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단신 (Notes)

An Efficient Synthesis of Alternariol

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INTRODUCTION

Alternariol (1) and alternariol-9-methyl ether (1a) are major toxins produced by *Alternaria* species (*Fig.* 1). Owing to their ubiquitous occurrence as well as their ability to grow and produce toxins even under unfavorable conditions such as low temperature and low water activity, fungi of the genus *Alternaria* are sources of contamination in refrigerated fruits, vegetables, and stored feedstuffs.[1,2] Toxins produced by *Alternaria* species have been encountered in corn flakes, cereals, fruits such as tomatoes and apples, and other crops.[3–5] Exposure to *Alternaria* has also been associated with adverse health effect. For example, cereals contaminated with high amounts of *Alternaria* have been reported to be related to an enhanced incidence of esophageal cancer in China.[6,7]

Alternariol (1) and alternariol-9-methyl ether (1a) have been isolated from infected fruits in submilligram amounts.[8] However, larger quantities of these of these compounds are needed if we are to achieve a detailed understanding of their formation, biosynthesis and metabolism; such knowledge is needed in order to minimize crop losses and toxicological residual risks. Despite this need, the effective synthetic methods for these compounds have yet to be developed.

Although the preparation of **1** from **1a** was reported in the early 1960s,[9] **1a** was obtained as the major side-product during the total synthesis of **1**.[10,11] By modifying the reported convergent strategy *via* the Suzuki-type formation of the biaryl moiety,[10] we hereby report the total synthesis of alternariol **1** in high yields without the generation of its side-product **1a**.

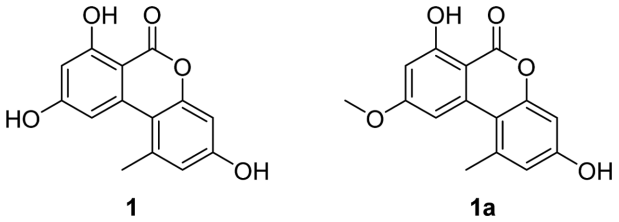


***Figure* 1.** Structures of alternariol **1** and alternariol-9-methyl ether **1a**.

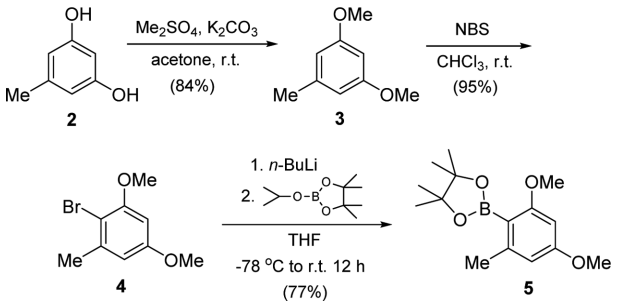
RESULTS AND DISCUSSION

As shown in *Scheme* 1, orcinol (1,3-dihydroxy-5-methylbenzene (2)) was first methylated, followed by bromination to afford the bromoorcinol derivative **4**.

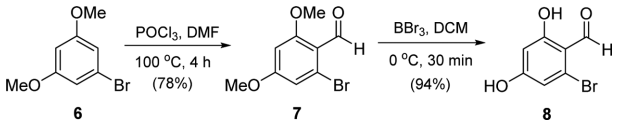
Because of the bulky dimethoxy group, selective bromination was achieved, affording **4** in high yield. The boronic ester was then introduced into **4** by a typical metal-halogen exchange reaction using butyllithium, followed by trapping with the corresponding triisopropyl borate to give **5** (*Scheme* 1).

The second building block was prepared using 1-bromo-3,5-dimethoxy benzene **6**. The carbaldehyde **7** was introduced by Vilsmeier-Haak reaction,[12] and further demethylation using BBr_3 produced bromodihydroxy benzaldehyde **8** (*Scheme* 2). To prevent the generation of the unwanted side-product, **1a**, both methoxy groups in **7** were removed before further functionalization.

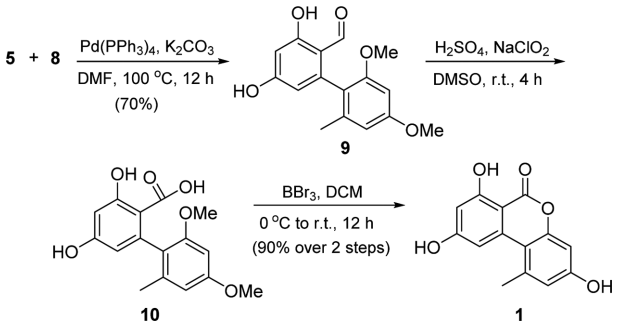
The subsequent palladium-catalyzed Suzuki coupling between the boronic ester **5** and the bromide **8** yielded biaryl **9** in 70% yield. Finally, alternariol **1** was synthesized via a two-step sequence. First, aldehyde **9** was oxidized using



***Scheme* 1.** Synthetic route to boronic ester **5**.



***Scheme* 2.** Synthetic route to **8**.



***Scheme* 3.** Synthetic route to the alternariol **1**.

sodium chlorite[13] and TLC analysis indicated a complete conversion to the corresponding acid **10**. This was used after simple filtration to remove any inorganic residue. Next, intramolecular lactonization using BBr_3 gave the desired compound **1** in 90% yield over two steps (*Scheme* 3). The phenoxide generated by BBr_3-promoted demethylation caused an efficient intramolecular cyclization with the neighboring carboxylic acid. Our group previously reported similar lactonization of the phenoxide by BBr3-promoted demethylation with the neighboring ester group which was fast and quantitative.[14] The use of excess amounts of BBr_3 and longer reaction time were necessary in this case to complete cyclization, as well as demethylation, since some of the BBr_3 could be coordinated to the acid group in **10**.

In summary, we successfully synthesized alternariol in high yield without the generation of the problematic side product, alternariol methyl ether.

EXPERIMENTAL SECTION

Synthesis of 1,3-dimethoxy-5-methylbenzene (3)

Dimethyl sulfate (2.29 cm^3, 21.2 mmol) and K_2CO_3 (2.45 g, 17.7 mmol) were added to a 100 cm^3 round bottom flask containing 1,3-dihydroxy-5-methylbenzene (2) (1.0 g 8.05 mmol) in acetone (10 cm^3). The resulting solution was left to stir at r.t. for 24 h under nitrogen, after which a 15% NaOH aqueous solution (10 cm^3) was added. The reaction mixture was extracted using EtOAc, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The crude product was purified by column chromatography (3:1 hexane:EtOAc) to afford product **3** as a colorless oil (1.04 g, 84%); R_f 0.6 (3:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 6.33 (2H, d, J=2.0, 2×Ar*H*), 6.28 (1H, t, J=2.0, Ar*H*), 3.77 (6H, s, 2×OCH_3), 2.30 (3H, s, CH_3); ν_{max}(KBr)/cm^{-1} 3037, 2997, 2954, 2836, 1595, 1457, 1320, 1204 and 1148.

Synthesis of 6-bromo-1,3-dimethoxy-5-methylbenzene (4)

First, while maintaining the reaction temperature below 10 °C, NBS (0.82 g, 4.6 mmol) was added to a solution of **3** (0.7 g, 4.6 mmol) in acetonitrile (10 cm^3) under nitrogen. Next, the reaction mixture was stirred at r.t. for 12 h. Finally, water (10 cm^3) was added, and the reaction mixture was extracted with EtOAc (3 × 10 cm^3). Then, the combined organic extracts were dried over anhydrous $MgSO_4$ and evaporated. The crude product **4** was purified by column chromatography (20:1 hexane:EtOAc) to obtain **4** as white needles (1.02 g, 95%); m.p. 52-54 °C; R_f 0.4 (20:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 6.42 (1H, d, J=2.5 Ar*H*), 6.34 (1H, d, J=2.5, Ar*H*), 3.86 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 2.39 (3H, s, CH_3); ν_{max}(KBr)/cm^{-1} 3007, 2959, 2921, 2835, 1588, 1459, 1202, 1161, and 609.

Synthesis of boronic ester 5

First, at -78 °C under nitrogen, *n*-BuLi (0.46 cm^3, 1.14 mmol) was added dropwise to a solution of **4** (0.18 g, 0.76 mmol) in THF (5 cm^3). After stirring at this temperature for 90 min, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was added to the mixture, and the mixture was left so as to allow the temperature to increase to r.t; the mixture was then left to stir at r.t. for 12 h. Water (5 cm^3) was then added, and then the reaction mixture was extracted with EtOAc (3 × 5 cm^3). The combined organic extracts were dried over $MgSO_4$ and evaporated. The crude product was purified by column chromatography (5:1 hexane:EtOAc) to afford **5** as a yellow viscous oil (0.17 g, 77%); R_f 0.42 (5:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 6.28 (1H, br signal, Ar*H*), 6.22 (1H, br signal, Ar*H*), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 2.34 (3H, s, CH_3), 1.36 (12H, s, 4×CH_3); ν_{max}(KBr)/cm^{-1} 2993, 2979, 2935, 2839, 1606, 1576, 1457, 1340, and 1145.

Synthesis of 1-bromo-3,5-dimethoxybenzaldehyde (7)

First, while maintaining the temperature at 0 °C using an ice bath, phosphoryl chloride (1.1 cm^3, 11.5 mmol) was slowly added to a solution of 1-bromo-3,5-dimethoxybenzene (6) (1.0 g, 4.61 mmol) in DMF (4 cm^3). Second, the reaction mixture was stirred at this temperature for another 10 min and at r.t. for 30 min. Next, the temperature was increased to 100 °C, and the mixture was stirred for 4 h.

Finally, water (5 cm^3) was added, and then the reaction mixture was extracted using EtOAc (3 × 5 cm^3). The combined organics were dried over $MgSO_4$ and evaporated. The crude product **7** was purified by column chromatography (3:1 hexane:EtOAc) to afford **7** as a white solid (0.88 g, 78%); m.p. 83-85 °C; R_f 0.25 (3:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 10.30 (1H, s, C*H*O), 6.77 (1H, d, *J*=2.0, Ar*H*), 6.43 (1H, d, *J*=2.0, Ar*H*), 3.89 (3H, s, OCH_3), 3.86 (3H, s, OCH_3); ν_{max}(KBr)/cm^{-1} 3003, 2967, 2866, 2783, 1683, 1592, 1558, 1450, 1414, 1229, 1134, and 632.

Synthesis of 1-bromo-3,5-dihydroxybenzaldehyde (8)

First, at 0 °C under nitrogen, BBr_3 in DCM (3.67 cm^3, 3.67 mmol) was carefully added to a solution of **7** (0.3 g, 1.23 mmol) in DCM (5 cm^3). Next, after stirring for 30 min at this temperature, methanol (5 mL) was carefully added, and then the solvent was evaporated. The reaction mixture was extracted with EtOAc (3 × 5 mL), and the combined organic extracts were dried over Na_2SO_4 and evaporated. The crude product **8** was purified by column chromatography (3:1 hexane:EtOAc), followed by recrystallization using hexane to afford **8** as a white solid (0.25 g, 94%); m.p. 205-207 °C; R_f 0.28 (3:1 hexane:EtOAc); ^{1}H NMR (400 MHz, MeOD, δ) 10.06 (1H, s, C*H*O), 6.67 (1H, d, *J*=2.0, Ar*H*), 6.25 (1H, d, *J*=2.0, Ar*H*); ν_{max}(KBr)/cm^{-1} 3390, 2967, 2936, 2850, 1624, 1585, 1436, 1215, and 640.

Synthesis of the cross-coupled biaryl compound (9)

First, boronic ester **5** (70 mg, 0.25 mmol), bromo aldehyde **8** (50 mg, 0.23 mmol), and tetrakis(triphenylphosphine)palladium (5.3 mg, 0.005 mmol) were added to a Schlenk flask containing a mixture of aqueous K_2CO_3 (2.0 M; 0.23 cm^3) and DMF (3 cm^3) under nitrogen. Next, after thorough degassing, the mixture was left to stir at 100 °C for 12 h under nitrogen, affording a black suspension. Third, the reaction mixture was cooled to r.t., and water (3 cm^3) was added. Finally, the mixture was extracted with EtOAc (3 × 3 cm^3), and the combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by column chromatography (2:1 hexane:EtOAc) to afford the product **9** as a yellow viscous liquid (47 mg, 70%); R_f 0.23 (2:1 hexane:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, δ) 9.28 (1H, s, C*H*O), 6.43 (1H, br signal, Ar*H*), 6.37 (1H, br signal, Ar*H*), 6.35 (1H, s, Ar*H*), 6.19 (1H, br signal, Ar*H*), 3.84 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.04 (3H, s, CH_3); ^{13}C NMR (100.5 MHz, $CDCl_3$, δ) 195.48, 165.43, 163.54, 160.40, 157.90, 145.71, 138.74, 117.94, 113.60, 111.46, 106.64, 102.13, 95.79, 55.58, 55.29, 20.64; ν_{max}(KBr)/cm^{-1} 3402, 2951, 2919, 1623, 1453, 1203, and 1156; *m/z* (FAB) 289 [(M+1)]$^+$, 40%], 154 (90%) and 57 (100%); [Found: (M+1)$^+$ 289.1085. $C_{16}H_{17}O_5$ requires *M*, 289.1018].

Synthesis of alternariol (1)

Alternariol was synthesized in a two-step sequence: first, the aldehyde was oxidized by adding sulfuric acid (9.9 μL), $NaClO_2$ (17.6 mg, 0.15 mmol), and DMSO (14.8 μL) to a water:acetonitrile (2:1, 3 cm^3) solution of **9** (30.0 mg, 0.104 mmol) at r.t. After the mixture was stirred for 4 h at this temperature, the solvents were evaporated, and the organic extracts were extracted with CH_2Cl_2 (2 × 3 cm^3). The organic layers were filtered through a silica plug to remove any inorganic residues to afford the product **10**, which was used for the next step without further purification. Second, cyclization was conducted by adding BBr_3 in DCM (0.83 mL, 0.83 mmol) to a solution of **10** in DCM (1 mL) at 0 °C. This was left to stir at r.t. for 12 h before methanol (1 mL) was added carefully and the solvents were evaporated. The reaction mixture was extracted with EtOAc (3 × 2 mL), and the combined organics were dried over Na_2SO_4 and evaporated. The crude product **1** was purified by column chromatography (3:1 hexane:EtOAc) to afford **1** as a white solid (24 mg, 90% over two steps); m.p. 268-269 °C; R_f 0.17 (3:1 hexane:EtOAc); ^{1}H NMR (400 MHz, CD_3OD, δ) 7.19 (1H, br signal, Ar*H*), 6.65 (1H, d, *J*=1.5, Ar*H*), 6.56 (1H, d, *J*=1.5, Ar*H*),), 6.32 (1H, br signal, Ar*H*), 2.70 (3H, s, CH_3); ^{13}C NMR (100.5 MHz, CD_3OD, δ) 167.65, 167.04, 166.34, 160.02, 154.59, 140.13, 139.94, 118.70, 111.08, 105.87, 102.91, 102.25, 95.79, 26.00; ν_{max}(KBr)/cm^{-1} 3318, 3081, 2982, 1652, 1616, 1466, 1357, 1231, 1203, and 1168; *m/z* (FAB) 259 [(M+1)]$^+$, 100%]; [Found: (M+1)$^+$, 259.0604. $C_{14}H_{11}O_5$ requires *M*, 259.0548].

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