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5-(2,2-Dimethyl-4*H*-1,3-benzodioxin) methanol: the synthetic precursor to *o*-formyl-*m*-hydroxycinnamic acid, the most oxidized salicylaldehyde-type phytotoxin isolated from rice blast fungus, *Magnaporthe grisea*

Abstract: *o*-Formyl-*m*-hydroxycinnamic acid, the most oxidized salicylaldehyde-type phytotoxin isolated from rice blast fungus, *Magnaporthe grisea*, was synthesized for the first time using 5-(2,2-dimethyl-4*H*-1,3-benzodioxin)methanol as the starting material, and the proposed structure was confirmed.

Keywords: *Magnaporthe grisea*; phytotoxins; pyriculone; rice blast fungus; synthesis.

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Introduction

Rice blast disease, caused by infection of rice blast fungus, *Magnaporthe grisea* (Hebert) Barr, is one of the most harmful diseases for rice [1]. Several salicylaldehyde derivatives, such as pyriculol (**2**) [2], pyriculariol (**3**) [3], pyriculone (**4**) [4], and pyricuol (**5**) [5], have been isolated from the fungus as suspicious compounds responsible for the disease; they induce dark necrotic spot, when being applied to wounded rice leaves. In addition, *o*-formyl-*m*-hydroxycinnamic acid (**6**), probably further oxidized compound derived from **4**, has also been found in the culture extract of the fungus [6] (Scheme 1). We have reported the synthesis of the derivatives **1**–**3**, **5** using a common intermediate, 5-(2,2-dimethyl-4*H*-1,3-benzodioxin)methanol (**7**) (Scheme 2) [7–10]. In continuation of our synthetic studies of these compounds [7–13], the most oxidized derivative **6** was prepared for the first time from **7**. Isolation and synthesis of o-carboxy-m-hydroxycinnamic acid, the related phytotoxin from other sources, has been reported [14–16]. Details of the synthesis are described in this report.

Results and discussion

We have already reported the preparation of compounds with the same carbon skeleton as **6**, as intermediates towards the synthesis of pyricuol (**5**) [9, 10]. Thus, we chose the intermediate **7** as the starting material. Partial oxidation of **7** and the Horner-Wadsworth-Emmons reaction afforded ester **8**, which was then reduced to give aldehyde **9** according to our procedure [10] (Scheme 3). At first, the aldehyde **9** was oxidized with Jones reagent to give acid **10**, and then the acetonide protecting group was removed under acidic conditions. However, the resulting dihydroxy acid **11** could barely be purified because of its high hydrophilicity. Thus, we restarted the synthesis from the ester **8**, and the acetonide group was removed under acidic conditions. The desired diol **12** was obtained as a colorless oil after silica gel purification in 45% yield. Then, the alcoholic hydroxy group

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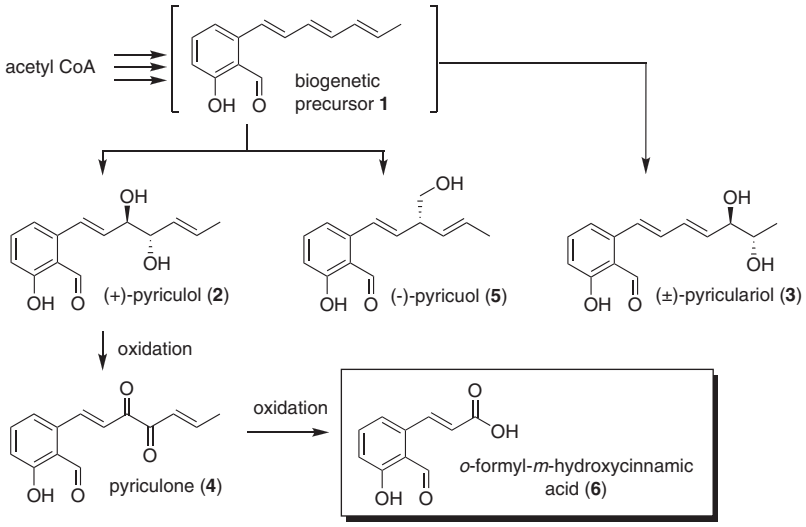
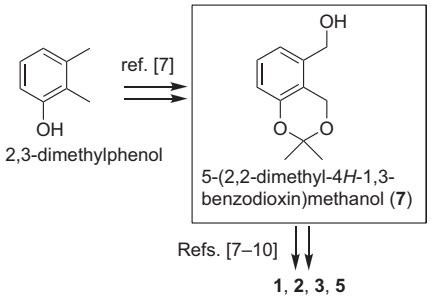
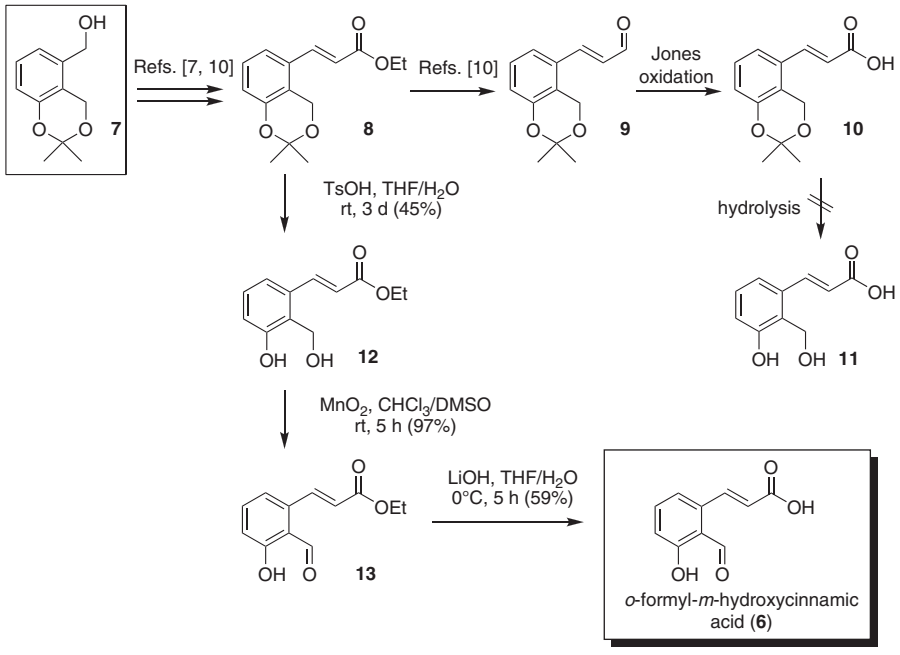


Scheme 1 Biogenetic pathways of salicylaldehyde-type phytotoxin isolated from rice blast fungus.



Scheme 2 5-(2,2-Dimethyl-4*H*-1,3-benzodioxin)methanol (**7**) as the key synthetic intermediate for the synthesis of the phytotoxins.

was oxidized using MnO_2 in DMSO/$CHCl_3$ [10] to give aldehyde **13** in 97% yield. The alkaline hydrolysis of the ester group was examined. The use of K_2CO_3 or KOH in EtOH/H_2O resulted in a complex mixture. Finally, we found that LiOH in EtOH/H_2O was the best choice that afforded the target compound **6** as colorless needles (mp 132–133°C) in 59% yield. The overall yield was 26% from **8**. The ^{1}H NMR spectra of the natural product **6** and synthetic compound **6** were virtually identical.



Scheme 3 Synthesis of *o*-formyl-*m*-hydroxycinnamic acid (**6**).

Conclusion

o-Formyl-*m*-hydroxycinnamic acid, the most oxidized salicylaldehyde-type phytotoxin isolated from rice blast fungus, *Magnaporthe grisea*, was successfully synthesized for the first time using 5-(2,2-dimethyl-4*H*-1,3-benzodioxin)methanol as the starting material.

Experimental

General

Melting point was measured on a Yanako MP-J3 instrument and is uncorrected. FT-IR spectra were recorded as films by a Jasco 4100 spectrometer (ATR, Zn-Se). ^{1}H NMR spectra were recorded with a Varian 400 MR (400 MHz) spectrometer in $CDCl_3$ with $CHCl_3$ (δ_H 7.26 ppm) or CD_3OD with CD_3OH (δ_H 3.30 ppm) as internal standard. Mass spectra were recorded with a Jeol JMS-700 spectrometer. Merck silica gel 60 (70–230 mesh) was used for column chromatography. Merck silica gel 60 F_{254} (0.25 mm thickness) was used for TLC analysis.

Ethyl (*E*)-3-(3′-hydroxy-2′-hydroxymethylphenyl)ethenoate (12)

A solution of **8** [9, 10] (82.0 mg, 0.31 mmol) and *p*-TsOH×H_2O (21.0 mg, mmol) in THF/H_2O (ca. 1 mL) was stirred at room temperature for 3 days and then treated with a saturated aqueous solution of $NaHCO_3$. The resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 3:1) to give **12** (31.1 mg, 0.14 mmol, 45%) as a colorless oil; R_f = 0.16 (hexane/EtOAc, 1:1); IR: ν 3450 (br. s, O–H), 2924 (m), 2854 (w), 1701 (w, C=O), 1640 (w), 1019 (s, C–O), 953 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.90 (1H, d, *J* = 15.6 Hz, H-3), 7.70 (1H, s, ArOH), 7.22 (1H, pseudo t, *J* = 8.0 Hz, H-5′), 7.08 (1H, d, *J* = 8 Hz), 6.93 (1H, d, *J* = 8 Hz), 6.30 (1H, d, *J* = 15.6 Hz, H-2), 5.08 (2H, d, *J* = 5 Hz, C*H*$_2$OH), 4.26 (2H, q, *J* = 7 Hz, C*H*$_2$CH$_3$), 2.24 (1H, br., CH$_2$O*H*), 1.34 (3H, t, *J* = 7 Hz, CH$_2$C*H*$_3$). HR-FABMS. Calcd for $C_{12}H_{12}O_4Na$ ([M+Na]$^+$): *m/z* 245.0789. Found: *m/z* 245.0792.

Ethyl (*E*)-3-(2′-formyl-3′-hydroxyphenyl)ethenoate (13)

A suspension of **12** (31.1 mg, 0.14 mmol) and MnO_2 (500 mg) in DMSO/$CHCl_3$ (7:3, 10 mL) was stirred at room temperature for 5 h. The mixture was filtered through a Celite pad and the filtrate was concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane/EtOAc, 2:1) to give **13** (30.0 mg, 0.14 mmol, 97%) as a pale yellow oil; R_f = 0.69 (hexane/EtOAc, 1:1); IR: ν 2982 (w), 2957 (w), 2925 (w), 1717 (s, C=O), 1651 (s), 1456 (m), 1335 (m), 1265 (m), 1184 (m), 1161 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.92 (1H, s, HC=O), 10.38 (1H, s, OH), 8.22 (1H, d, *J* = 15.8 Hz, H-3′), 7.52 (1H, t, *J* = 8.0 Hz, H-5′), 7.06 (1H, d, *J* = 7.5 Hz), 7.02 (1H, d, *J* = 8.8 Hz), 6.37 (1H, d, *J* = 15.8 Hz), 4.26 (2H, q, *J* = 7.2 Hz, C*H*$_2$CH$_3$), 1.34 (3H, t, *J* = 7.2 Hz, CH$_2$C*H*$_3$). HR-EIMS. Calcd for $C_{12}H_{12}O_4$ (M$^{+\cdot}$): *m/z* 220.0736. Found: *m/z* 220.0736.

(*E*)-3-(2′-Formyl-3′-hydroxyphenyl)ethenoic acid [(*E*)-*o*-formyl-*m*-hydroxycinnnamic acid] 5

A solution of **13** (20.0 mg, 0.091 mmol) and LiOH×H_2O (40.8 mg, 0.972 mmol) in THF/H_2O (3:1, 2 mL) was stirred at 0°C for 5 h. The solution was neutralized with citric acid and the mixture extracted with CH_2Cl_2. The combined organic layer was concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$/MeOH, 15:1) and crystallized from hexane/EtOAc to give **6** (10.2 mg, 0.053 mmol, 59%) as colorless needles; mp 132–133°C; R_f = 0.18 ($CHCl_3$/MeOH, 15:1); IR: ν 3400 (br. s, O–H), 2948 (m), 2833 (w), 1653 (w), 1449 (w), 1021 (s) cm^{-1}; ^{1}H NMR (CD_3OD, 400 MHz): δ 10.46 (1H, s, HC=O), 8.31 (1H, d, *J* = 15.7 Hz, H-2), 7.54 (1H, t, *J* = 8 Hz, H-5′), 7.17 (1H, d, *J* = 8 Hz), 6.99 (1H, d, *J* = 8 Hz), 6.39 (1H, d, *J* = 15.7 Hz, H-3); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 11.92 (1H, s, HC=O), 10.39 (1H, s, OH), 8.31 (1H, d, *J* = 15.8 Hz, H-3′), 7.54 (1H, t, *J* = 8 Hz, H-5′), 7.09 (1H, d, *J* = 8 Hz), 7.05 (1H, d, *J* = 8 Hz), 6.40 (1H, d, *J* = 15.7 Hz). HR-FABMS. Calcd for $C_{10}H_7O_4$ ([M–H]$^-$): *m/z* 191.0344. Found: *m/z* 191.0341.

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