JOC*Note*

Total Synthesis of Alternariol

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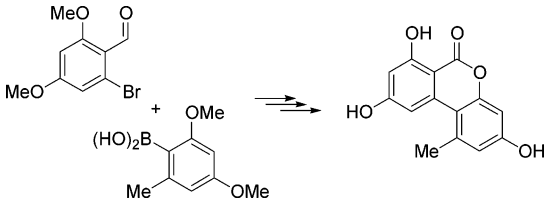

Total synthesis of alternariol, a toxic secondary metabolite of various *Alternaria* fungi, was achieved in seven steps starting with orcinol and 3,5-dimethoxybromobenzene. The longest linear sequence consists of six steps. Key reaction is a palladium-catalyzed Suzuki-type coupling of an orcinol-derived boronic acid with a brominated resorcylic aldehyde. The final demethylation furnished alternariol in 73% yield containing a smaller fraction of alternariol 9-methyl ether (~20%).

The resorcylic lactones alternariol (**1**) and alternariol 9-methyl ether (**2**) are main metabolites of toxin-producing *Alternaria* fungi (Figure 1).[1] Although the toxicity of these mycotoxins is low as compared with others (e.g., aflatoxins),[2] they lead to significant crop losses by fouling of tomatoes, apples, and other fruits.[1,3,4] They are isolated from infected fruits in submilligram amounts.[4] Detailed knowledge of their formation, their biosynthesis and their metabolism is essential for a minimization of crop losses and toxicological residual risks. For this purpose, considerable amounts of theses substances are needed, which we tried to synthesize by following an existing nine-step synthesis of alternariol published in 1990.[5] Unfortunately, we were not able to reproduce parts of this synthesis and decided to develop a new, convergent synthesis which is described in this Note. The synthesis

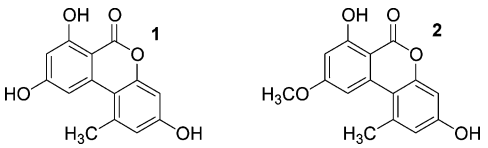

FIGURE 1. Metabolites in *Alternaria* fungi.

of alternariol methyl ether from alternariol has been published already in the early 1960s.[6] We planned a convergent strategy with a Suzuki-type formation of the biaryl moiety, which should allow for a similar synthesis of related resorcylic lactones.

Starting with orcinol (1,3-dihydroxy-5-methylbenzene, **3**), we prepared the bromoorcinol derivative **4** by methylation[7] and subsequent bromination with *N*-bromosuccinimide (NBS) in virtually quantitative yield (Scheme 1).[8] The boronic acid ready for Suzuki coupling was obtained by halogen metal interchange with butyllithium and trapping of the thus formed lithiated compound with triisopropyl borate.[9] The labile boronic acid **5** formed after hydrolytic workup was not stored but immediately reacted further.

The second building block was prepared starting with 3,5-dimethoxybromobenzene **6**. Vilsmeyer formylation[10] gave the carbaldehyde **7**, which was further oxidized with sodium chlorite (Kraus conditions)[11] and esterified with diazomethane, yielding methyl ester **8** (Scheme 2).

While ester **8** could not be coupled with boronic acid **5** in a palladium-catalyzed Suzuki coupling[12] with all tested variations, we succeeded in coupling carbaldehyde **7** to yield biaryl **9**. Nevertheless, we had to use 3 equiv of boronic ester **5** to achieve a 78% yield (Scheme 3). Oxidation of carbaldehyde **9** furnishing the alternariol precursor **10** was again achieved with Kraus conditions.

Alternative attempts to oxidize an eventually formed hemiacetal after demethylation of carbaldehyde **9** failed.

Deprotection of the hydroxy functions was achieved with boron tribromide.[5] Although the reaction of the corresponding methyl ester was reported to work without problems, the demethylation of carboxylic acid **10** worked only with very specific conditions. While the use of 16

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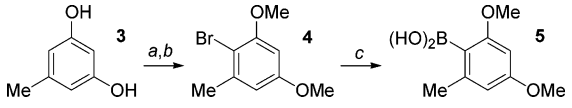
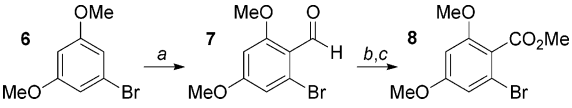
SCHEME 1. Synthesis of Boronic Acid 5[a]



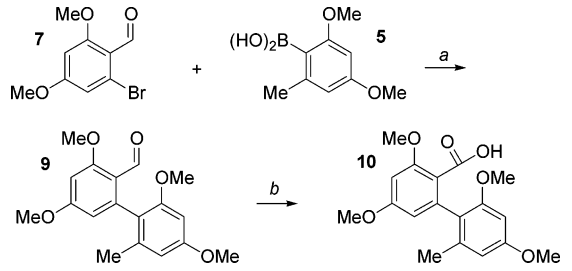
[a] Conditions: (a) 2.2 equiv of Me_2SO_4, 2.6 equiv of K_2CO_3, acetone, reflux, 4 h, 99%; (b) 1 equiv of NBS, $CHCl_3$, rt, 99%; (c) 1.05 equiv of *n*-BuLi, 1.3 equiv of $B(OiPr)_3$, THF, −78 °C, 15 min, then rt, 12 h, 99%.

SCHEME 2. Synthesis of Brominated Coupling Partners 7 and 8[a]



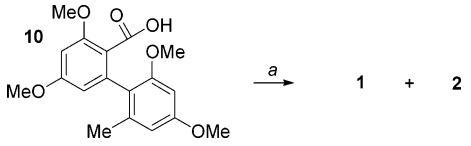
[a] Conditions: (a) 2.5 equiv of $POCl_3$, DMF, 100 °C, 4 h, 78%; (b) 1.5 equiv of NaH_2PO_4, 4 equiv of $NaClO_2$, 6 equiv of 2-methyl-2-butene, *t*BuOH/H_2O (5:1), rt, 2 h, 85%; (c) CH_2N_2, Et_2O, 70%.

SCHEME 3. Synthesis of Alternariol Precursor 10[a]



[a] Conditions: (a) 1 equiv of **7**, 3 equiv of **5**, 2 equiv of K_2CO_3, 0.1 equiv of $Pd(PPh_3)_4$, DMF, 100 °C, 4 h, 78%; (b) 1.5 equiv of NaH_2PO_4, 4 equiv of $NaClO_2$, 6 equiv of 2-methyl-2-butene, *t*BuOH/H_2O (5:1), rt, 2 h, 85%.

SCHEME 4. Synthesis of Alternariol (1)[a]



[a] Conditions: (a) 8 equiv of BBr_3, CH_2Cl_2, 0 °C, 24 h, 73% **1**.

equiv led to significant decomposition of the material, we obtained satisfactory results when we used 8 equiv of boron tribromide. With even less Lewis acid, the reaction became very sluggish and yields were poor. But even with these optimized reaction conditions (Scheme 4) alternariol was produced together with about 20% of alternariol 9-methyl ether.[13] Nevertheless, pure alternariol was obtained with conventional chromatography (silica gel, CH_2Cl_2/MeOH).

Experimental Section

2,4-Dimethoxy-6-(2,4-dimethoxy-6-methylphenyl)-benzaldehyde (9). To a solution of 2-bromo-4,6-dimethoxybenzaldehyde (**7**, 1.44 g, 6.29 mmol) in DMF (30 mL) were added 2,4-dimethoxy-6-methylphenylboronic acid (**5**, 3.02 g, 18.4 mmol), K_2CO_3 (1.74 g, 12.6 mmol), and $Pd(PPh_3)_4$ (727 mg, 0.629 mmol). After stirring for 24 h at 80 °C, the mixture was poured into a saturated NH_4Cl solution (20 mL), and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with H_2O (5 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvents and chromatography of the residue (flash chromatography (cyclohexane/ethyl acetate 2:1) and MPLC (hexane/ethyl acetate 2:1)) yielded the title compound **9** as a yellowish oil (1.55 g, 4.90 mmol, 78%) and 3,5-dimethoxytoluene (661 mg, 4.34 mmol). Mp: 84 °C. ^{1}H NMR (600.1 MHz, $CDCl_3$): δ 2.04 (s, 3 H, Me), 3.69, 3.86, 3.87, 3.96 (4 s, 12 H, 4 OMe), 6.31 (d, J = 2.2 Hz, 1 H, Ar−H), 6.39 (d, J = 2.1 Hz, 1 H, Ar−H), 6.45 (d, J = 2.1 Hz, 1 H, Ar−H), 6.50 (d, J = 2.2 Hz, 1 H, Ar−H), 9.83 (s, 1 H, CHO). ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 20.5 (Me), 55.3, 55.5, 55.7, 55.8 (4 OMe), 96.0, 97.7, 106.4, 108.4 (4 Ar−CH), 117.9, 120.6, 137.9, 145.5 (4 Ar−C), 157.6, 160.1, 162.6, 164.5 (4 Ar-*C*-OMe), 190.1 (CO). MS (FAB pos) *m/z* (%): 317 (100, $[M + H]^+$), 289 (40). IR (KBr): $\tilde{\nu}$ 2940, 2839, 2771, 1719, 1685, 1593, 1498, 1456, 1406, 1321, 1277, 1228, 1205, 1154, 1138, 1093, 1050, 1024, 949, 834 cm^{-1}. HRMS-EI (*m/z*): M^+ calcd for $C_{18}H_{20}O_5$ 316.1311, found 316.1307.

2,4-Dimethoxy-6-(2,4-dimethoxy-6-methylphenyl)-benzoic Acid (10). To a solution of **9** (319 mg, 1.00 mmol) in *t*BuOH/H_2O (5:1, 30 mL) were added NaH_2PO_4 (234 mg, 1.50 mmol), $NaClO_2$ (233 mg, 84.0 mmol), and 2-methyl-2-butene (4.5 mL, 9.0 mmol). After the mixture was stirred for 2 h, the solvents were evaporated and the residue was extracted with CH_2Cl_2 (2 × 15 mL). The organic layers were evaporated and purified with MPLC (hexane/ethyl acetate 1:10), yielding a white solid of **10** (268 mg, 0.848 mmol, 85%). ^{1}H NMR (500.0 MHz, $CDCl_3$): δ 2.06 (s, 3 H, Me), 3.64, 3.83, 3.84, 3.92 (4 s, 12 H, 4 OMe), 6.33 (d, J = 2.3 Hz, 1 H, Ar−H), 6.36 (d, J = 2.2 Hz, 1 H, Ar−H), 6.41 (d, J = 2.2 Hz, 1 H, Ar−H), 6.51 (d, J = 2.3 Hz, 1 H, Ar−H), 10.00−11.00 (br. s, 1 H, CO_2H). ^{13}C NMR (125.0 MHz, $CDCl_3$): δ 20.5 (Me), 55.2, 55.5, 55.7, 55.1 (4 OMe), 96.2, 97.7, 106.3, 108.2 (4 Ar−CH), 115.2, 122.1, 137.9, 140.7 (4 Ar−C), 157.4, 158.7, 159.8, 161.9 (4 Ar-*C*-OMe), 169.4 (CO_2H). MS (FAB pos) *m/z* (%): 332 (100, M^+), 315 (75, $[M - H_2O]^+$). IR (KBr): $\tilde{\nu}$ 2994, 2946, 2843, 2659, 2553, 1694, 1604, 1580, 1503, 1467, 1420, 1320, 1290, 1231, 1205, 1182, 1158, 1139, 1096, 1063, 1045, 1023, 951, 936, 864, 855, 836 cm^{-1}. HRMS-EI (*m/z*): M^+ calcd for $C_{18}H_{20}O_6$ 332.1260, found 332.1257.

Alternariol (1). To a solution of **10** (180 mg, 0.542 mmol) in CH_2Cl_2 (5 mL) was carefully added at 0 °C a solution of 1 M BBr_3 in CH_2Cl_2 (4.56 mL, 4.56 mmol). The solution changed to an intense red color. After the mixture was stirred for 24 h at room temperature, MeOH (0.5 mL) was *carefully* (!) added within 30 min. The formed precipitate redissolved. When further addition of MeOH no longer led to an evolution of gas, further MeOH was added in one portion (10 mL). The solvents were evaporated, and the remaining residue was purified by chromatography (CH_2Cl_2/MeOH 50:1 → CH_2Cl_2/MeOH 10:1), yielding **1** as a white solid (102 mg, 394 μmol, 73%). ^{1}H NMR (500.0 MHz, CD_3OD): δ 2.77 (s, 3 H, Me), 6.38 (d, ^4J = 1.9, 1 H, Ar−H), 6.32 (d, ^4J = 2.6, 1 H, Ar−H), 6.71 (d, J = 2.6 Hz, 1 H, Ar−H), 7.27 (d, J = 2.0 Hz, 1 H, Ar−H). ^{13}C NMR (125.0 MHz, CD_3OD): δ 24.39 (Me), 97.70 (Ar−C), 100.57 (Ar−CH), 101.35 (Ar−CH), 104.08 (Ar−CH), 109.54 (Ar−C), 117.13 (Ar−CH), 138.40 (Ar−C), 138.65 (Ar−C), 153.07, 158.45, 164.79, 165.47, 165.53 (4 × Ar-*C*-OMe, CO). MS (FAB pos) *m/z* (%): 259 (17, M^+). IR (KBr): $\tilde{\nu}$ 3447, 3187, 2974, 2557, 2382, 1663, 1613, 1581, 1515, 1462, 1422, 1354, 1286, 1263, 1250, 1204, 1165, 1127, 1107, 1056, 1031, 992, 968, 937, 851, 796, 749, 709, 660, 638 cm^{-1}.

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Supporting Information Available: Experimental procedures and spectroscopic data for all compounds and spectra of **9**, **10**, and alternariol (**1**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Constitutional identity of monomethyl ether **2** was proved by means of two-dimensional NMR spectroscopy.