Short Communication

Synthesis of Optically Active Pyriculol, a Phytotoxic Metabolite Produced by *Pyricularia oryzae* Cavara

Masanobu SUZUKI, Takeyoshi SUGIYAMA,
Masashi WATANABE* and
Kyohei YAMASHITA

Department of Agricultural Chemistry,
Faculty of Agriculture, Tohoku
University, Sendai 980,
Japan

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Pyriculol (**1**) is a phytotoxic metabolite that was isolated from the culture broth of a rice blast fungus, *Pyricularia oryzae*, and was shown to cause dark necrotic spots on rice leaves.¹⁾ Pyriculol (**1**) has a salicylaldehyde skeleton bearing an unsaturated side chain with two asymmetric centers at the glycol moiety. The relative stereochemistry of the glycol part was estimated to be *erythro*, however, the absolute configuration remains to be elucidated.²⁾

In our recent papers on the syntheses of salicylaldehyde-type phytotoxic substances, we reported the total syntheses of optically active

monilidiol (**2**),³⁾ dechloromonilidiol (**3**)³⁾ and pyriculariol (**4**).⁴⁾ In this communication, we describe the first synthesis of optically active pyriculol (**1**) and the determination of its absolute configuration.

This molecule was synthesized from two parts, that is, an aromatic moiety and an unsaturated side chain with a protected *erythro* diol, through Wittig condensation between them.

The aromatic synthon was prepared from 2,3-dimethylphenol (**5**) in accordance with the synthetic sequence of dechloromonilidiol (**3**).³⁾

For preparation of the side chain moiety, 2,3-*O*-cyclohexylidene-D-glyceraldehyde (**7**)⁵⁾ was chosen as a chiral starting material. Propyne was lithiated with *n*-butyllithium at -70°C in THF and then coupled with **7** at $-70 \sim -10^{\circ}\text{C}$ in the presence of zinc chloride. The resulting acetylene alcohol was reduced with lithium aluminum hydride to afford a separable diastereomeric mixture of (*E*)-allylic alcohols, (*erythro*:*threo*=2.1:1), in a 72% overall yield. The *erythro* product **8** ($[\alpha]_{\text{D}}^{22} = +20.5^{\circ}$ ($c = 1.77$ CHCl_3)) was converted to the carbonate, **9** (mp 79°C , $[\alpha]_{\text{D}}^{22} = +41.8^{\circ}$ ($c = 1.06$, CHCl_3)), through the following sequence: i) the removal of a cyclohexylidene group from **8** with 70% acetic acid at $70 \sim 80^{\circ}\text{C}$ (84% yield), ii) tritylation of a primary hydroxyl group (68% yield), iii) cyclic car-

* Present address: Chugai Pharmaceutical Co., Tokyo, Japan.

bonation of a residual 2,3-diol with dimethyl carbonate and sodium hydride (mp 147~148°C; 81% yield) and iv) acid hydrolysis of the trityl ether with *p*-TsOH in aqueous THF and methanol at 70~80°C to give the crystalline alcohol **9**, in a 90% yield.

Oxidation of **9** under Swern's conditions⁶⁾ gave an aldehyde which was used without further purification for the Wittig reaction with **6**, and a geometrical mixture ((*E*):(*Z*) = *ca.* 4:1) was obtained, in an around 30% yield, from **9**.

The desired (*E*)-isomer **10** could be separated from the (*Z*)-isomer by preparative thin-layer chromatography with development with dichloromethane. The acetal, **10**, was treated with *p*-TsOH in refluxing aqueous THF to remove the acetonide group (70% yield), and then was oxidized with active manganese dioxide in dichloromethane to give (3'*R*,4'*S*)-pyriculol 3',4'-carbonate (**11**), in a 72% yield. The carbonate, **11**, was hydrolyzed with potassium carbonate to afford (3'*R*,4'*S*)-pyriculol (**12**) (mp 97.4~98.2°C, natural **1**: 98~98.5°C⁷⁾), in a 60% yield.

The synthetic **12** was identical with natural pyriculol (**1**) as to the following data: 100 MHz ¹H-NMR, IR, HPLC (reversed phase column; acetonitrile:water=9:1) and optical rotation (synthetic **12**: $[\alpha]_D^{22} = +41.0^\circ$ (*c* = 0.730, CHCl₃), natural **1**: $[\alpha]_D^{22} = +41.3^\circ$ (*c* = 0.455, CHCl₃)⁸⁾).

From the above observations, the absolute structure of pyriculol (**1**) was determined to be 6-((3'*R*,4'*S*)-3',4'-dihydroxy-1'(*E*),5'(*E*)-heptadienyl)-2-hydroxybenzaldehyde.

We have also synthesized an enantiomer of **12** ($[\alpha]_D^{22} = -40.0^\circ$ (*c* = 0.526, CHCl₃)) and its diastereomer. Biological tests on these compounds are in progress, the details of which will be reported later.

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- 8) The optical rotation of pyriculol, $[\alpha]_D = -54.3^\circ$ (CHCl₃), reported in ref. 1 should be corrected because the natural sample provided by Dr. Nukina showed a value of $[\alpha]_D^{22} + 41.3^\circ$.