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First synthesis and absolute configuration of (−)-pyriculariol, a phytotoxin isolated from rice blast fungus, *Magnaporthe grisea*. Use of microwave irradiation to control Stille coupling reaction products

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ABSTRACT

First total synthesis of (−)-pyriculariol, a phytotoxin isolated from rice blast fungus, *Magnaporthe grisea*, was achieved to determine the absolute configuration of the natural product to be 5′*R*,6′*S*. The key step was Stille coupling reaction using microwave irradiation from −78 °C to control the reaction.

(−)-Pyriculariol (**1**) was isolated from the culture filtrate of the rice blast disease fungus, *Magnaporthe grisea* (Hebert) Barr, which induced a typical disease symptom on rice leaves.[1] Besides **1**, a series of salicylaldehyde-type phytotoxins such as pyriculol (**2**),[2] pyriculone (**3**),[3] and pyricuol (**4**)[4] have been found in this fungus. Although the absolute configuration of **2**[5] and **4**[6] was determined by total syntheses, the absolute configuration of **1** has still remained unknown over 28 years since the isolation. In this Letter we describe the first synthesis and the absolute configuration of **1** (Fig. 1, Scheme 1).

We set the synthetic target to be (5′*R*,6′*S*)-**1** possessing a similar stereochemistry to natural (+)-(3′*R*,4′*S*)-pyriculol (**2**). We employed anti diol function of the known aldehyde **6**.[7] L-Rhamnal diacetate (**5**) was converted to **6** by Ferrier reaction, and the free hydroxy group was protected with acetyl group to give **7**. Corey–Fuchs reaction transformed the formyl group into dibromo olefin (**8**), and then the diacetyl group was removed to afford **9**. Treatment of **9** with BuLi gave enynediol **10**,[8] which was converted to vinyl stannane **11** by radical-mediated hydrostan-

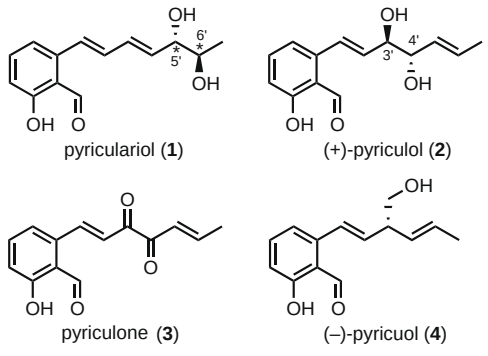
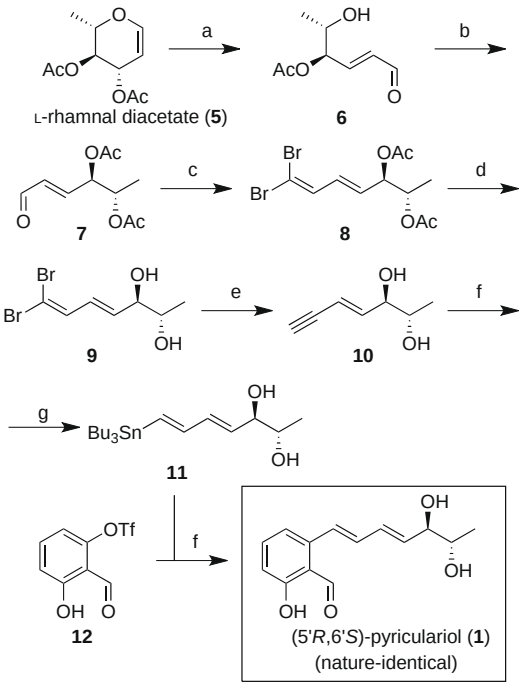


Figure 1. Salicylaldehyde-type phytotoxins isolated from rice blast fungus.



Scheme 1. Synthesis of (5′*R*,6′*S*)-pyriculariol. (a) lit. 7; (b) Ac_2O, Py (85%, 2 steps); (c) PPh_3, CBr_4, CH_2Cl_2 (54%); (d) K_2CO_3, MeOH (99%); (e) BuLi, THF −78 °C (75%); (f) Bu_3SnH, AIBN, toluene reflux (33%); (g) Pd_2dba_3, $AsPh_3$, LiCl, DMF, microwave, −78 to 33 °C (69%).

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nylation. Then the key and final Stille coupling reaction with the known triflate **12**[9] was examined. The yield of coupling product **1** was up to 30% in the presence of a variety of catalysts [$Pd(PPh_3)_4$, $Pd(OAc)_2$, Pd_2dba_3, etc.] and additives (dppf, $AsPh_3$, LiCl, CuCl, etc.) because of a preferential formation of a dimer derived from stannane **11** between 0 and 110 °C. The formation of the dimer was suppressed when an unreacted mixture (pre-cooled at −78 °C) was irradiated with microwave[10,11] to raise the temperature to 33 °C immediately. The yield of **1** increased to 69%.[12] The effect of microwave could be direct activation of the molecule rather than immediate application of heat. The yield dropped to <3% under the similar reaction conditions except microwave irradiation. The overall yield was 7.8% from **5** in 7 steps. The optical rotation value of **1** {$[\alpha]_D^{24}$ −1.3° (*c* 1.0, $CHCl_3$)} revealed that the absolute configuration of the natural **1** {$[\alpha]_D^{24}$ −3.4° (*c* 1.0, $CHCl_3$)} to be 5′*R*,6′*S*.

In conclusion, our concise synthesis of (−)-pyriculariol (**1**) determined the absolute configuration of the natural **1** to be 5′*R*,6′*S* which is quite similar to that of (+)-pyriculol (**2**). Studies of the unknown biosynthetic pathway of these phytotoxins are in progress.

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12. A 10 ml pressurized microwave vessel (CEM) equipped with a magnetic stirring bar was charged with Pd_2dba_3 (1.4 mg, 1.5 mmol, 0.02 equiv), $AsPh_3$ (1.9 mg, 6.2 mmol, 0.08 equiv), LiCl (16.2 mg, 0.382 mmol, 5.0 equiv), and DMF (1.5 ml), and the solution was stirred at 20 °C for 5 min under nitrogen atmosphere. Then to this was added triflate **12** (FW: 270.18, 20.7 mg, 76.6 mmol) in DMF (1.5 ml), and the mixture was stirred at 20 °C for 15 min before being cooled to −78 °C using dry ice-MeOH Dewar flask. To this was added a pre-cooled (−78 °C) solution of **11** (FW: 417.21, 34.9 mg, 83.7 mmol, 1.1 equiv) in DMF (2 ml). The vessel was immediately placed into the CEM Focused Microwave® Synthesis System (Model Discover), and the mixture was stirred under microwave irradiation for 30 min (mode: standard, solvent: DMF, temperature: 25 °C, run time: 0 min, hold time: 30 min, Watt: 300 W), while the temperature of the reaction raised to 33 °C within 3 min. The CEM multimode cavity system continuously adjusts the applied wattage (26–1 W) to maintain the temperature. The reaction mixture was replaced into a round-bottomed flask, and most of DMF was removed in vacuo. The residue was diluted with EtOAc and washed twice with water, dried with $MgSO_4$, and concentrated in vacuo. The crude oil was purified with preparative TLC (SiO_2, $CHCl_3$/EtOH = 98:2) to give (−)-**1** (FW: 248.27, 13.1 mg, 52.8 mmol, 69%) as pale yellow needles: mp 106–107 °C (recrystallized from CCl_4–$CHCl_3$,[1] and then from toluene–hexane–EtOAc; lit.[1] 105.5–106.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$) d: 1.19 (3H, d, *J* = 6.3 Hz, H-7′), 2.31 (1H, br, OH), 2.49 (1H, br, OH), 3.95 (1H, m, H-6′), 4.23 (1H, m, H-5′), 5.96 (1H, dd, *J* = 15.1, 6.3 Hz, H-4′), 6.53 (1H, dd, *J* = 15.1, 10.7 Hz, H-3′), 6.66 (1H, dd, *J* = 15.1, 10.3 Hz, H-2′), 6.87 (1H, d, *J* = 8.3 Hz), 6.98 (1H, d, *J* = 7.8 Hz), 7.06 (1H, d, *J* = 15.1 Hz, H-1′), 7.44 (1H, t, *J* = 8.1 Hz, H-4), 10.30 (1H, s, CHO), 11.90 (1H, s, OH). HR-EI-MS: calcd for $C_{14}H_{16}O_4$ ($M^{+\bullet}$), 248.1049; found, 248.1049.