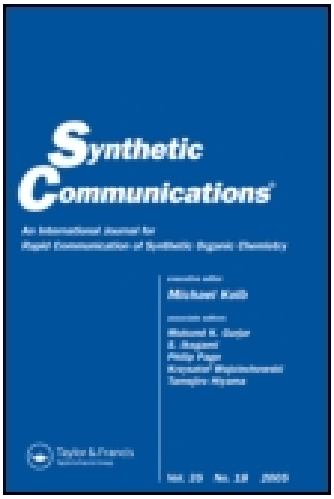

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FIRST ASYMMETRIC TOTAL SYNTHESIS OF (*R,E*)-1-[4-(3-HYDROXYPROP-1-ENYL)PHENOXYL]-3-METHYLBUTANE-2,3-DIOL

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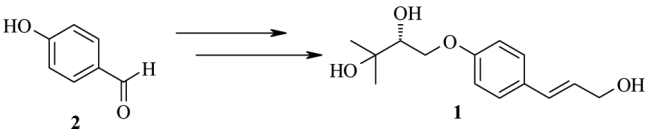
GRAPHICAL ABSTRACT



Abstract *A new anti-inflammatory active phenylpropenoid, (*R,E*)-1-[4-(3-hydroxyprop-1-enyl) phenoxyl]-3-methylbutane-2,3-diol (***1***), isolated from the stem wood of* Zanthoxylum integrifoliolum*, has been synthesized for the first time using commercially available 4-hydroxy benzaldehyde (***2***). The key step involves the Sharpless asymmetric dihydroxylation of olefin (***3***).*

Keywords Phenylpropenoid; (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol; sharpless asymmetric dihydroxylation

INTRODUCTION

Many phenylpropenoids have been isolated from natural sources, some of which have antimicrobial,[1] cytotoxic, and radical scavenging activities.[2] Natural and synthetic liginins stimulate macrophase nitroblue tetrazolium (NBT)-reducing activity, polymorphonuclear cell (PMN) iodination, and splenocyte DNA synthesis and inhibit poly(ADP-ribose) glycohydrolase, RNA-dependent DNA polymerase (reverse transcriptase), and RNA-dependent RNA polymerase activities. The synthetic liginins are prepared by polymerization of phenylpropanoid precursors.[3] Some phenylpropenoids are also esterified to phytosterols present in grain products, such as rice and corn bran, and thus are common components of the human diet.[4] Recently, a new phenylpropenoid, (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol (**1**), was isolated by Chen et al.[5] from *Zanthoxylum integrifoliolum* (Merr.) Merr.

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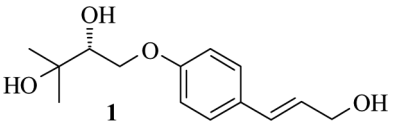
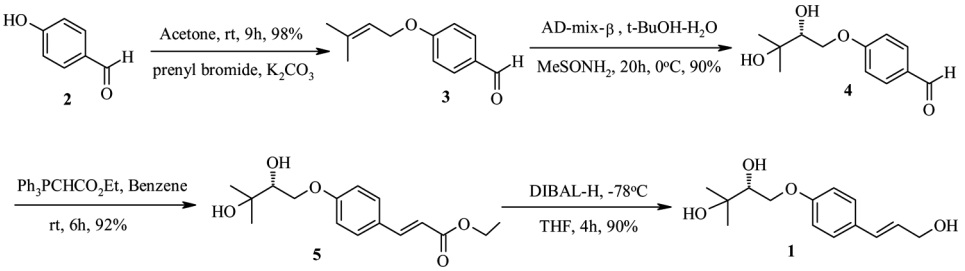


Figure 1.

(Rutaceae). It shows anti-inflammatory activity ($IC_{50} = 32.55 \pm 7.54$) on N-formylmethionylleucylphenylalanine (fMLP)–induced production of superoxide anion by neutrophils. *Zanthoxylum integrifoliolum* (Merr.) Merr. (Rutaceae) is large evergreen tree that grows only in the northern Philippines and Lanyu Island in Taiwan.[6] Its bark is utilized as a folk remedy for snakebite by Ya-Mei aborigines in Lanyu Island, and it is also a good source for antiplatelet agents such as chelerythrine and avicine pseudocyanide.[7] Chemical constituents of this plant's roots,[8] bark,[9] and fruit[10] yielded benzo[c]phenanthridines, coumarins, quinolines, N-isobutylamides, liganans, triterpenoids, indolopyridoquinazolines, flavonoids, and bishordeninyl terpene alkaloids. The biological potential of these compounds has stimulated significant interest in the synthesis of (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol **1**. To the best of our knowledge, there is no report on the total synthesis of (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol **1**. We report here our results on the first asymmetric total synthesis of (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol (**1**) using the Sharpless asymmetric dihydroxylation.

RESULTS AND DISCUSSION

We commenced the synthesis of target molecule **1** from the commercially available 4-hydroxybenzaldehyde **2**, an inexpensive starting material. The aromatic hydroxyl group in compound **2** was prenylated using prenyl bromide and K_2CO_3 in acetone to afford **3** in 98% yield. Sharpless asymmetric dihydroxylation (AD)[11] of compound **3** with AD-mix-β at 0 °C furnished diol aldehyde **4** in 90% yield with 95.8% *ee* as established by chiral high-performance liquid chromatographic (HPLC) analysis. The absolute stereochemistry of compound **4** was assigned, in a preliminary fashion, as (*R*) using the Sharpless mnemonic.[12] The diol aldehyde (**4**), upon Wittig



Scheme 1. Synthesis of compound **1**.

olefination with the stabilized ylide[13] (ethoxycarbonyl methylene) triphenylphosphorane in benzene at room temperature exclusively furnished the *E*-isomer in the form of α,β-unsaturated ester **5** in 92% yield, which on selective reduction with diisobutylaluminiumhydride (DIBAL-H)[14] in CH_2Cl_2 at $-78\,^{\circ}C$ gave the desired compound (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol (**1**) in 90% yield. The physical and spectroscopic data of compound **1** [mass spectra (MS ^1H and ^{13}C NMR, infrared (IR), optical rotation] were found to be identical with those reported natural product[5] (Scheme 1).

CONCLUSION

In conclusion, we have achieved a simple, short, and efficient first asymmetric total synthesis of (*R,E*)-1-[4-(3-hydroxyprop-1-enyl)phenoxyl]-3-methylbutane-2,3-diol (**1**) from the readily available starting material 4-hydroxybenzaldehyde **2** utilizing Sharpless asymmetric dihydroxylation of olefin (**3**).

EXPERIMENTAL

All solvents and reagents were purified by standard techniques. Crude products were purified by column chromatography on silica gel of 60–120 mesh. Fourier transform (FTIR–spectra were measured with a Thermo Nicolet Nexus 670 spectrometer. Optical rotations were recorded on a Horiba highly sensitive polarimeter, in a 10-mm cell. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on Varian Gemini 400, 500, and Brucker Avance 300 instruments. Chemical shifts were reported in parts per million with respect to internal tetramethylsilane (TMS). Coupling constants (*J*) are quoted in hertz. Mass spectra were acquired on a micromass Quattro micro atmospheric photo ionization (API) (Waters) and high-resolution Qstarxl hybrid MS/MS system (Applied Biosystems, USA) mass spectrometers.

Preparation of 4-(3-Methylbut-2-enyloxy)benzaldehyde (3)

Prenyl bromide (0.73 g, 0.56 mL, 4.90 mmol) was added through a syringe to a stirred solution of 4-hydroxybenzaldehyde **2** (0.5 g, 4.09 mmol) and K_2CO_3 (2.82 g, 20.45 mmol) in dry acetone (10 mL), and stirring continued at room temperature for 9 h. After completion of the reaction, acetone was removed under reduced pressure, diluted with water (20 mL), and extracted into ethyl acetate (2×30 mL). Combined ethyl acetate extract was washed with brine (30 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield the crude **3**, which was purified on a silica-gel column (60–120 mesh) using EtOAc–hexane (1:9) to give **3** (0.76 g, 98% yield) as a white solid; IR (neat): 2975, 2930, 2736, 1690, 1601, 1251, 1162, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.85 (s, 1H), 7.77 (d, 2H, $J = 8.68$ Hz), 6.95 (d, 2H, $J = 8.68$ Hz), 5.46 (m, 1H), 4.56 (d, 2H, $J = 6.79$), 1.80 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (75 Mz, $CDCl_3$): δ 189.83, 163.61, 138.22, 131.59, 129.64, 118.88, 114.62, 64.8, 25.5, 18.0; EI-MS: m/z 190 $[M]^+$.

Preparation of 4-{[(2R)-2,3-Dihydroxy-3-methylbutyl]oxy}-benzaldehyde (4)

AD-mix-β (3.68 g, 2.63 mmol) and $MeSO_2NH_2$ (0.25 g 0.26 mmol) were added to a solution of *tert*-butylalcohol and water (10:10 mL) and stirred at room temperature until both phases were clear, then cooled to 0 °C. The olefin (**3**, 0.5 g, 2.63 mmol) was added at once to this solution and the heterogeneous slurry was stirred vigorously at 0 °C for about 20 h. After completion of the reaction, the reaction was quenched at 0 °C by addition of sodium sulfite (1 g), warmed to room temperature, and stirred for 30 min. The reaction mixture was poured into water (30 mL) and extracted into EtOAc (3×40 mL). The combined organic layer was washed with brine (30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure to yield the crude diol, which was purified on a silica gel column (60–120 mesh) using EtOAc–hexane (7:3) to yield pure diol (**4**, 530 mg, 90% yield, 95.8% *ee*) as a colorless liquid; $[\alpha]_D + 30.6$ (*c* 0.1, $CHCl_3$). IR (film): 3429 (OH), 2973, 1684, 1598, 1256, 1161 cm^{-1}. ^1H NMR (300 Mz, $CDCl_3$): δ 9.88 (s, 1H), 7.82 (d, 2H, $J = 8.68$), 7.01 (d, 2H, $J = 8.68$), 4.22 (m, 1H), 4.10 (m, 1H), 3.85 (m, 1H), 2.93 (br s, 1H), 2.42 (br s, 1H), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 Mz, $CDCl_3$): δ 190.75, 163.44, 131.99, 130.33, 114.85, 75.73, 71.60, 69.47, 26.53, 24.97; ESI-MS: *m/z* 247 $[M + Na]^+$, chiral pak IC 250×4.6 mm, 5 μ, mobile phase: 15% IPA in hexane, flow rate: 0.7 ml/min, detection: 210 nm, ret. time: 24.161–2.096% and 25.701–97.904%, 95.8% *ee*.

Preparation of Ethyl (E)-3-(4-[(2R)-2,3-Dihydroxy-3-methylbutyl]-oxyphenyl)-2-propenoate (5)

Wittig ylide Ph_3PCHCO_2Et (2.16 g, 6.22 mmol) was added at room temperature to a stirred solution of diol aldehyde **4** (400 mg, 1.78 mmol) in dry benzene (10 mL) under an inert atmosphere. The reaction mixture was stirred at room temperature for 6 h. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by silica-gel column chromatography using hexane–ethyl acetate (1:1) to afford the unsaturated ester **5** (483 mg, 92% yield) as a white solid; $[\alpha]_D + 16.8$ (*c* 0.2, $CHCl_3$). IR (film): 3380 (OH), 3336 (OH), 1677, 1599, 1174 cm^{-1}. ^1H NMR (500 Mz, $CDCl_3$): δ 7.56 (s, 1H, $J = 15.27$), 7.44 (d, 2H, $J = 8.14$), 6.88 (d, 2H, $J = 9.16$), 6.25 (d, 1H, $J = 15.27$), 4.25–4.07 (m, 3H), 4.01 (m, 1H), 3.77 (m, 1H), 2.65 (dd, 1H, OH, $J = 10.18, 3.05$), 1.33 (t, 3H, $J = 7.12$), 1.31 (s, 3H), 1.25 (s, 3H), ^{13}C NMR (75 Mz, $CDCl_3$): δ 166.89, 160.20, 143.79, 129.30, 126.94, 115.49, 114.67, 75.63, 71.18, 69.20, 59.94, 25.91, 24.74, 14.01; ESI-MS: *m/z* 317 $[M + Na]^+$.

(*R,E*)-1-(4-(3-Hydroxyprop-1-enyl)phenoxy)-3-methylbutane-2,3-diol (1)

DIBAL-H (1.09 mL, 1.4 M, 1.53 mmol in hexane) was added drop wise to a stirred solution of ester **5** (100 mg, 0.34 mmol) in dry THF (5 mL) at −78 °C over a period of 5 min under a nitrogen atmosphere. After completion of the reaction, the reaction was quenched with MeOH (0.5 mL), and a saturated aqueous solution

of sodium potassium tartarate (5 mL) was added and extracted into CH_2Cl_2 (2×20 mL). The combined organic layer was washed with water and brine solution and dried over anhydrous Na_2SO_4 concentrated under vacuum. The crude product was purified on silica-gel column using hexane–ethyl acetate (1:9) to afford (*R,E*)-1-(4-(3-hydroxyprop-1-enyl)phenoxy)-3-methylbutane-2,3-diol **1** (77 mg, 90% yield) as a colorless oil; $[\alpha]_D + 15.5$ (c 0.1, $CHCl_3$). IR (film): 3381 (OH), 1604, 1510, 1461, 1246 cm^{-1}; ^1H NMR (400 Mz, $CDCl_3$): δ 7.28 (d, 2H, $J = 8.05$), 6.85 (d, 2H, $J = 8.79$), 6.55 (d, 1H, $J = 15.38$), 6.25 (dt, 1H, $J = 15.38$, 5.86), 4.29 (d, 2H, $J = 5.86$), 4.15 (dd, 1H, $J = 9.52$, 2.93), 4.03 (dd, 1H, $J = 9.52$, 8.05), 3.80 (m, 1H), 3.15 (br s, 1H, OH), 2.67 (br s, 1H, OH), 1.32 (s, 3H), 1.27 (s, 3H), ^{13}C NMR (75 Mz, $CDCl_3$): δ 157.09, 129.69, 129.19, 126.74, 125.75, 113.74, 74.73, 70.71, 68.27, 62.77, 25.62, 24.09; HREI-MS: m/z 275.1269 $[M + Na]^+$.

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