon-carbon or carbon-oxygen bonds, and the syntheses of neolignans have already been developed in our laboratory.[1] Within the great structural variety of neolignans, the 8-O-4′-type represents a small group. Many show strong activity against the penetration of cercaria of *Schistosoma mansoni*,[2] inhibition of the growth of silkworm larvae,[3] and antileukemic activity in rats.[4] In order to study the relationship of structure and biological activity, several 8-O-4′ neolignans have been synthesized.[5] But these methods were racemic synthesis routes and led to the mixture of *erythro* and *threo* isomers. An asymmetric synthesis of 8-O-4′ neolignans was reported in 1996, but equal amounts of two diastereoisomers were obtained finally.[6] Now we report an asymmetric synthetic approach to 8-O-4′ neolignans.

Rhaphidecursinol A **1**, an optically active substance with varying degrees of antimalarial activity, was isolated from the dried leaves and stems of *Rhaphidophora decursiva*[7] and was determined to be an 8-O-4′ neolignan. Virolongin B **2**, an analog of **1**, was first isolated from nutmeg,[8] which are the seeds of the fruit of the trees, *Myristica fragrans* Houtt, *Licaria aurea*,[9] *Licaria chrysophylla*,[10] and *Aristolochia birostris*.[11] These plants have been used in folk medicine for many years for their alleged abortifacient, narcotic, and therapeutic properties. We noticed that neither their absolute configurations nor their asymmetric syntheses have yet been reported. Herein, we wish to report the first asymmetric syntheses of Rhaphidecursinol A and Virolongin B, and the absolute configuration of Rhaphidecursinol A deduced from its optical rotation.

RESULTS AND DISCUSSION

As shown in Scheme I, 2,6-Dimethoxyphenol **3** was easily protected with allyl bromide to give 2-(allyloxy)-1,3-dimethoxybenzene **4**, which underwent Claisen rearrangement to give 3-(4-hydroxy-3,5-dimethoxyphenyl)-1-propene **5**. Methylation of the hydroxy group afforded 3-(3,4,5-tri-



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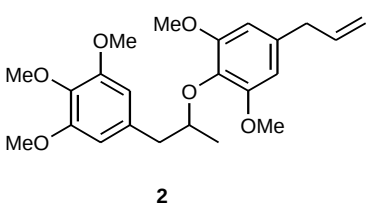

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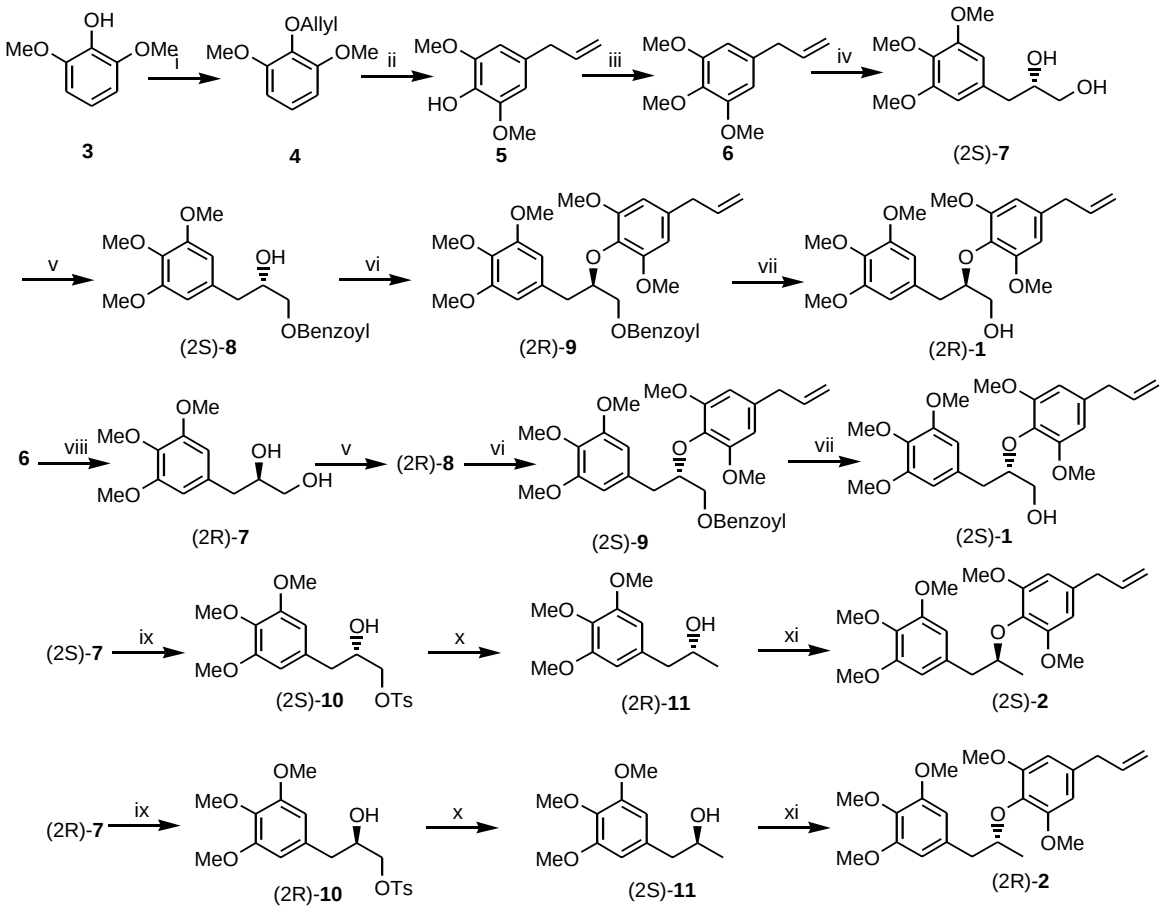
Scheme I



Reagents and conditions: (i) allyl bromide, K_2CO_3, acetone, rt, 24 h, 94%; (ii) 200 °C, 2 h, 92%; (iii) MeI, K_2CO_3, acetone, rt, 24 h, 96%; (iv) AD-mix-α, *t*-BuOH, H_2O, 0 °C, 20 h, 88%; (v) Et_3N, benzoyl chloride, CH_2Cl_2, -10 °C, 6 h, 82%; (vi) DIAD, Ph_3P, THF, **5**, rt, 24 h, 52%; (vii) K_2CO_3, methanol and H_2O (9:1), rt, 6 h, 72%; (viii) AD-mix-β, *t*-BuOH, H_2O, 0 °C, 20 h, 90%; (ix) Et_3N, TsCl, CH_2Cl_2, 0 °C, 6 h, 85%; (x) LAH, THF, 4 h, 82%; (xi) DIAD, Ph_3P, THF, **5**, rt, 24 h, 57%.

methoxyphenyl)-1-propene **6**. Sharpless asymmetric dihydroxylation of **6** with AD-mix-α yielded compound **7**. Depending on the experimental result of K. B. Sharpless,[12] the absolute configuration of compound **7** could be determined as *S*. Treatment of (2*S*)-**7** with benzoyl chloride provided (2*S*)-**8**, which was converted into (2*R*)-**9** using the Mitsunobu reaction[13] with **5** as nucleophile. According to the mechanism of Mitsunobu reaction, in this reaction the absolute configuration of C-8 in **8** was inverted completely by the S_N2-type nucleophilic displacement with **5**. The benzoyl group on (2*R*)-**9** was removed with potassium carbonate to give (2*R*)-**1**. Compound (2*S*)-**1** was obtained in a similar manner using AD-mix-β in the Sharpless reaction. Protecting (2*S*)-**7** with TsCl, followed by reduction with LAH, and the Mitsunobu reaction[13] with **5**, yielded (2*S*)-**2**. Compound (2*R*)-**2** was obtained in a similar manner using (2*R*)-**7**.

In summary, here we demonstrated a high enantioselective synthesis of 8-O-4′ neolignans Rhaphidecursinol A and Virolongin B. Therefore the route could be used for asymmetric synthesis of both neolignans. All spectral data were in agreement with those in the literature.[7-10] Compound (2*R*)-**1** has an optical rotation of +3.1, which is in good agreement with the literature value of +2.61 for Rhaphidecursinol A.[6]

EXPERIMENTAL SECTION

Melting points were measured on a Kofler apparatus and were uncorrected. The ^{1}H NMR and ^{13}C NMR data were recorded with a Bruker AM-80, Avance-200 MHz and Avance-400 MHz spectrometers. Chemical shifts (δ) are reported in ppm relative to TMS. Mass spectra were recorded on a ZAB-HS spectrometer. Optical rotations were determined on a Perkin Elmer 341 polarimeter. Chiral analysis was performed on a Varian Dynamax SD-300 using a chiralcel column CDMPC (150 × 4.6 mm D) with hexane/isopropyl alcohol as eluant. IR spectra were recorded on a Nicolet FT-170 SX spectrometer. Flash column chromatography was performed on silica gel (200-300 mesh) eluting with petroleum ether/ethyl acetate. TLC inspections were performed on silica gel GF_{254} plates with petroleum ether/ethyl acetate as eluant, unless otherwise state.

2-(Allyloxy)-1,3-dimethoxybenzene (4)

To a solution of **3** (4 g, 0.026 mol) in acetone (60 mL) was added potassium carbonate (4.3 g, 0.031 mol) and allyl bromide (4.72 g, 0.039 mol). The suspension was stirred overnight. The solvent was removed, 3N HCl (15 mL) was added, and the mixture was extracted with EtOAc. The organic fraction was washed with brine, dried over Na_2SO_4, and the solvent removed under reduced pressure. Flash chromatography of the residue using petroleum ether/ethyl acetate (15:1, v/v) as eluant afforded **4** (4.74 g, 94%) as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.84 (s, 6H), 4.52 (d, 2H, *J* = 6.0 Hz), 5.18 (dd, 1H, *J* = 10.4, 1.0 Hz), 5.30 (dd, 1H, *J* = 17.2, 1.6 Hz), 6.14 (m, 1H), 6.54-7.02 (m, 3H). MS (EI), *m/z* 194 (M^+), 153, 125, 110, 93.

3-(4-Hydroxy-3,5-dimethoxyphenyl)-1-propene (5)

Compound **4** (2.5 g, 12.9 mmol) was heated to 200 °C for 2 h. Flash chromatography of the residue using petroleum ether/ethyl acetate (7:1, v/v) as eluant afforded **5** (2.3 g, 92%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.33 (d, 2H, *J* = 6.6 Hz), 3.88 (s, 6H), 5.08 (dd, 1H, *J* = 10.2, 1.0 Hz), 5.10 (dd, 1H, *J* = 17.6, 1.6 Hz), 5.44 (s, 1H), 5.98 (m, 1H), 6.42 (s, 2H). MS (EI), *m/z* 194 (M^+), 179, 153, 131, 91, 77.

3-(3,4,5-Trimethoxyphenyl)-1-propene (6)

To a solution of **5** (2 g, 10.3 mmol) in acetone (50 mL), potassium carbonate (1.71 g, 12.4 mmol) was added. The suspension was stirred for 10 min, iodomethane (2.2 g, 15.5 mmol) was added and stirred overnight. The solvent was evaporated, 3N HCl (10 mL) was added, and the mixture was extracted with EtOAc. The organic fraction was washed with brine, dried over Na_2SO_4 and the solvent removed. Flash chromatography of the residue using petroleum ether/ethyl acetate (12:1, v/v) as eluant gave a colorless oil **6** (2.06 g, 96%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.34 (d, 2H, *J* = 6.6 Hz), 3.84 (s, 9H), 5.09 (dd, 1H, *J* = 9.6, 1.2 Hz), 5.11 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.98 (m, 1H), 6.42 (s, 2H). MS (EI), *m/z* 208 (M^+), 193, 165, 133, 121, 105, 91, 77.

(S)-3-(3,4,5-Trimethoxyphenyl)-1,2-propanediol [(2S)-7]

To a stirred solution of *t*-BuOH (20 mL) and H_2O (20 mL), AD-mix-α (5.6 g) was added. The mixture was stirred at room temperature until both phases were clear, and cooled to 0 °C. Compound **6** (832 mg, 4 mmol) was added, and the mixture stirred vigorously at 0 °C until TLC revealed complete consumption of **6**. The reaction was quenched at 0 °C by addition of Na_2SO_3 (6 g), warmed to room temperature and stirred for 0.5 h. After extraction with ethyl acetate, the organic fraction was washed with water and dried over Na_2SO_4. The solvent was removed and flash chromatography of the residue using petroleum ether/ethyl acetate (1:2, v/v) as eluant gave a white powder (2*S*)-**7** (852 mg, 92% e.e., 88%) (Chiralcel column CDMPC, *n*-hexane:isopropyl alcohol, 50:1, 1 mL/min, 25 °C, retention times 17.6 min). M.p. 73-75 °C. $[\alpha]_D^{25}$ -4 (*c* 2.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.60 (dd, 1H, *J* = 13.6, 7.2 Hz), 2.75 (dd, 1H, *J* = 13.8, 6.0 Hz), 3.51 (dd, 1H, *J* = 11.8, 3.8 Hz), 3.69 (dd, 1H, *J* = 11.0, 3.0 Hz), 3.82 (s, 9H), 3.97 (m, 1H), 6.43 (s, 2H). MS (EI), *m/z* 242 (M^+), 211, 181, 167, 151, 91, 65.

(R)-3-(3,4,5-Trimethoxyphenyl)-1,2-propanediol [(2R)-7]

Compound (2*R*)-**7** was prepared in an analogous manner to (2*S*)-**7**, using **6** (850 mg, 4.09 mmol) and AD-mix-β (5.7 g) to give a white powder (890 mg, 93% e.e., 90%). M.p. 80-83 °C. $[\alpha]_D^{25}$ +5 (*c* 1.7, $CHCl_3$). Other spectral data were the same as for (2*S*)-**7**.

(S)-3-(3,4,5-Trimethoxyphenyl)-1-O-benzoyl-1,2-propanediol [(2S)-8]

To a solution of compound (2*S*)-**7** (0.55 g, 2.27 mmol) in dichloromethane (20 mL) at -10 °C under N_2, triethylamine (0.34 g, 3.4 mmol) was added. After stirring the reaction mixture for 15 min, benzoyl chloride (0.34 g, 2.39 mmol) was added. The mixture was stirred at -10 °C for 6 h, the sol-

vent was removed, and water (10 mL) was added to the residue. The mixture was extracted with ethyl acetate, the organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue using petroleum ether/ethyl acetate (5:1, v/v) as eluant yielded (2*S*)-**8** (0.65 g, 82%) as a white powder. M.p. 76-79 °C. $[\alpha]_D^{25}$ +3.3 (*c* 2.1, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.78 (dd, 1H, *J* = 13.4, 7.0 Hz), 2.90 (dd, 1H, *J* = 13.8, 6.2 Hz), 3.83 (s, 9H), 4.24 (m, 1H), 4.37 (dd, 1H, *J* = 12.0, 3.8 Hz), 4.42 (dd, 1H, *J* = 11.4, 3.0 Hz), 6.47 (s, 2H), 7.27-8.08 (m, 5H). MS (EI), *m/z* 346 (M^+), 328, 223, 181, 167, 105, 77.

(R)-3-(3,4,5-Trimethoxyphenyl)-1-O-benzoyl-1,2-propanediol [(2R)-8]

Compound (2*R*)-**8** was prepared in an analogous manner to (2*S*)-**8**, using (2*R*)-**7** (700 mg, 2.89 mmol), triethylamine (438 mg, 4.4 mmol) and benzoyl chloride (427 mg, 3.04 mmol) to give a white powder (850 mg, 85%). M.p. 79-81 °C. $[\alpha]_D^{25}$ -3.5 (*c* 3.2, $CHCl_3$). Other spectral data were the same as for (2*S*)-**8**.

(R)-3-(3,4,5-Trimethoxyphenyl)-1-O-benzoyl-2-O-(4-allyl-2,6-dimethoxyphenyl)-1,2-propanediol [(2R)-9]

To a solution of **5** (141 mg, 0.73 mmol) and DIAD (147 mg, 0.73 mmol) in dry THF at room temperature under nitrogen a solution of PPh_3 (191 mg, 0.73 mmol) and (2*S*)-**8** (210 mg, 0.6 mmol) in dry THF (10 mL) was added dropwise. After stirring the mixture overnight, the solvent was removed. Flash chromatography of the residue using petroleum ether/ethyl acetate (7:1, v/v) as eluant yielded a colorless oil (2*R*)-**9** (164 mg, 52%). $[\alpha]_D^{25}$ +5.2 (*c* 3.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.07 (dd, 1H, *J* = 13.8, 7.2 Hz), 3.26 (dd, 1H, *J* = 14.0, 6.0 Hz), 3.33 (d, 2H, *J* = 6.4 Hz), 3.69 (s, 6H), 3.82 (s, 9H), 4.40 (dd, 1H, *J* = 12.2, 3.6 Hz), 4.43 (dd, 1H, *J* = 12.2. 2.6 Hz), 4.64 (m, 1H), 5.09 (dq, 1H, *J* = 10.6, 1.2 Hz), 5.11 (dq, 1H, *J* = 17.6, 1.6 Hz), 5.97 (m, 1H), 6.37 (s, 2H), 6.56 (s, 2H), 7.37-7.96 (m, 5H). MS (EI), *m/z* 522 (M^+), 417, 329, 207, 193, 176, 105, 77.

(S)-3-(3,4,5-Trimethoxyphenyl)-1-O-benzoyl-2-O-(4-allyl-2,6-dimethoxyphenyl)-1,2-propanediol [(2S)-9]

Compound (2*S*)-**9** was prepared in an analogous manner to (2*R*)-**9**, using (2*R*)-**8** (300 mg, 0.87 mmol) and **5** (202 mg, 1.04 mmol) to give a colorless oil (226 mg, 49%). $[\alpha]_D^{25}$ -4 (*c* 0.65, $CHCl_3$). Other spectral data were the same as for (2*R*)-**9**.

(R)-3-(3,4,5-trimethoxyphenyl)-2-O-(4-allyl-2,6-dimethoxyphenyl)-1,2-propanediol [(2R)-1]

Compound (2*R*)-**9** (104 mg, 0.2 mmol) was dissolved in methanol (9 mL) and water (1 mL), potassium carbonate (82 mg, 0.6 mmol) was added and the suspension was stirred for 6 h at room temperature. The solvent was evaporated, water (15 mL) added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and the solvent removed. Flash chromatography of the residue using petroleum ether/ethyl acetate (4:1, v/v) as eluant gave a colorless oil (2*R*)-**1** (60 mg, 72%). $[\alpha]_D^{25}$ +3.1 (*c* 1.5, MeOH). IR (KBr), υ/cm^{-1}: 3508, 2936, 2838, 1590, 1504, 1460, 1422, 1331, 1239, 1127 and 1015. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.99 (dd, 1H, *J* = 13.6, 8.3 Hz), 3.24 (dd, 1H, *J* = 13.6, 5.4 Hz), 3.35 (d, 2H, *J* = 6.6 Hz), 3.45 (dd, 1H, *J* = 12.4, 3.8 Hz), 3.59 (dd, 1H, *J* = 12.4, 2.3 Hz), 3.83 (s, 6H), 3.86 (s, 9H), 4.22 (m, 1H), 5.11 (dq, 1H, *J* = 10.6, 1.2 Hz), 5.13 (dq, 1H, *J* = 17.6, 1.6 Hz), 5.98 (m, 1H), 6.44 (s, 2H), 6.54 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 38.1, 40.5, 56.1, 60.8, 62.4, 84.1, 105.6, 106.5, 116.1, 134.2, 136.2, 137.0, 152.9, 153.2. MS (EI), *m/z* 418 (M^+), 326, 224, 207, 194, 181, 91, 77. HRFABMS *m/z* 436.2337 ($C_{23}H_{34}O_7N$ requires 436.2330).

(S)-3-(3,4,5-trimethoxyphenyl)-2-O-(4-allyl-2,6-dimethoxyphenyl)-1,2-propanediol [(2S)-1]

Compound (2*S*)-**1** was prepared in an analogous manner to (2*R*)-**1**, using (2*S*)-**9** (150 mg, 0.29 mmol) and potassium carbonate (119 mg, 0.86 mmol) to give a colorless oil (89 mg, 74%). $[\alpha]_D^{25}$ -2.8 (*c* 2.0, MeOH). Other spectral data were the same as for (2*R*)-**1**.

(S)-3-(3,4,5-trimethoxyphenyl)-1-O-tosyl-1,2-propanediol [(2S)-10]

To a solution of compound (2*S*)-**7** (0.78 g, 3.22 mmol) in dichloromethane (20 mL) at 0 °C under N_2, triethylamine (0.49 g, 4.85 mmol) was added. After stirring the reaction mixture for 15 min, TsCl (0.64 g, 3.36 mmol) was added. The mixture was stirred at 0 °C for 6 h, the solvent was removed and water (10 mL) water was added to the residue. The mixture was extracted with ethyl acetate, the organic phase was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash chromatography of the residue using petroleum ether/ethyl acetate (3:1, v/v) as eluant yielded (2*S*)-**10** (1.08 g, 85%) as a white powder. M.p. 105-106 °C. $[\alpha]_D^{25}$ -2 (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.45 (s, 3H), 2.72 (dd, 1H, *J* = 13.6, 6.8 Hz), 2.75 (dd, 1H, *J* = 13.8, 6.4 Hz), 3.82 (s,

9H), 3.88 (m, 1H), 3.96 (dd, 1H, *J* = 11.8, 3.6 Hz), 4.02 (dd, 1H, *J* = 11.6, 3.0 Hz), 6.40 (s, 2H), 7.35 (d, 2H, *J* = 7.8 Hz), 7.79 (d, 2H, *J* = 8.2 Hz). MS (EI), *m/z* 396 (M^+), 284, 268, 253, 224, 209, 195, 181, 167, 155, 91.

(R)-3-(3,4,5-trimethoxyphenyl)-1-O-tosyl-1,2-propanediol [(2R)-10]

Compound (2*R*)-**10** was prepared in an analogous manner to (2*S*)-**10**, using (2*R*)-**7** (600 mg, 2.48 mmol), triethylamine (375 mg, 3.71 mmol) and TsCl (496 mg, 2.60 mmol) to give a white powder (815 mg, 83%). M.p. 107-108 °C. $[\alpha]_D^{25}$ +3 (*c* 2.0, $CHCl_3$). Other spectral data were the same as for (2*S*)-**10**.

(R)-1-(3,4,5-trimethoxyphenyl)-2-propanol [(2R)-11]

To a suspension of LAH (13.8 mg, 0.36 mmol) in dry THF (20 mL), (2*S*)-**10** (120 mg, 0.3 mmol) was added. The suspension was stirred for 4 h at room temperature, and quenched with ethyl acetate and water. The mixture was extracted with ethyl acetate, the organic layer washed with brine, dried over Na_2SO_4, and the solvent was removed. Flash chromatography of the residue using petroleum ether/ethyl acetate (4:1, v/v) as eluant yielded (2*R*)-**11** (56 mg, 82%) as a colorless oil. $[\alpha]_D^{25}$ -9 (*c* 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, 3H, *J* = 6.2 Hz), 2.59 (dd, 1H, *J* = 13.4, 8.4 Hz), 2.75 (dd, 1H, *J* = 13.4, 4.4 Hz), 3.85 (s, 9H), 3.99 (m, 1H), 6.43 (s, 2H). MS (EI), *m/z* 226 (M^+), 181, 167, 151, 107, 91, 77.

(S)-1-(3,4,5-trimethoxyphenyl)-2-propanol [(2S)-11]

Compound (2*S*)-**11** was prepared in an analogous manner to (2*R*)-**11**, using (2*R*)-**10** (150 mg, 0.38 mmol) and LAH (17.3 mg, 0.46 mmol) to give a colorless oil (72 mg, 84%). $[\alpha]_D^{25}$ +8 (*c* 1.6, $CHCl_3$). Other spectral data were the same as for (2*R*)-**11**.

(S)-1-(3,4,5-trimethoxyphenyl)-2-O-(4-allyl-2,6-dimethoxyphenyl)-2-propanol [(2S)-2]

To a solution of **5** (159 mg, 0.82 mmol) and DIAD (166 mg, 0.82 mmol) in dry THF at room temperature under nitrogen a solution of PPh_3 (215 mg, 0.82 mmol) and (2*R*)-**11** (154 mg, 0.68 mmol) in dry THF (10 mL) was added dropwise. After stirring the mixture overnight, the solvent was removed. Flash chromatography of the residue using petroleum ether/ethyl acetate (9:1, v/v) as eluant yielded a colorless oil (2*S*)-**2** (159 mg, 57%). $[\alpha]_D^{25}$ +1.9 (*c* 4.7, $CHCl_3$). IR (KBr), υ/cm^{-1}: 3393, 2933, 2837, 1588, 1503, 1459, 1421, 1330, 1239, 1126. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, 3H, *J* = 6.2 Hz), 2.74 (dd, 1H, *J* = 13.4, 7.8 Hz), 3.13 (dd, 1H, *J* = 13.4, 5.2 Hz), 3.34 (d, 2H, *J* = 6.6 Hz), 3.79 (s, 6H), 3.82 (s, 9H), 4.36 (m, 1H), 5.10 (dq, 1H, *J* = 10.4, 1.4 Hz), 5.13 (dq, 1H, *J* = 17.2, 1.8 Hz), 5.97 (m, 1H), 6.40 (s, 2H), 6.47 (s, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.7, 40.5, 43.6, 55.9, 56.0, 60.8, 79.6, 105.5, 106.5, 115.9, 134.2, 134.8, 135.4, 136.2, 137.2, 152.8, 153.6. MS (EI), *m/z* 402 (M^+), 362, 209, 194, 181, 168, 107, 91. HRFABMS *m/z* 425.1930 ($C_{23}H_{30}O_6Na$ requires 425.1935).

(R)-1-(3,4,5-trimethoxyphenyl)-2-O-(4-allyl-2,6-dimethoxyphenyl)-2-propanol [(2R)-2]

Compound (2*R*)-**2** was prepared in an analogous manner to (2*S*)-**2**, using (2*S*)-**11** (120 mg, 0.53 mmol) and **5** (124 mg, 0.64 mmol) to give a colorless oil (117 mg, 55%). $[\alpha]_D^{25}$ -2.3 (*c* 2.15, $CHCl_3$). Other spectral data were the same as for (2*S*)-**2**.

ACKNOWLEDGMENTS

Support from the National Natural Science Foundation of China (No. 29972015; 20172023) is gratefully acknowledged.

Received September 16, 2003.

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