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Concise Synthesis of Rodgersinol and Determination of the C-10 Absolute Configuration

Seung-Yong Seo,† Jong-Wha Jung,† Jae-Kyung Jung,‡ Nam-Jung Kim,† Young-Won Chin,† Jinwoong Kim,† and Young-Ger Suh*,†

College of Pharmacy, Seoul National University, Seoul 151-742, Korea, and College of Pharmacy, Chungbuk National University, Cheongju 361-763, Korea

ygsuh@snu.ac.kr

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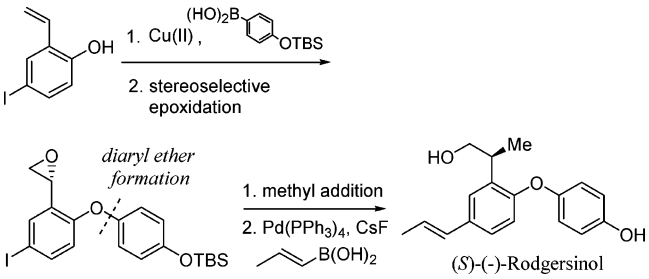

Rodgersinol was synthesized via seven linear steps in 31% overall yield, and the absolute configuration of the C-10 stereogenic center was elucidated. The key feature of the synthesis involves the efficient Cu(II)-mediated coupling of two aromatic moieties for the diaryl ether intermediate and the enantioselective construction of the hydroxypropyl substituent by a regio- and stereoselective methyl addition to the chiral aryloxiranes in an inversion manner.

Recently, rodgersinol (**1**) was isolated from the aerial parts of *Rodgersia podophylla*, from which rhizomes have traditionally been used for the treatment of enteritis and bacillary dysentery as well as for pain relief. In particular, this novel component exhibited significant inhibitory effects on both *i*NOS and COX-2 expression in LPS-activated macrophages (IC_{50} values of 2 and 3 μM, respectively).[1] The structural determination of **1**, by an extensive spectroscopic analysis,[1] revealed a C-4 (refer to the numbering system of rodgersinol) diaryl ether skeleton containing a *p*-hydroquinone, appended with a propenyl group (C-1) and a hydroxylpropanyl group (C-3), as shown in Figure 1. However, the absolute configuration of the C-10 stereogenic center remained undetermined. Interestingly, rodgersinol, as a potential antiinflammatory agent, possesses a 2-arylpropanol moiety, which is rarely observed in natural antiinflammatory products. It is usually found in an intermediate

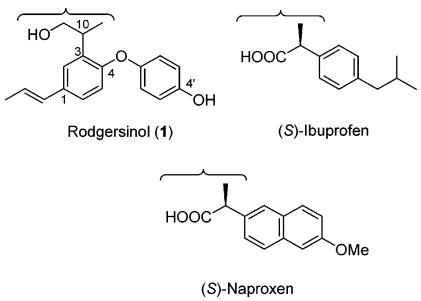

FIGURE 1. Structures of rodgersinol and the anti-inflammatory 2-arylpropanoic acids.

or biotransformational prodrug, while the (*S*)-2-arylpropanoic acid[2] moiety is well recognized in an important class of nonsteroidal anti-inflammatory agents, such as ibuprofen and naproxen.[3]

The exciting biological activity of rodgersinol, possessing the unique 2-arylpropanol, combined with an effort to elucidate the absolute configuration of the C-10 stereogenic center, led us to undertake the total synthesis of rodgersinol. We herein report the concise and versatile synthesis of both enantiomers of rodgersinol (**1**).

In consideration of concise and convergent synthesis of **1**, we sought an efficient synthetic procedure for the common intermediate **2**, which could be readily transformed into both enantiomers of **1** by the regio- and stereoselective methyl additions to **2**, followed by direct (*E*)-propenyl installation at C-1 by Suzuki cross-coupling[4] (Scheme 1). The chiral epoxide of **2** would be efficiently prepared by sequential asymmetric dihydroxylation[5] of the diaryl ether **3** and epoxidation of the resulting diol. With seeking efficient construction[6] of the key diaryl ether intermediate **3**, we were intrigued by the pioneering report by Evans[7]on Cu-mediated coupling. Thus, we considered the coupling of the properly functionalized phenol **4** and the boronic acid **5**.

Our approach commenced with the preparation of the chiral epoxide **2**, as shown in Scheme 2. The reaction of 4-iodo-2-vinylphenol **4**[8] and boronic acid **5**, in the presence of $Cu(OAc)_2$ and Et_3N, produced the coupling product **3** in 67% yield (91% based on the recovered **4**). The incomplete conversion was likely

* To whom correspondence should be addressed. Tel: 82-2-880-7875. Fax: 82-2-880-0649.
† Seoul National University.
‡ Chungbuk National University.

(1) Chin, Y.-W.; Park, E. Y.; Seo, S.-Y.; Yoon, K.-D.; Ahn, M.-J.; Suh, Y.-G.; Kim, S. G.; Kim, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4600−4602.

(2) For a review on the synthesis of 2-arylpropanoic acid, see: Sonawane, H. R.; Bellur, N. S.; Ahuja, J. R.; Kulkarni, D. G. *Tetrahedron: Asymmetry* **1992**, *3*, 163−192.

(3) For selected reports, see: (a) Hayball, P. J. *Drugs* **1996**, *52*, 47−58. (b) Landoni, M. F.; Soraci, A. *Curr. Drug. Metab.* **2001**, *2*, 37−51.

(4) For reviews on the Suzuki cross-coupling reaction, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147−168.

(5) For reviews on asymmetric dihydroxylation, see: (a) Zaitsev, A. B.; Adolfsson, H. *Synthesis* **2006**, *11*, 1725−1756. (b) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1996**, *94*, 2483−2547. In this case, neither the asymmetric epoxidation nor the asymmetric hydroboration was sufficient for application to the stereoselective synthesis of 2-arylpropanol from the diaryl ether **3**.

(6) For recent reviews on diaryl ether formation, see: (a) Sawyer, J. S. *Tetrahedron* **2000**, *56*, 5045−5065. (b) Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345−2347. (c) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(7) (a) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937−2940. (b) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933−2936.

(8) The compound **4** was synthesized from the commercially available 4-iodosalicylaldehyde using Wittig olefination.

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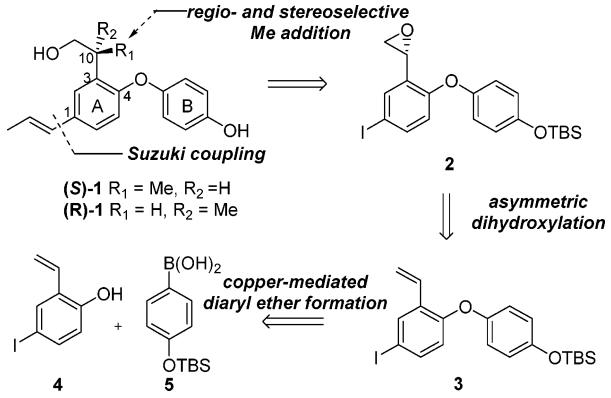
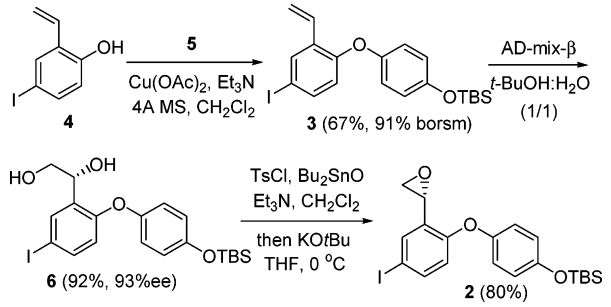
SCHEME 1. Retrosynthetic Analysis of Rodgersinol (1)



SCHEME 2. Synthesis of the Chiral Epoxide 2



due to the steric factor of the *o*-vinyl substituent.[9] Sharpless asymmetric dihydroxylation of **3** using AD-mix-β[5,10] afforded the diol **6** in 93% enantiomeric excess (ee).[11] Selective tosylation of the primary alcohol of **6** using dibutyltin oxide[12] followed by KO-*t*-Bu treatment of the resulting tosylate led to the exclusive formation of the desired epoxide **2** in 80% overall yield.

Having established a reliable route to the requisite chiral epoxide **2**, we focused on securing both enantiomers **7** and **8** via regio- and stereoselective epoxide opening by a methyl addition. Pleasingly, we found that two different nonracemic adducts, consisting of the 2-arylpropanol skeleton, could be prepared by employing two types of protocols for the stereoselective methyl introduction[13] at C-10 (Scheme 3). Upon methyl cuprate treatment of (*R*)-epoxide **2**, (*S*)-2-arylpropanol **7** was produced in an inversion fashion in 70% yield and 91% ee.[11,13a] On the other hand, methyl aluminum treatment of the same (*R*)-epoxide **2** afforded the (*R*)-2-arylpropanol **8** as the major product, with retention fashion in 75% yield and 89% ee,[11,13b] along with a small amount of regioisomer (15%). The total synthesis of (*S*)-rodgersinol (**1**) was completed by the Suzuki reaction[4,14] of **7** with (*E*)-propenylboronic acid and concurrent TBS-deprotection in the presence of $Pd(PPh_3)_4$ and CsF. Initially, the coupling product turned out to possess a mixture of *E*/*Z* olefins in a 6.5:1 ratio, on the basis of spectral analysis. However, the olefin isomerization catalyzed by $(CH_3CN)_2PdCl_2$ provided the desired (*S*)-**1** with only (*E*)-geometry.[15] The (*R*)-**1** was also synthesized from the aryl iodide **8**, by analogy to (*S*)-**1**.

The spectroscopic properties (IR, ^1H and ^{13}C NMR, MS) of the synthetic rodgersinol were compatible with those of the natural **1**. The absolute configuration of the C-10 stereogenic center of the natural **1** was determined as (*S*) by comparison[16] of the optical rotations [synthetic (*S*)-**1**, $[\alpha]^{20}_D$ −12.7 (*c* 0.17, MeOH); natural **1**, $[\alpha]^{20}_D$ −14.6 (*c* 0.04, MeOH)[1]] and their retention times on chiral HPLC.

In conclusion, the first concise synthesis of (*S*)-(−)-rodgersinol has been achieved via efficient diaryl ether formation, together with the stereoselective methyl group addition to the chiral aryloxirane, for elaboration of the 2-arylpropanol moiety. The absolute configuration of the C-10 stereogenic center was also determined through the present synthesis. Studies on the biological properties of the (*R*)-antipode **1**, as well as structural analogues of (*S*)-rodgersinol based on the current synthetic route, are progressing well.

Experimental Section

***tert*-Butyl(4-(4-iodo-2-vinylphenoxy)phenoxy)dimethylsilane (3).** To a solution of 4-iodo-2-vinylphenol **4** (0.98 g, 4.0 mmol), boronic acid **5** (3.0 g, 12.0 mmol), and copper acetate (0.73 g, 4.0 mmol) in the presence of 4A molecular sieves in CH_2Cl_2 (20 mL) was added triethylamine (2.8 mL, 20.0 mmol). The reaction mixture was vigorously stirred for 24 h at ambient temperature and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified via flash column chromatography on silica gel (EtOAc/hexanes = 1:100) to afford 1.2 g (67%) of **3** as a colorless oil and 0.26 g of the starting phenol **4** (EtOAc/hexanes = 1:5): FT-IR (thin film, neat) ν_{max} 2929, 1501, 1229 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (d, 1H, J = 2.2 Hz), 7.42 (dd, 1H, J = 8.6, 2.2 Hz), 6.93 (dd, 1H, J = 17.6, 11.2 Hz), 6.84−6.75 (m, 4H), 6.51 (d, 1H, J = 8.6 Hz), 5.76 (dd, 1H, J = 17.6, 1.1 Hz), 5.30 (dd, 1H, J = 11.1, 1.1 Hz), 0.96 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0, 151.8, 150.6, 137.4, 135.3, 131.1, 129.9, 129.4, 121.0, 120.1, 119.9, 116.3, 86.1, 25.7, 18.2, −4.4; LR-MS (FAB) *m*/*z* 452 (M^+); HR-MS (FAB) calcd for $C_{20}H_{25}IO_2Si$ (M^+) 452.0669, found 452.0667.

(*S*)-2-(2-(4-(*tert*-Butyldimethylsilyloxy)phenoxy)-5-iodophenyl-)propan-1-ol (7). To a solution of copper cyanide (114 mg, 1.25 mmol) in THF (1 mL) was added methyllithium (780 μL of 1.60 M solution in THF, 1.25 mmol) at −40 °C. The reaction mixture was stirred for 30 min, and $BF_3{\cdot}OEt_2$ (157 μL, 1.25 mmol) and a solution of the epoxide **2** (90 mg, 0.25 mmol) was added dropwise at −80 °C. The reaction mixture was stirred for 2 h, quenched with saturated aqueous NH_4Cl and NH_4OH, and then diluted with Et_2O. The organic phase was washed with water and brine, dried over

(9) The coupling reaction of an electron-poor phenol with an aldehyde or ketone group instead of an alkyl group, such as 5-bromo-2-hydroxybenzaldehyde or 1-(5-bromo-2-hydroxyphenyl)ethanone, failed to provide the desired product.

(10) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785−3786.

(11) The enatiomeric excess (ee) was determined by chiral HPLC. For details, see the Supporting Information.

(12) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447−450.

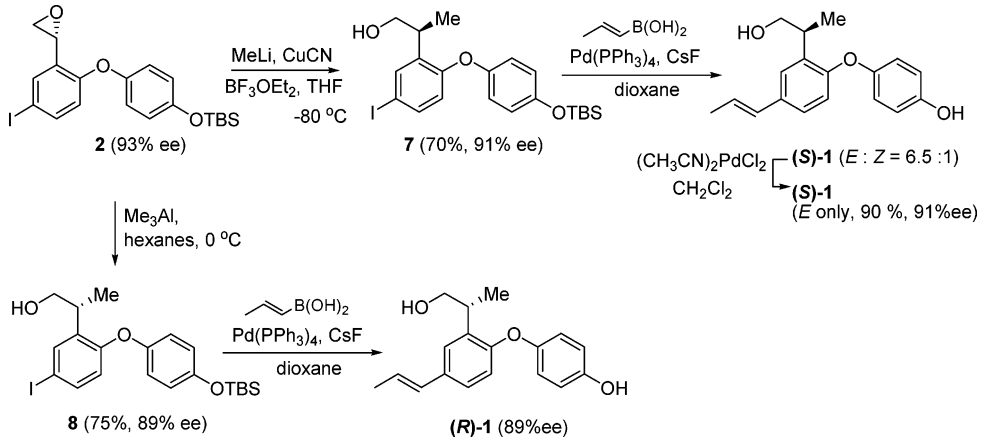
(13) (a) Botuha, C. B.; Haddad, M.; Larcheveque, M. *Tetrahedron: Asymmetry* **1998**, *9*, 1929−1931. (b) The retention of the stereochemistry is explained by an intramolecular methyl migration via aluminum-complexed phenyloxirane through an intermediary carbenium ion while the inversion can be understood by the BF_3-promoted intermolecular backside attack of the methyl nucleophile. Fukumasa, M.; Furuhashi, K.; Umezawa, J.; Takahashi, O.; Hirai, T. *Tetrahedron Lett.* **1991**, *32*, 1059−1062. For reports on related conditions, see: (c) Carde, L.; Davies, H.; Geller, T. P.; Roberts, S. M. *Tetrahedron Lett.* **1999**, *40*, 5421−5424. (d) Takano, S.; Yanase, M.; Sugihara, T.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1538−1540 and references therein.

(14) For a report on related conditions, see: Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761−1763. and references therein.

(15) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627−4629.

(16) Optical rotation of the synthetic (*R*)-**1**: $[\alpha]^{20}_D$ +12.3 (*c* 0.05, MeOH).

SCHEME 3. Completion of Total Synthesis of Rodgersinol (1)



$MgSO_4$, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes = 1:2) afforded 65 mg (70%) of the 2-arylpropanol **7** as a colorless oil: $[\alpha]^{20}_D$ −10.5 (*c* 1.7, CH_3OH); FT-IR (thin film, neat) ν_{max} 2927, 1501, 1228 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, 1H, J = 2.2 Hz), 7.42 (dd, 1H, J = 2.2, 8.6 Hz), 6.82−6.71 (m, 4H), 6.52 (d, 1H, J = 8.6 Hz), 3.79−3.67 (m, 2H), 3.43 (m, 1H), 1.27 (d, 3H, J = 6.9 Hz), 0.96 (s, 9H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.0, 151.8, 150.6, 136.8, 136.4, 121.0, 119.8, 86.3, 67.4, 35.5, 25.7, 18.2, 16.7, −4.5; LR-MS (EI) *m*/*z* 484 (M^+); HR-MS (EI) calcd for $C_{21}H_{29}IO_3Si$ (M^+) 484.0931, found 484.0929.

(*S*)-Rodgersinol (1). To a refluxing solution of the 2-arylpropanol **7** (60 mg, 0.12 mmol), *trans*-propenylboronic acid (32 mg, 0.37 mmol), and cesium fluoride (73 mg, 0.50 mmol) in dioxane (1 mL) was added $Pd(PPh_3)_4$ (15 mg, 0.01 mmol). The reaction mixture was stirred for 3 h, cooled to ambient temperature, and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes = 1:2) afforded an *E*/*Z* mixture (6.5:1) of rodgersinol **1**.

To a solution of above rodgersinol **1** in CH_2Cl_2 (1 mL) was added bis(acetonitrile)dichloride palladium(II) (3 mg, 0.01 mmol). The reaction mixture was stirred for 12 h and concentrated in vacuo. Purification of the residue via flash column chromatography on silica gel (EtOAc/hexanes = 1:2) afforded 44 mg (90%) of (*E*)-isomer of (*S*)-rodgersinol **1** as a colorless oil: $[\alpha]^{20}_D$ −12.7 (*c* 0.17, MeOH) (lit.[1] natural **1** $[\alpha]^{20}_D$ −14.6 (*c* 0.04, MeOH)); FT-IR (thin film, neat) ν_{max} 2924, 1505, 1214 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.22 (m, 1H), 7.12 (dd, 1H, J = 2.2, 8.4 Hz), 6.89−6.69 (m, 5H), 6.37 (m, 1H), 6.18 (m, 1H), 4.88 (m, 1H), 3.82−3.69 (m, 2H), 3.45 (m, 1H), 1.86 (dd, 3H, J = 1.5, 6.4 Hz), 1.28 (d, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 151.4, 151.0, 133.9, 133.3, 130.3, 125.4, 124.9, 119.9, 119.7, 118.4, 116.3, 67.8, 35.6, 18.4, 16.8; LR-MS (EI) *m*/*z* 284 (M^+); HR-MS (EI) calcd for $C_{18}H_{20}O_3$ (M^+) 284.1412, found 284.1409.

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Supporting Information Available: Experimental procedures, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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