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Synthesis of (12*R*,13*S*)-pyriculariol and (12*R*,13*S*)-dihydropyriculariol revealed that the rice blast fungus, *Pyricularia oryzae*, produces these phytotoxins as racemates

Yuta Nagashima,[1,†] Ayaka Sasaki,[1,†] Ryoya Hiraoka,[2] Yuko Onoda,[2] Koji Tanaka,[1] Zi-Yi Wang,[2] Atsuki Kuwana,[2] Yuki Sato,[1,2] Yuji Suzuki,[3,‡] Minoru Izumi,[2] Shigefumi Kuwahara,[1] Manabu Nukina,[4] and Hiromasa Kiyota[2,*]

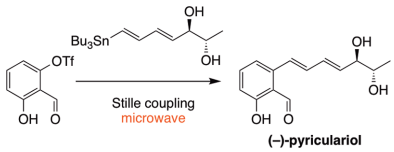
[1]Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan; [2]Graduate School of Environmental and Life Science, Okayama University, Okayama, Japan; [3]Laboratory of Plant Nutrition and Function, Graduate School of Agricultural Science, Tohoku University, Sendai, Japan; and [4]Professor Emeritus, Yamagata University, Japan

*Correspondence: Hiromasa Kiyota, kiyota@okayama-u.ac.jp
†These authors contributed equally.
‡Present address: Faculty of Agriculture, Iwate University, Ueda, Morioka, Japan.

ABSTRACT

Synthesis of assumed natural (12*R*,13*S*)-enantiomers of pyriculariol (**1**) and dihydropyriculariol (**2**), phytotoxins isolated from rice blast disease fungus, *Pyricularia oryzae*, was achieved using Wittig reaction or microwave-assisted Stille coupling reaction as the key step. The synthesis revealed that the natural **1** and **2** are racemates. Foliar application test on a rice leaf indicated that both the salicylaldehyde core and side chain were necessary for phytotoxic activity. The fungus is found to produce optically active phytotoxins when incubated with rotary shaker, but racemic ones when cultured using an aerated jar fermenter.

Graphical Abstract



Synthesis of assumed natural (12*R*,13*S*)-enantiomers of pyriculariol and dihydropyriculariol, phytotoxins isolated from rice blast disease fungus, *Pyricularia oryzae*, revealed that the natural phytotoxins were racemates.

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Keywords: *Pyricularia oryzae*, rice blast disease, structure revision, total synthesis

Rice blast disease, caused by infection of rice blast fungus *Pyricularia oryzae*, has been the most serious pest for rice (Umetsu *et al.* 1972; Khush 1989, 2005; Zeigler *et al.* 1994). Nukina *et al.* isolated (−)-pyriculariol (**1**) (Nukina *et al.* 1981) and (+)-dihydropyriculariol (**2**) (Nukina 1987) from the culture filtrate of the fungus incubated with a jar fermenter in the onion–soy–sucrose medium (Figure 1). **1** caused a dark necrotic spot on a rice leaf similar to that of blast lesion and also inhibited the growth of rice seedlings. From the fungus, a series of salicylaldehyde-type phytotoxins (Nukina *et al.* 1997; Nukina 1998, 1999), such as (+)-pyriculol (**3**) (Iwasaki *et al.* 1969), (+)-dihydropyriculol (**4**) (Iwasaki *et al.* 1973) and their 10*S*-epimers (Kono *et al.* 1991), pyriculone (**5**) (Nukina *et al.* 1996), and (−)-pyricuol (**6**) (Kim *et al.* 1998), were isolated. Their absolute configurations were determined by synthetic studies (Suzuki *et al.* 1986, 1987a,b; Nakamura *et al.* 2005; Tanaka *et al.* 2009). In a preliminary communication, we had achieved the first asymmetric synthesis of **1**, elucidating its absolute configuration to be 12*R*,13*S* from a comparison of the sign of optical rotation (Sasaki *et al.* 2009). However, further studies revealed that natural **1** and **2** were racemates (Kiyota *et al.* 2011; Kiyota 2019). Here, detailed synthesis and structural analysis of **1** and **2** are described. In addition, necrotic activity of rice leaves of the related compounds is reported.

Results and discussion

Synthetic plan

The absolute configuration of natural enantiomers of (−)-**1** and (+)-**2** was assumed to be 12*R*,13*S*, considering that of its congener, (+)-(10*R*,11*S*)-**3**, from the same microbial origin. We planned to synthesize (12*R*,13*S*)-**1** and (12*R*,13*S*)-**2** by coupling of the aromatic fragment and side chain using Wittig olefination (**A** (Suzuki *et al.* 1987) and **B** (White *et al.* 1986, Scheme 1) or Stille coupling reaction (**C** (Bajwa and Jennings 2006) and **D**).

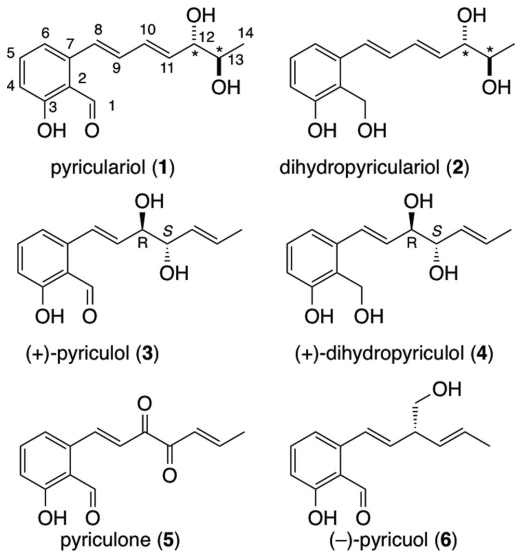


Figure 1. Structures of saplicylaldehyde-type phytotoxins from rice blast fungus, *Pyricularia oryzae*.

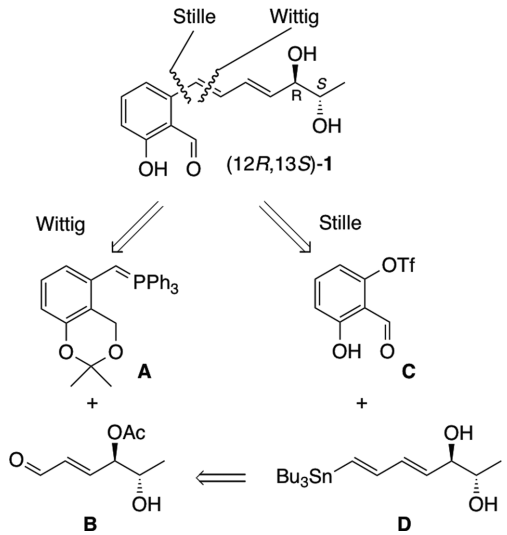
Wittig reaction route

We first examined the former route (Scheme 2). The two asymmetric centers on the side chain would be derived from L-rhamnal diacetate (**7**). Thus, **7** was converted to the aldehyde **8** (= **B**) according to White's procedure (White *et al.* 1986). The free hydroxy group was protected with acetyl group to give **9**, which was subjected to the Wittig reaction with a semi-stabilized ylid prepared from phosphonium salt **10** (= **A**) (Suzuki *et al.* 1987) with BuLi. However, the reaction proceeded non-regioselectively (*E*/*Z* = 1:1) at low yield probably due to lability of the acetyl protecting groups under basic conditions. The yield of desired **11** was 12% after purification with preparative TLC. Then the acetonide group of **11** was deprotected under acidic conditions (**12**), and the benzylic hydroxy group was oxidized with MnO_2, giving aldehyde **13**. Finally, the two acetyl groups were removed to afford (−)-**1**. The yield was 6.3% in 5 steps from **9**.

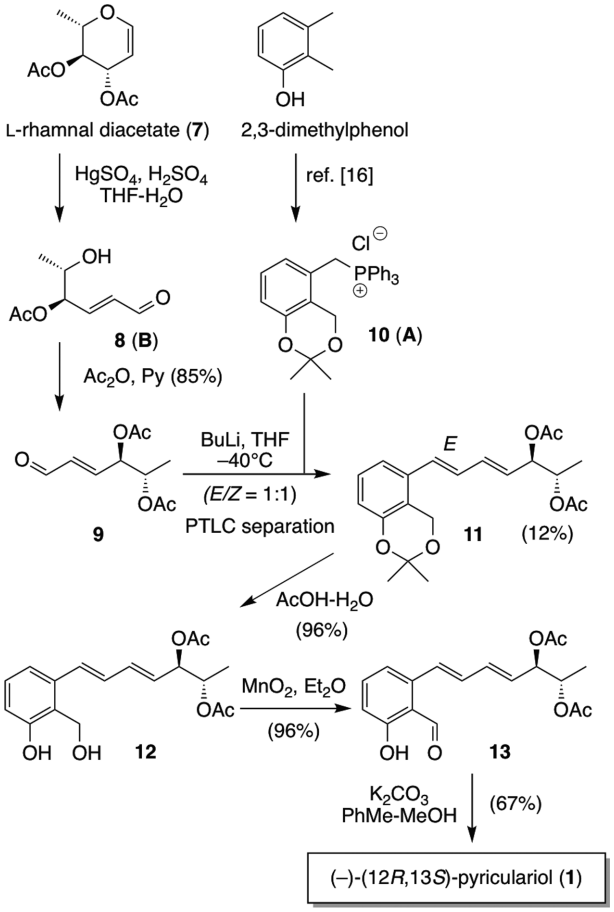
Stille coupling reaction route

Since the key Wittig reaction in the above scheme suffered from the low yield and poor selectivity, we examined the latter route using Stille coupling reaction. The hydroxy and formyl groups are tolerable during this reaction, so the synthetic route could be shortened (see supporting information in press). As shown in Scheme 3, aldehyde **9** was converted to dibromo olefin (Corey and Fuchs 1972) **14**, and the two acetyl groups were hydrolyzed, giving diol **15**. Then, treatment of **15** with excess BuLi afforded alkyne **16**. This compound has the same connectivity of the natural product, *trans*-scobinynediol, isolated from the culture fluid of the white-rot fungus *Psathyrella scobinacea* (Taha 2000). Examination of the Stille coupling reaction between stannane **17** (= **D**) derived from **16** and the known triflate **18** (= **C**) (Bajwa and Jennings 2006) is listed in Table 1.

A variety of conditions were examined (entries 1-4) and the combination of tris(dibenzylideneacetone)dipalladium(0) (Pd_2dba_3), Ph_3As, LiCl in DMF gave a good result, though a



Scheme 1. Retrosynthetic analysis of (−)-pyriculariol (**1**).



Scheme 2. Synthesis of (–)-pyriculariol (**1**). (1) The Wittig route.

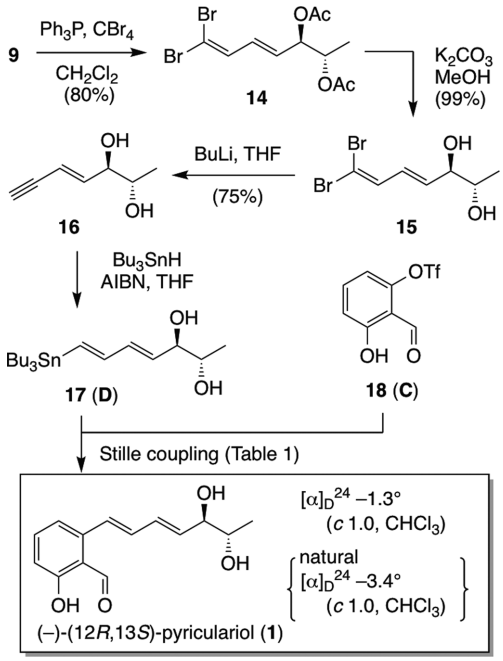
homo-coupled polyenic compound derived from **17** was the major product. We found that the side reaction occurred rapidly even at 0 °C. As in entry 5, microwave irradiation increased the yield of **1** but the by-product was also formed (Lidström *et al.* 2001; Perreux and Loupy 2001; Larhed *et al.* 2002; Nilsson *et al.* 2006; Appukkuttan and Van der Eycken 2008). The best result was obtained when the reagents and substrates were mixed at −78 °C just before the microwave irradiation (entry 6). The reaction temperature raised from −78 °C to 33 °C within 3 min and was kept for 30 min. In this case, none of the by-product was observed. The same conditions without microwave irradiation decreased the yield of **1** and the by-product was major again. This clearly demonstrates that microwave irradiation accelerated the cross-coupling rather than the homo-coupling.

On the other hand, Stille coupling reaction between **17** and the lactone **19** (Molander and Dehmel 2004), a synthetic precursor for **18** (**C**), proceeded under the usual conditions (Pd_2dba_3, Ph_3As, LiCl, DMF, 65 °C) to give **20** in 70% yield. Thus, the reactivity of triflates controlled the reaction (Scheme 4). Reduction of the lactone ring with $LiAlH_4$ afforded (+)-dihydropyriculariol (**2**).

The yield of (−)-**1** was 41% in 5 steps from **9**. The signals of ^{1}H- and ^{13}C-NMR spectral data were fully reassigned by HH-COSY, TOCSY, HMQC, HMBC and NOESY spectra (Table 2).

Determination of absolute configuration

In the preliminary communication, we had reported the absolute configuration of natural **1** {$[\alpha]_D^{24}$ − 3.4 (*c* 1.0, $CHCl_3$)} to be 12*R*,13*S*, because synthetic **1** showed the same sign of optical



Scheme 3. Synthesis of (–)-pyriculariol (**1**). (2) The Stille coupling route.

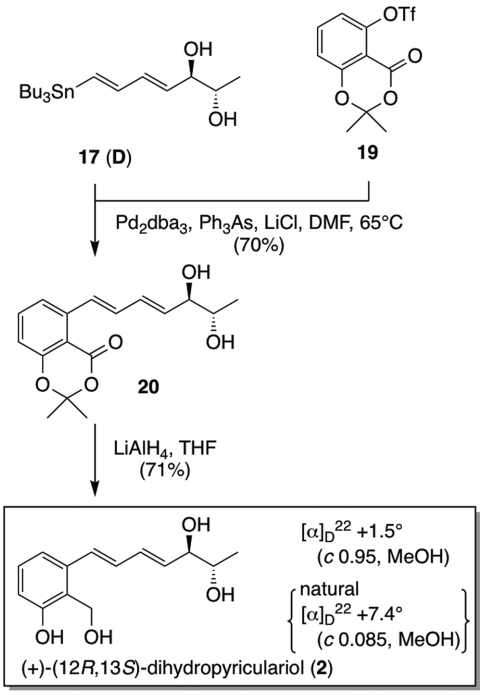
Table 1. Stille coupling reaction of **17** and **18**

Entry	Conditions	Temp. (°C)	Yield (%)
1	$Pd(OAc)_2$, dppf,[a] LiCl, DMSO	65	25
2	$Pd(PPh_3)_4$, LiCl, THF	Reflux	26
3	Pd_2dba_3, $(2\text{-Fur})_3P$,[b] LiCl, THF	65	10
4	Pd_2dba_3, Ph_3As, LiCl, DMF	65	35
5	Pd_2dba_3, Ph_3As, LiCl, DMF, microwave	20∼30	42
6	Pd_2dba_3, Ph_3As, LiCl, DMF, microwave	−78∼33[c]	69
7	Pd_2dba_3, Ph_3As, LiCl, DMF	−78∼30	19

[a]1,1′-bis(diphenylphosphino)ferrocene.
[b]tri(2-furyl)phosphine.
[c]raised from −78 to 33 °C within 3 min and kept at 33 °C for 30 min.

rotation {$[\alpha]_D^{24}$ − 1.3 (*c* 1.0, $CHCl_3$)} (Sasaki *et al.* 2009). However, the synthetic (12*R*,13*S*)-**2** showed higher value {$[\alpha]_D^{22}$ + 7.4 (*c* 0.085, MeOH)} than natural **2** {$[\alpha]_D^{24}$ + 1.5 (*c* 0.95, MeOH)}. Later, we measured the CD spectra of both natural and synthetic **1** to confirm the absolute configuration. To our astonishment, natural **1** showed no significant absorption in the CD spectrum, on the contrary to synthetic **1** (Figure 2). To further confirm the possibility of natural **1** being a racemate, tris-(α-methoxy-α-trifluoromethylphenylacetyl) (MTPA) esters of synthetic and natural **1** were prepared, respectively. As a result, the ^{1}H-NMR spectral chart of the natural derivative (**21**, Figure 3c) contains both the corresponding signals as in tris-(*R*)-MTPA ester (**22**, Figure 3a) and tris-(*S*)-MTPA ester (**23**, Figure 3b) of synthetic **1** in *ca.* 1:1. Tetrakis-MTPA ester of natural **2** (**24**) showed the similar results (Figure 4). Consequently, natural **1** and **2**, produced from rice blast disease fungus, were racemates.

This study revealed that the rice blast fungus produced a different series of metabolites depending on the conditions, ie optically active (+)-pyriculol (**3**) and (−)-pyricuol (**6**) were formed when incubated with rotary shaker, but racemic pyriculariol (**1**) and dihydropyriculariol (**2**) were formed when cultured using an aerated jar fermenter. Recently, we have indicated that not a triene aldehyde **25** but a triene alcohol **26** is a



Scheme 4. Synthesis of (+)-dihydropyriculariol (**2**). (+)-**2** could be also prepared by reduction of (−)-**1** using DIBAL.

plausible biosynthetic precursor for these salicylaldehyde-type phytotoxins (Furuyama *et al.* 2020). Further synthetic and fermentative studies along with genetic analysis will clarify the key mechanism of induction of these two series of the biosynthetic enzymes.

Plant growth inhibition

Phytotoxic activity of synthetic **1** and the related compounds were assessed by foliar application test on rice leaves (Tanaka *et al.* 2009). As shown in Table 3, (−)-pyricuol (**6**), a triene aldehyde **25** (Tanaka *et al.* 2011), and (−)-pyriculariol (**1**) induced dark necrotic lesions; however, **26** (Tanaka *et al.* 2011) and salicylaldehyde showed no significant activity. These results indicate that both a salicylaldehyde moiety and a side chain are necessary for the activity and the presence of a hydroxy group is not important.

Conclusion

Synthesis of assumed natual (12*R*,13*S*)-enantiomers of pyriculariol (**1**) and dihydropyriculariol (**2**), phytotoxins isolated from rice blast disease fungus, *Pyricularia oryzae*, was achieved starting from di-*O*-acetyl-L-rhamnal in two ways: one route using Wittig reaction and another using microwave-assisted Stille coupling reaction as the key step. Spectroscopic analysis of **1** and its MTPA esters as well as **2** revealed that the natural **1** and **2** were racemates. The fungus produces optically active metabolites under shaking conditions or racemic phytotoxins according to the different fermentation methods. Foliar application test on rice leaves indicated that both the salicylaldehyde core and side chain were necessary for phytotoxic activity. The fungus is found to produce optically active phytotoxins when incubated with rotary shaker, but racemic ones when cultured using an aerated jar fermenter. Genetic studies of difference in metabolic pathway using labeled intermedial compounds are in progress (Furuyama *et al.* 2020).

Table 2. ^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectral data of (−)-**1** and (+)-**2**

	1 ($CDCl_3$)			2 (CD_3OD)		
No.	δ_H (mult.)	J (Hz)	δ_C	δ_H (mult.)	J (Hz)	δ_C
1	10.33 (s)		195.05	3.30 (s)		56.35
2	-		117.12	-		125.32
3	-		162.88	-		157.45
4	6.89 (d)	8.4	117.08	6.70 (dd)	7.0 2.1	115.41
5	7.46 (t)	8.0	137.12	7.07 (m)		129.74
6	6.99 (d)	7.6	118.36	7.05 (m)		118.02
7	-		142.21	-		139.67
8	7.08 (d)	15.0	126.81	6.97 (d)	15.6	131.02
9	6.68 (dd)	15.0 10.5	134.83	6.76 (dd)	15.6 10.8	131.89
10	6.53 (dd)	15.3 10.5	132.12	6.48 (dd)	15.0 10.8	133.74
11	5.96 (dd)	15.3 6.7	133.98	5.89 (dd)	15.0 6.8	134.52
12	4.23 (m)		75.77	3.98 (dd)	6.8 5.4	77.63
13	3.95 (m)		70.27	3.70 (dq)	5.4 6.4	71.75
14	1.19 (d)	6.7	17.67	1.16 (d)	6.4	18.78
3-OH	11.91 (s)			-		
12-OH	2.08 (br s)[a]			-		
13-OH	1.94 (br s)[a]			-		

[a]Exchangeable.

Experimental

General

Melting points were uncorrected. Optical rotation values were measured by a Horiba Sepa-300 polarimeter. UV spectrum was recorded by a Shimadzu UV-1600 spectrometer. CD spectra were recorded by a Jasco J-820 spectrometer. FT-IR spectra were recorded as films by a Jasco 4100 spectrometer (ATR, Zn-Se). IR spectra were recorded as films by a Jasco Report-100 spectrometer. ^{1}H-NMR spectra were recorded with a Varian Inova 600 (600 MHz), Inova 500 (500 MHz), 400-MR (400 MHz), and Gemini 2000 (300 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard unless otherwise noted. Mass spectra were recorded with a Jeol JMS–700 spectrometer. Merck silica gel 60 and Kanto silica gel 60N (neutral) were used for column chromatography. Merck silica gel 60 F_{254} (0.50 mm thickness) was used for preparative TLC.

(2E,4R,5S)-4,5-Diacetoxyhex-2-enal (9)

A solution of di-*O*-acetyl-L-rhamnal (**7**, Mw: 214.215, 3.18 g, 14.8 mmol) and $HgSO_4$ (100 mg, 0.34 mmol) in aq. H_2SO_4 (5 mM, 10 mL)-THF (20 mL) was stirred for 14 h at 20 °C. The solution was neutralized with aq. NaOH-$NaHCO_3$, saturated with NaCl, and extracted twice with EtOAc. The combined extract was washed with sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$, and concd. *in vacuo* to give (2*E*,4*R*,5*S*)-4-acetoxy-5-hydroxyhex-2-enal (**8**) (White *et al.* 1986) as a pale yellow oil. A solution of this crude oil (2.9 g) and acetic anhydride (2.5 g, 32 mmol) was stirred in pyridine (2.5 g, 24 mmol) at 0 °C for 5 h. The reaction was

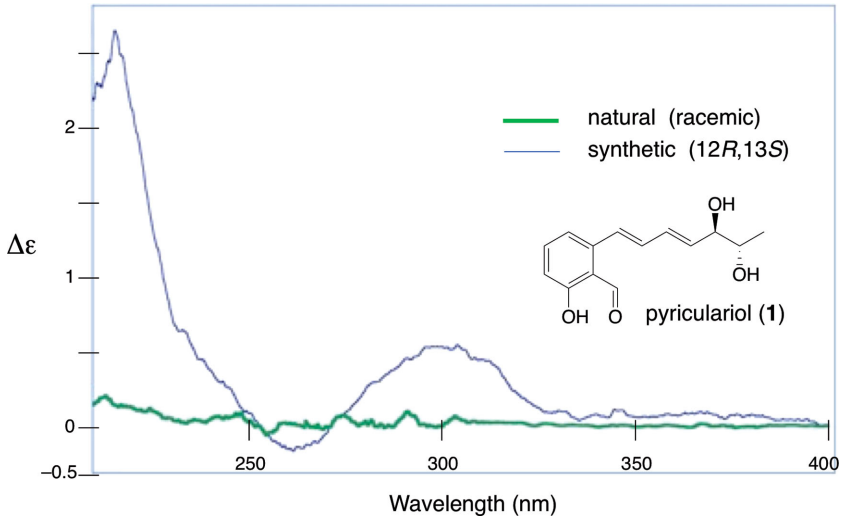


Figure 2. CD spectral charts of (a) synthetic and (b) natural **1** in EtOH. Reproduced from ref. (Kiyota 2019, 177).

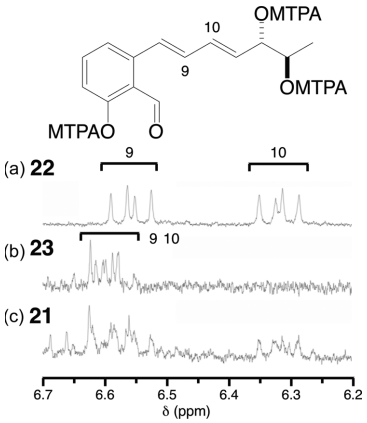


Figure 3. ^{1}H-NMR spectral charts of (a) tris-(*R*)-MTPA ester (**22**) and (b) tris-(*S*)-MTPA ester (**23**) of synthetic **1**, and (c) tris-(*R*)-MTPA ester (**21**) of natural **1** in $CDCl_3$ (400 MHz).

quenched with ice and the organic layer was washed with 2 M aq. HCl, H_2O, sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, 30 g; hexane/EtOAc = 8:1∼6:1) to give **9** (Mw: 214.215, 2.70 g, 12.6 mmol, 85.2%) as a colorless oil. $R_f = 0.57$ (toluene/Et_2O = 1:1). $[\alpha]_D^{27}$ − 36.4 (*c* 2.03, $CHCl_3$). FT-IR: ν = 2825 (w, 1-C–H), 2737 (w, 1-C–H), 1739 (s, C=O), 1692 (s, 1–C=O), 1372 (s), 1219 (s), 1065 (m), 975 (m) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$): δ = 1.26 (d, J = 6.6 Hz, 3 H, 6-H), 2.06 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 5.17 (dq, J = 6.6, 3.7 Hz, 1 H, 5-H), 5.66 (ddd, J = 4.9, 3.7, 1.5 Hz, 1 H, 4-H), 6.23 (ddd, J = 15.6, 7.7, 1.5 Hz, 1 H, 2-H), 6.75 (dd, J = 15.6, 4.9 Hz, 1 H, 3-H), 9.59 (d, J = 7.7 Hz, 1 H, 1-H) ppm. ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 14.96 (6), 20.62 (Ac), 20.87 (Ac), 69.66, 73.14, 133.49 (2), 148.69 (3), 169.55 (Ac), 170.08 (Ac), 192.51 (1) ppm. FABMS: 215 $[M+H]^+$, 171 $[M–Ac]^+$, 155 $[M+H–AcOH]^+$, 111 $[M–2Ac]^+$, 95 $[M+H–2AcOH]^+$, 43 $[Ac]^+$. HR-FABMS: calcd. for $C_{10}H_{15}O_5$ $[M+H]^+$ 215.0914; found 215.0914.

(1′*E*,3′*E*,5′*R*,6′*S*)-5-(5′,6′-Diacetoxyhepta-1′,3′-dienyl)-2,2-dimethyl-4H-benzo[e][1,3]dioxin (11)

To a suspension of the phosphonium salt **10** (Suzuki *et al.* 1987) (Mw: 474.96, 237 mg, 0.499 mmol) in dry THF (3 mL) was added dropwise BuLi (1.6 M in hexane, 0.32 mL, 0.50 mmol) at −40 °C under argon, and the mixture was stirred at −40 °C for 1 h. Then to this was added dropwise a solution of aldehyde **9** (Mw: 214.215, 100 mg, 0.467 mmol) in dry THF (3 mL) at −10 °C, and the resulting mixture was stirred at this temperature for 2 h and at room temperature for 12 h. The mixture was poured into water and extracted with EtOAc. The organic layer was separated and washed with aq. citric acid soln., sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$, and concentrated *in vacuo*. ^{1}H-NMR analysis of the crude residue revealed that *E*/*Z* ratio of 1′-position of **11** was almost 1:1. It was purified by preparative TLC (SiO_2, hexane/Et_2O = 2:1) to give **11** (Mw: 374.43, 20.3 mg, 0.0541 mmol, 11.6%) as a colorless oil, $[\alpha]_D^{26}$ − 50.8 (*c* 0.185, $CHCl_3$). $R_f = 0.82$ (hexane/EtOAc = 1:1). IR: ν = 3070 (w), 3040 (w), 1740 (s, C=O), 1580 (s), 1370 (s), 1240 (s), 1220 (s), 875 (m), 780 (m), 680 (m) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$): δ = 1.23 (d, J = 6.6 Hz, 3 H, 7′-H), 1.54 (s, 3 H, gem-Me), 1.57 (s, 3 H, gem-Me), 2.06 (s, 3 H, Ac), 2.07 (s, 3 H, Ac), 4.89 (s, 2 H, 4-H), 5.11 (dq, J = 3.5, 6.6 Hz, 1 H, 6′-H), 5.45 (ddd, J = 8.1, 3.5, 1.0 Hz, 1 H, 5′-H), 5.75 (dd, J = 15.4, 8.1 Hz, 1 H, 4′-H), 6.457 (d, J = 15.4 Hz, 1 H, 1′-H), 6.465 (ddd, J = 15.3, 10.1, 1.0 Hz, 1 H, 3′-H), 6.69 (dd, J = 15.3, 10.9 Hz, 1 H, 2′-H), 6.74 (dd, J = 7.5, 1.4 Hz, 1 H), 7.08 (dd, J = 7.5, 1.4 Hz, 1 H), 7.14 (t, J = 7.5 Hz, 1 H, 7-H) ppm. FABMS: 397 $[M+Na]^+$, 373, 316. HR-FABMS: calcd. for $C_{21}H_{26}O_6Na$ $[M+Na]^+$ 397.1622; found 397.1629.

(1′*E*,3′*E*,5′*R*,6′*S*)-3-(5′,6′-Diacetoxyhepta-1′,3′-dienyl)-2-hydroxymethylphenol (12)

A solution of **11** (Mw: 374.427, 220 mg, 0.59 mmol) in 70% aq. AcOH (10 mL) was stirred at 60 °C for 2 h under argon. After being cooled to 20 °C, the reaction mixture was extracted with ether. The organic layer was washed with water, sat. aq. $NaHCO_3$ soln. and brine, dried with $MgSO_4$ and concentrated *in vacuo* to give **12** (Mw: 334.364, 190 mg, 0.57 mmol, 96%). Analytical sample was purified by column chromatography (SiO_2, hexane/EtOAc = 3:1) to afford a colorless oil, $[\alpha]_D^{25}$ − 59 (*c* 0.50, $CHCl_3$). R_f = 0.26 (hexane/EtOAc = 2:1). IR: ν = 3450 (br. s, O–H), 3030 (w), 1740 (s, C=O), 1710 (s), 1595 (s), 1580 (s), 1370 (s), 1240 (s), 990 (s), 775 (m), 710 (w) cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.23 (d, J = 6.5 Hz, 3 H, 7″-H), 2.06 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 2.6 (1H, br s, OH), 4.98 (s, 2 H, CH_2OH), 5.11 (dq, J = 3.4, 6.5 Hz, 1 H, 6″-H), 5.42 (dd, J = 7.6, 3.4 Hz, 1 H, 5′-H), 5.73 (dd, J = 15.3, 7.6 Hz, 1 H, 4′-H), 6.46 (dd,

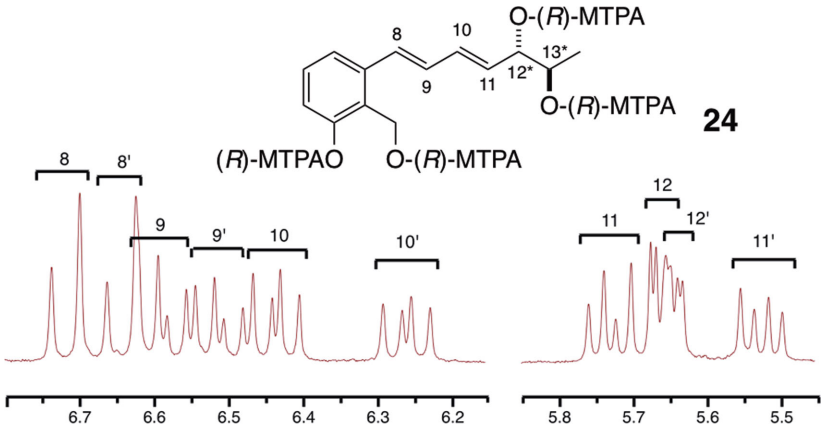


Figure 4. ^{1}H-NMR spectral charts of tetrakis-(*R*)-MTPA ester (**24**) of natural **2** in $CDCl_3$ (400 MHz).

J = 15.3, 10.9 Hz, 1 H, 3′-H), 6.58 (dd, *J* = 15.3, 10.6 Hz, 1 H, 2′-H), 6.77 (d, *J* = 15.3 Hz, 1 H, 1′-H), 6.81 (d, *J* = 7.9 Hz, 1 H), 7.01 (d, *J* = 7.9 Hz, 1 H), 7.14 (t, *J* = 7.9 Hz, 1 H, 5-H), 7.7 (br s, 1 H, ArOH) ppm. EIMS: 334 ($M^{+\bullet}$), 274 $[M–AcOH]^+$, 214 $[M–2AcOH]^+$, 196, 187 $[M+H–2AcOH–CO]^+$, 170, 157, 144. HR-EIMS: calcd. for $C_{18}H_{22}O_6$ ($M^{+\bullet}$) 334.1411; found 334.1414.

(1′*E*,3′*E*,5′*R*,6′*S*)-3-(5′,6′-Diacetoxyhepta-1′,3′-dienyl)-2-formylphenol (13)

A suspension of **12** (Mw: 334.364, 10.0 mg, 0.299 mmol) and activated MnO_2 (Mw: 86.94, 75 mg, 0.86 mmol) in Et_2O (5 mL) was vigorously stirred at reflux for 2 h under ultrasonic irradiation. MnO_2 was removed by filtration with a Celite pad and the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexane/EtOAc = 10:1) to give **13** (Mw: 332.348, 8.5 mg, 0.026 mmol, 86%) as a pale yellow oil, $[\alpha]_D^{25}$ − 79.7 (*c* 0.215, $CHCl_3$). R_f = 0.80 (toluene/EtOAc = 3:1). IR: ν = 3450 (br. s, O–H), 3030 (w), 1740 (s, C=O), 1710 (s), 1595 (s), 1580 (s), 1370 (s), 1240 (s), 990 (s), 775 (m), 710 (w) cm^{-1}. ^{1}H-NMR (600 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.5 Hz, 3 H, 7′-H), 2.07 (s, 3 H, Ac), 2.12 (s, 3 H, Ac), 5.12 (dq, *J* = 3,5, 6.5 Hz, 1 H, 6′-H), 5.45 (dd, *J* = 7.0, 3.5 Hz, 1 H, 5′-H), 5.84 (dd, *J* = 15.3, 7.3 Hz, 1 H, 4′-H), 6.51 (dd, *J* = 15.3, 10.6 Hz, 1 H, 3′-H), 6.65 (dd, *J* = 15.3, 10.9 Hz, 1 H, 2′-H), 6.90 (d, *J* = 8.5 Hz, 1 H), 6.99 (d, *J* = 7.3 Hz, 1 H), 7.11 (d, *J* = 15.3 Hz, 1 H, 1′-H), 7.46 (t, *J* = 7.8 Hz, 1 H, 5-H), 10.33 (s, 1 H, ArOH), 11.91 (s, 1 H, CHO) ppm. EIMS: 332 ($M^{+\bullet}$), 279, 272 $[M–AcOH]^+$, 230 $[M–AcOH\text{-}CH_2C{=}O]^+$, 212 $[M–2AcOH]^+$, 186, 149. HR-EIMS: calcd. for $C_{18}H_{20}O_6$ ($M^{+\bullet}$) 332.1254; found 332.1255.

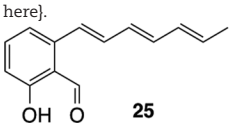
(1′*E*,3′*E*,5′*R*,6′*S*)-3-(5′,6′-Dihyroxyhepta-1′,3′-dienyl)-2-formylphenol [Pyriculariol, (−)-1]

A solution of **13** (Mw: 332.348, 4.2 mg, 0.013 mmol) and K_2CO_3 (Mw: 138.21, 40 mg, 0.29 mmol) in toluene-MeOH (1:2, 6 mL) was stirred at 20 °C for 1 h. Then to this was added NH_4Cl and the mixture was concentrated *in vacuo*. To the residue was added water and EtOAc, and the resulting suspension was filtered through a Celite pad. The filtrate was concentrated *in vacuo* and the residue was purified by PTLC (SiO_2, $CHCl_3$/EtOH = 100:1 × 5, and hexane/EtOAc = 1:4) to give **1** (Mw: 248.274, 2.1 mg, 0.0085 mmol, 67%), $[\alpha]^{24}_D$ − 1.3 (*c* = 1.0, $CHCl_3$) {$[\alpha]^{24}_D$ − 3.4 (*c* 1.0, $CHCl_3$)} (Nukina *et al.* 1981). R_f = 0.19 (toluene/EtOAc = 3:1). UV: ε^{24} (*c* = 2.42 × 10^{-5} mol/L in EtOH) = 29 200 (λ = 253 nm), 18 800 (λ = 290 nm), 8970 (λ = 368 nm){ε (EtOH) = 26 800 (λ = 251 nm), 16 600 (λ = 292 nm), 8700 (λ = 366 nm)} (Nukina *et al.* 1981). CD: $\Delta\varepsilon^{20}$ (*c* = 2.42 × 10^{-5} mol/L in EtOH) = +2.65 (λ = 216 nm), −0.17 (λ = 262 nm), +0.53 (λ = 300 nm). FT-IR: ν = 3384 (s, O–H), 3040 (w), 2955 (w), 2925 (w), 2900 (w), 1638 (s, C = O), 1602 (m), 1568 (w), 1452 (m), 1237 (m), 991 (m), 754 (w), 722 (w) cm^{-1}. ^{1}H and ^{13}C NMR: see Table 2. The experimental procedure from **17** and **18**, and HR-MS datum were shown in the previous paper (Sasaki *et al.* 2009).

Table 3. Foliar application test on rice leaves

Entry	Compounds	Necrotic activity[a]
1	(−)-**1**	+
2	(−)-(*R*)-**6** (nature identical)[b]	++++
3	heptatrienylsalicylaldehyde (**25**)[c]	++
4	heptatrienylsalicylalcohol (**26**)	–
5	Salicylaldehyde	–

[a]+: active, –: not active. Siegel–Tukey method (*n* = 14) was used for statistical significance test. The activity was compared with the datum of (−)-(*R*)-**6** in ref. (Tanaka *et al.* 2009) as a positive control.
[b]Synthesis of (−)-(*R*)-**6** is shown in ref. (Tanaka *et al.* 2009).
[c]Synthesis of **25** and **26** is shown in ref. (Tanaka *et al.* 2011) {Figure for Table 3 here}.



(5R,6S)-5,6-Diacetoxy-1,1-dibromohepta-1,3-diene (14)

A solution of triphenylphosphine (6.5 g, 25 mmol) and tetrabromomethane (4.1 g, 12 mmol) in CH_2Cl_2 (20 mL) was stirred at 0 °C for 15 min. After being warmed to rt, to this was added **9** (1.3 g, 6.2 mmol) in CH_2Cl_2 (9.0 mL), and the mixture was stirred for 15 h. The reaction mixture was filtered through a Celite pad which was rinsed with EtOAc. The filtrate was stirred for 24 h and filtered again. The filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel. Elution with hexane/EtOAc (6:1) gave **14** (1.9 g, 5.0 mmol, 81%) as a yellow oil, $[\alpha]^{24}_D$ − 56 (*c* 3.3, $CHCl_3$). FT-IR: ν = 1738 (s, C=O), 1371 (s), 1224 (s), 970 (m), 815 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.21 (d, *J* = 6.8 Hz, 3 H, 7-H), 2.05 (s, 3 H, Ac), 2.10 (s, 3 H, Ac), 5.09 (m, 1 H, 6-H), 5.37 (m, 1 H, 5-H), 5.83 (dd, *J* = 7.1, 15.6 Hz, 1 H, 4-H), 6.34 (dd, *J* = 10.3, 15.6 Hz, 1 H, 3-H), 6.96 (d, *J* = 10.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 15.0, 20.6, 20.9, 69.7,

73.1, 133.5, 148.7, 169.6, 170.1, 192.5 ppm. EIMS: 372 [M($^{81}Br_2$)$^{+\bullet}$], 370 [M($^{81}Br^{79}Br$)$^{+\bullet}$], 368 [M($^{79}Br_2$)$^{+\bullet}$], 312, 310, 308 [M–AcOH]$^+$; 270, 268, 266 [M+H–AcOH–Ac]$^+$; 243, 241, 239 [M+H–AcOH–Ac–C_2H_3]$^+$; 189, 187 [M+H–AcOH–Ac–Br]$^+$; 161, 159 [M+H–AcOH–Ac–C_2H_3–Br]$^+$; 108 [M+H–AcOH–Ac–Br_2]$^+$, 81 [M+H–AcOH–Ac–C_2H_3–Br_2]$^+$. HR-EIMS: calcd. for $C_{11}H_{14}O_4{}^{79}Br_2$ (M$^{+\bullet}$) 367.9253; found 367.9255.

(5R,6S)-1,1-Dibromohepta-1,3-diene-5,6-diol (15)

A solution of **14** (2.7 g, 7.2 mmol) and K_2CO_3 (70 mg, 0.51 mmol) in MeOH (9 mL) was stirred at 20 °C for 48 h. The reaction mixture was filtered through a Celite pad which was rinsed with EtOAc. The filtrate was concentrated *in vacuo* and the residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1) gave **15** (2.0 g, 7.0 mmol, 97%) as a colorless oil, $[\alpha]^{25}{}_D$ + 12 (c = 2.9, $CHCl_3$). FT-IR: ν = 3361 (s, O–H), 2976 (s), 1074 (s), 969 (s), 815 (s) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, J = 10.3 Hz, 3 H, 7-H), 3.91 (br. s, 1 H, 6-H), 4.16 (br. s, 1 H, 5-H), 5.93 (dd, J = 6.6, 15.6 Hz, 1 H, 4-H), 6.34 (dd, J = 10.3, 15.6 Hz, 1 H, 3-H), 6.98 (d, J = 10.3 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.4, 70.0, 75.5, 92.0, 128.9, 134.8, 136.0 ppm. EIMS: 288 [M($^{81}Br_2$)$^{+\bullet}$], 286 [M($^{79}Br^{81}Br$)$^{+\bullet}$], 284 [M($^{79}Br_2$)$^{+\bullet}$], 270, 268, 266 [M–H_2O]$^+$; 243, 241, 239 [M–CH_3CHOH]$^+$; 207, 205 [M–Br]$^+$; 163, 161 [M–CH_3CHOH–Br]$^+$; 81 [M–CH_3CHOH–Br_2]$^+$. HR-EIMS: calcd. for $C_7H_{10}O_2{}^{79}Br_2$ (M$^{+\bullet}$) 283.9042; found 283.9045.

(5R,6S)-Hept-3-en-1-yne-5,6-diol (16)

To a solution of **15** (270 mg, 0.94 mmol) in dry THF (30 mL) was added dropwise BuLi (1.6 M in hexane, 3.0 mL, 4.8 mmol) at −78 °C under nitrogen. To this was added sat. aq. NH_4Cl soln. and the mixture was warmed to room temperature. Then the mixture was extracted with EtOAc. The organic layer was separated, washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (5:1) gave **16** (98 mg, 0.77 mmol, 82%) as a colorless oil, $[\alpha]^{25}{}_D$ − 1.1 (c 0.51, $CHCl_3$). FT-IR: ν = 3400 (vs, O–H), 3290 (s, H–C≡), 2928 (s), 2105 (w, C≡C), 1077 (m), 962 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, J = 6.3 Hz, 3 H, 7-H), 2.96 (s, 1 H, 1-H), 3.53 (br. s, 1 H, OH), 3.83 (br. s, 1 H, OH), 3.87 (m, 1 H, 6-H), 4.15 (m, 1 H, 5-H), 5.76 (d, J = 16.1 Hz, 1 H, 3-H), 6.25 (dd, J = 6.3, 10.3 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.5, 70.0, 75.3, 76.7, 81.4, 111.3, 142.4 ppm. FABMS: 127 [M+H]$^+$, 109 [M+H–H_2O]$^+$, 93 [M+H–2H_2O]$^+$. HR-FABMS: calcd. for $C_7H_{11}O_2$ [M+H]$^+$ 127.0754; found 127.0752.

(5R,6S)-1-Tributylstannylhepta-1,3-diene-5,6-diol (17)

To a solution of **16** (196 mg, 1.55 mmol) in dry THF (25 mL) was added 2,2-azobisisobutyronitrile (26 mg, 0.16 mmol) and tributyltin hydride (0.5 µL, 1.86 mmol), and the mixture was refluxed for 24 h. The mixture was filtered through a Celite pad which was rinsed with EtOAc. The filtrate was concentrated under reduced pressure. The bulk of the product was used without purification, but for characterization purposes, a sample was chromatographed on silica gel. Elution with hexane/EtOAc (7:1) gave **17** as a colorless oil, $[\alpha]^{25}{}_D$ + 0.28 (c 1.1, $CHCl_3$). FT-IR: ν = 3387 (s, O–H), 2955 (s), 2925 (s), 1072 (m), 1000 (s), 663 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.2 Hz, 9 H, 4′-H), 0.88 (t, J = 8.0 Hz, 6 H, 1′-H), 1.28 (sext, J = 7.2 Hz, 6 H, 3′-H), 1.48 (m, 6 H, 2′-H), 3.06 (br. s, 2 H, OH), 3.83 (br. s, 1 H, 6-H), 4.08 (m, 1 H, 5-H), 5.62 (dd, J = 7.1, 15.7 Hz, 1 H, 4-H), 6.20 (dd, J = 11.0, 15.6 Hz, 1 H, 3-H), 6.24 (d, J = 18.5 Hz, 1 H, 1-H), 6.51 (dd, J = 11.0, 18.5 Hz, 1 H, 2-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.3, 13.5, 17.2, 27.1, 28.9, 70.3, 76.0, 129.5, 135.4, 136.1, 146.0 ppm. FABMS: 361 [M(^{120}Sn)+H–BuH]$^+$, 359 [M(^{118}Sn)+H–BuH]$^+$, 305, 303 [M+H–2BuH]$^+$; 291, 289 [Bu_3Sn]$^+$; 251, 249; 235, 233 [Bu_3Sn–BuH]$^+$; 179, 177 [Bu_3Sn–2BuH]$^+$, 137, 135, 93, 91. HR-FABMS: calcd. for $C_{19}H_{38}O_2NaSn$ [M+Na]$^+$ 441.1786; found 441.1789.

(1′E,3′E,5′R,6′S)-6-(5′,6′-Dihydroxyhepta-1′,3′-dienyl)-2,2-dimethyl-4H-benzo[e][1,3]dioxin-4-one (20)

To a solution of **19** (416 mg, 1.28 mmol), Pd_2dba_3 (7.8 mg, 8.5 µmol), LiCl (72 mg, 1.7 mmol) and Ph_3As (5.2 mg, 0.017 mmol) in DMF (3 mL) was added a solution of **17** (72 mg, 0.17 mmol) in DMF (2 mL) over 2 h using a syringe pump at 20 °C, and the mixture was stirred for further 6 h at this temperature. To this was added sat. aq. NH_4Cl soln. and the aqueous layer was extracted with EtOAc. The combined organic layer was separated, washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1∼1:1) gave **20** (36.2 mg, 0.119 mmol, 70%) as an amorphous solid, $[\alpha]^{22}{}_D$ + 81 (c 0.25, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.17 (d, J = 6.5 Hz, 1 H, 7′-H), 1.72 (s, 6 H, 2-Me), 2.27 (br, 1 H, OH), 2.37 (br, 1 H, OH), 3.94 (dq, 1 H, J = 6.4, 2.4 Hz, 6′-H), 4.20 (dd, 1 H, J = 6.6, 3.4 Hz, 5′-H), 5.93 (dd, 1 H, J = 15.3, 7.1 Hz, 4′-H), 6.57 (dd, 1 H, J = 15.3, 10.6 Hz, 3′-H), 6.78 (dd, 1 H, J = 15.5, 10.6 Hz, 2′-H), 6.86 (dd, 1 H, J = 8.1, 0.9 Hz), 7.30 (d, 1 H, J = 7.9 Hz), 7.45 (t, J = 8.0 Hz, 7-H), 7.71 (d, 1 H, J = 15.5 Hz, 1′-H). HR-FABMS: calcd. for $C_{17}H_{20}O_5Na$ [M+Na]$^+$ 327.1208; found 327.1210.

(1′E,3′E,5′R,6′S)-3-(5′,6′-Dihyroxyhepta-1′,3′-dienyl)-2-hydroxymethylphenol [Dihydropyriculariol, (+)-2]

To a suspension of $LiAlH_4$ (5.0 mg, 0.13 mmol) in THF (5 mL) was added to a solution of **20** (20.0 mg, 0.0657 mmol) in THF (5 mL) at −78 °C, and the mixture was stirred for 3 h, while the temperature of the suspension gradually arrowed to warm to 0 °C. Then the mixture was poured into sat. aq. NH_4Cl soln. and the aqueous layer was extracted with EtOAc. The combined organic layer was separated, washed with water, dried with $MgSO_4$, and concentrated *in vacuo*. The residue was purified by preparative TLC. Development with $CHCl_3$/MeOH (15:1 and 10:1) gave **2** (11.5 mg, 0.0459 mmol, 70%) as a colorless needles, mp °C ($CHCl_3$), $[\alpha]^{22}{}_D$ + 7.4 (c 0.085, MeOH) {mp 156-158 °C, $[\alpha]^{23}{}_D$ + 1.5 (c = 0.95, MeOH)} (Nukina 1987). R_f = 0.19 (toluene/EtOAc = 3:1). ^{1}H and ^{13}C NMR: see Table 2. HR-FABMS: calcd. for $C_{14}H_{18}O_4Na$ [M+Na]$^+$ 273.1102; found 273.1101.

3,12,13-Tris-MTPA esters (22 and 23) of synthetic (12R,13S)-pyriculariol

Synthetic (−)-(12*R*,13*S*)-pyriculariol [(−)-**1**] (0.8 mg each) was converted to the corresponding tris-(*R*)- and (*S*)-MTPA esters using (*S*)- and (*R*)-MTPA chlorides (>99%ee, Aldrich, *ca*. 20 mg), respectively, in pyridine (1 mL) in the presence of *N*, *N*-dimethylaminopyridine (*ca*. 10 mg). The completion of the reaction was confirmed by TLC analysis (hexane/EtOAc = 1:5 and 1:1), and the product was purified by preparative TLC (haxane/EtOAc = 1:1). Tris-(*R*)-MTPA ester (**22**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36 (d, J = 6.7 Hz, 3 H, 14-H), 3.46 (s, 3 H, OMe), 3.48 (s, 3 H, OMe), 3.70 (s, 3 H, OMe), 5.40 (dq, J = 3.0, 6.7 Hz, 1 H, 13-H), 5.59 (dd, J = 15.2, 7.2 Hz, 1 H, 11-H), 5.67 (dd,

J = 7.5, 3.0 Hz, 1 H, 12-H), 6.32 (dd, J = 15.2, 10.6 Hz, 1 H, 10-H), 6.55 (dd, J = 15.3, 10.6 Hz, 1 H, 9-H), 7.12 (d, J = 7.9 Hz), 7.24 (d, J = 15.2 Hz, 1 H, 8-H), 7.29-7.52 (m, 13 H), 7.56 (t, J = 7.9 Hz, 5-H), 7.64-7.68 (m, 3 H), 10.100 (s, 1 H, 1-H). HR-FABMS: calcd. for $C_{44}H_{38}O_{10}F$ $[M+H]^+$ 897.2321; found 897.2327. Tris-(*S*)-MTPA ester (**23**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.4 Hz, 3 H, 14-H), 3.42 (s, 3 H, OMe), 3.47 (s, 3 H, OMe), 3.70 (s, 3 H, OMe), 5.34 (dq, J = 3.3, 6.4 Hz, 1 H, 13-H), 5.68 (dd, J = 7.9, 3.3 Hz, 1 H, 12-H), 5.79 (dd, J = 14.8, 7.9 Hz, 1 H, 11-H), 6.59 (dd, J = 16.0, 10.4 Hz, 1 H, 10-H), 6.58-6.70 (m, 2 H), 7.13 (d, J = 6.8 Hz), 7.24 (d, J = 15.2 Hz, 1 H, 8-H), 7.29-7.52 (m, 13 H), 7.57 (t, J = 7.9 Hz, 5-H), 7.64-7.68 (m, 3 H), 10.089 (s, 1 H, 1-H).

1,3,12,13-Tetrakis-MTPA ester (24) of natural (12RS,13SR)-dihydropyriculariol

In a similar manner as described for **22** and **23**, natural racemic dihydropyriculariol was converted to the corresponding (*S*)-MTPA ester (**24**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 6.5 Hz, 1.5 H, 14′-H), 1.34 (d, J = 6.6 Hz, 1.5 H, 14-H), 3.39, 3.40, 3.42, 3.45, 3.46, 3.47 (s, each 1.5 H, OMe), 3.64 (s, 3H, OMe), 5.13 (d, J = 12.2 Hz, 0.5 H, 1-H), 5.15 (d, J = 12.3 Hz, 0.5 H, 1-H), 5.21 (d, J = 12.3 Hz, 1 H, 1-H), 5.33 (dq, J = 3.2, 6.6 Hz, 0.5 H, 13-H), 5.40 (dq, J = 2.9, 6.5 Hz, 0.5 H, 13′-H), 5.53 (dd, J = 15.4, 7.4 Hz, 0.5 H, 11′-H), 5.63-5.68 (m, 1 H, 12 and 12′-H), 5.73 (dd, J = 14.9, 8.2 Hz, 0.5 H, 11-H), 6.26 (dd, J = 15.4, 10.4 Hz, 0.5 H, 10′-H), 6.44 (dd, J = 14.9, 10.3 Hz, 0.5 H, 10-H), 6.51 (dd, J = 15.5, 10.4 Hz, 0.5 H, 9′-H), 6.59 (dd, J = 15.3, 10.3 Hz, 0.5 H, 9-H), 6.65 (d, J = 15.5 Hz, 0.5 H, 8′-H), 6.72 (d, J = 15.3, 0.5 H, 8-H), 7.07 (d, J = 6.4 Hz, 1 H), 7.30-7.45 (m, 20 H), 7.48 (t, J = 6.7 Hz, 1 H, 5-H), 7.64 (d, J = 7.2 Hz, 1 H). HR-FABMS: calcd. for $C_{54}H_{46}O_{12}FNa$ $[M+Na]^+$ 1137.2696; found 1137.2692.

Foliar application test for rice leaves

Acetone solution of the sample (10 μg/μL) with 0.02% of Tween-20 was pasted onto the rice leaf, and the whole plant was incubated at 25 °C under fluorescent light (6500 lux) for 7 d. The decolorized lesion was counted (n = 14).

Supplementary material

Supplementary material is available at *Bioscience, Biotechnology, and Biochemistry* online.

Author contribution

H.K. designed this study; Y.N., A.S., R.H., Y.O., K.T., ZY.W., A.K. carried out the synthetic experiments; Y.S. carried out the plant assay. M.N. provided the natural samples of pyriculariol and dihydropyriculariol. S.K., M.N., and M.I. contributed to the interpretation of the results. H.K. wrote the manuscript and supervised the research with assistance from all authors.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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