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Synthesis and fungicidal activity of enantiomerically pure (*R*)- and (*S*)-silicon-containing azole fungicides

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Abstract—Enantiomerically pure (*R*)- and (*S*)-1-(1*H*-1,2,4-triazol-1-yl)-2-(4-fluorophenyl)-3-trimethylsilylpropan-2-ol **1** were prepared via an enantioselective Grignard reaction. The absolute stereochemistry of **1** was determined by X-ray analysis. In a comparison of in vitro antifungal activities of the enantiomers, the (−)-enantiomer with the *R*-absolute configuration was far more potent than the (+)-enantiomer.

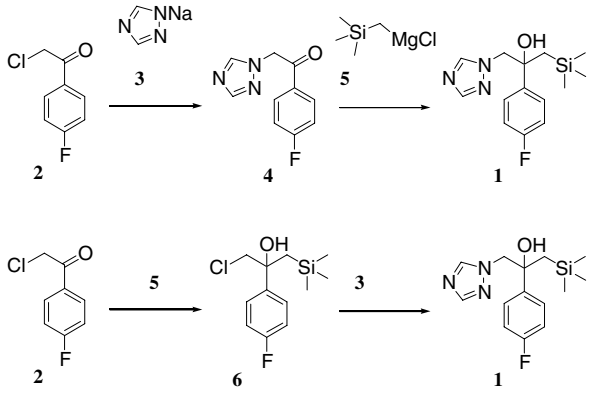
1. Introduction

In our search for azole fungicides, we found that 1-(1*H*-1,2,4-triazol-1-yl)-2-(4-fluorophenyl)-3-trimethylsilylpropan-2-ol **1** had excellent fungicidal activities for various crops. In a previous paper, we reported our experience in synthesizing racemic **1** and evaluating its fungicidal activities as a racemic compound.[1–3] Enantiomers are well known to exhibit frequent and diverse biological activities. In one study by Carelli et al., for example, cytochrome P450 from phytophathogen was found to interact in interesting ways with azole fungicide in enantiomerically pure form.[4] To follow along in a similar vein, other groups went on to study the synthesis of optical active azole fungicides.[5–7]

Both (*R*)-and (*S*)-**1** must be available in enantiomerically pure forms in order to properly evaluate the effectiveness of **1**. In this paper we report an efficient synthesis of both enantiomers of **1** in enantiomerically pure forms using (1*R*,2*S*)- or (1*S*,2*R*)-phenylcyclohexanol as a chiral auxiliary.

2. Chemistry

Earlier we reported the two procedures for the synthesis of **1** as shown in Scheme 1. Method A involves the Grignard reaction to a triazolylacetophenone **4** in the last step.[1,2] Method B, the turn of a reaction process was replaced, involves the reaction of 1*H*-1,2,4-triazole sodium salt **3** with 1-chloro-2-(4-fluorophenyl)-3-trimethylsilylpropan-2-ol **6** obtained by the Grignard reaction to a phenacyl chloride **2**.[3] Since the Grignard reaction was used to generate the chiral carbon in both routes, we decided to make the Grignard reaction enantioselective.



Scheme 1. Our previous method for the preparation of **1**.

Keywords: Fungicidal activities; Enantiomer; Synthesis; X-ray analysis.
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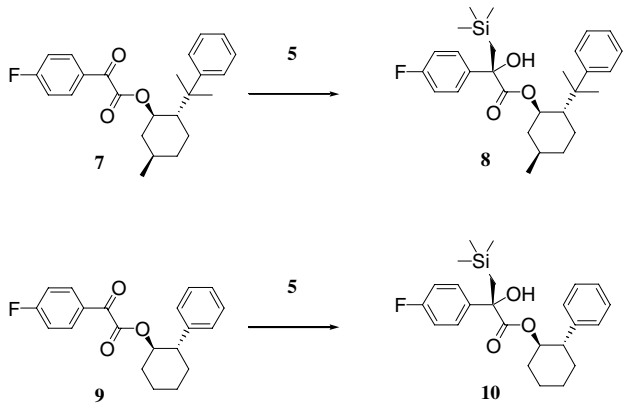


Scheme 2. The Grignard reaction of **5** with phenylglyoxylates.

Whitesell et al. reported the use of 8-phenylmenthyl esters to allow the enantioselective addition of a Grignard reagent to α-keto esters.[8,9] The enantioselectivity of the addition to phenylglyoxylates is quite high when conducted at dry ice/acetone bath temperature. This method was adapted for the reaction of (−)-8-phenylmenthyl 2-(4-fluorophenyl)glyoxylate **7** with trimethylsilylmethyl Grignard reagent **5** as shown in Scheme 2. An analysis of the diastereomixture **8**, obtained as an oily product, by reverse phase HPLC (Shiseido Capcellpak C18 (4.6×150 mm), 80% acetonitrile–water used as eluent, 3 mL/min) showed only 50% de.

In their subsequent study, Whitesell et al. also reported that *trans*-2-phenylcyclohexanol can be used in place of 8-phenylmenthol for asymmetric reactions of α-keto esters.[10] Thereafter, Peter and Helmut compared the diastereoselectivity between 8-phenylmenthyl phenylglyoxylate and *trans*-2-phenylcyclohexyl phenylglyoxylate in several kinds of reactions.[11] While the commercial availability of the (1*R*,2*S*)- and (1*S*,2*R*)-*trans*-2-phenylcyclohexanols and their ability to synthesize both enantiomers makes them attractive, the de value in the methyl Grignard reaction was unsatisfactory in Peter and Helmut's results. Predictably, the addition of **5** to racemic *trans*-2-phenylcyclohexyl 2-(4-fluorophenyl)glyoxylate **9** resulted in the generation of diastereomixture **10** of 50% de. Since the diastereomixture was solidified, we attempted to recrystallize from ethanol. This strategy proved successful, and diastereomixture **10** could be converged on a single diastereomer of >99% de by HPLC.

Next, we carried out the addition reaction with (1*R*,2*S*)- and (1*S*,2*R*)-*trans*-2-phenylcyclohexanols to provide the corresponding diastereomixture in the same diastereoselectivity and then recrystallized them from ethanol to give the single diastereomers **10**(−) and **10**(+) of >99% de by HPLC.

Next, we used X-ray diffraction to verify that the absolute configuration of the generated chiral carbon of the product from (1*R*,2*S*)-*trans*-2-phenylcyclohexyl 2-(4-fluorophenyl)glyoxylate **10**(−) was *R* (Fig. 1).

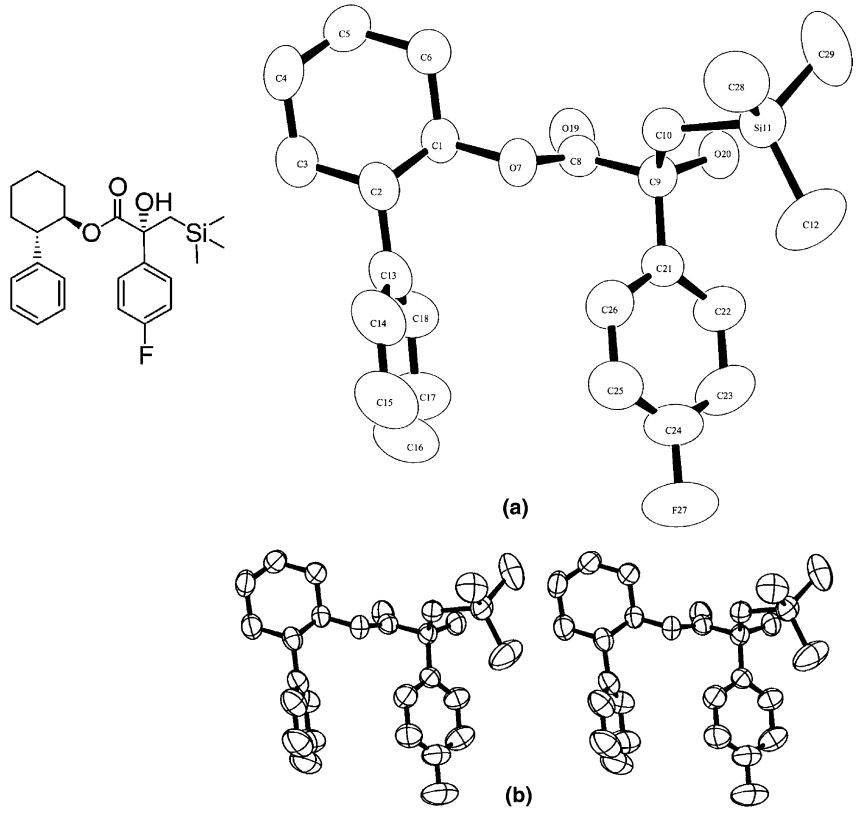
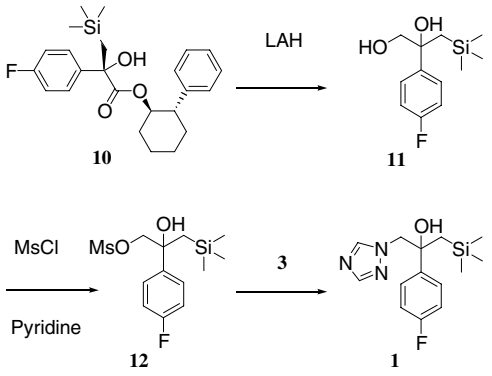


Figure 1. (a) Molecular structure of **10**(−) with atomic numbering and (b) stereoscopic view of **10**(−).



Scheme 3. Novel method for the preparation of **1**.

As outlined in Scheme 3, the racemic **1** was produced by reducing the ester **10** with lithium aluminum hydride in tetrahydrofuran to give diol **11** in 70% yield, treating diol **11** with methanesulfonyl chloride in pyridine to give mesylate **12** in 90% yield, and reacting mesylate **12** with 1*H*-1,2,4-triazole sodium salt in *N*,*N*-dimethylformamide. The resulting to afford racemic **1** was provided in 40% yield.

Once a novel method for the preparation of racemic **1** was developed, the single diastereomers **10**(−) and **10**(+) were treated in the same manner to obtain **1**(−) and **1**(+).

Analysis of **1**(−) and **1**(+) by chiral HPLC (Chiralcell OJ (4.6×250 mm), 3% ethanol–hexane used as eluent, 1.2 mL/min) showed >99% ee. We verified that the absolute configuration of **1**(+) was *S* by X-ray diffraction (Fig. 2).

3. X-ray crystal structure

The atom labeling and thermal ellipsoids of **10**(−) are shown in Figure 1. The absolute configuration of C1 and C2 atoms of the cyclohexane ring in **10**(−) were determined *R* and *S*, respectively, by starting material. As the atomic configurations were standard, the configuration at the C9 atom was determined to be *R* as shown in Figure 1. The cyclohexane ring of **10**(−) takes the chair conformation. The crystal was stabilized by intramolecular hydrogen bonding between O19 and O20 to enable the fractional crystallization of **10**(−).

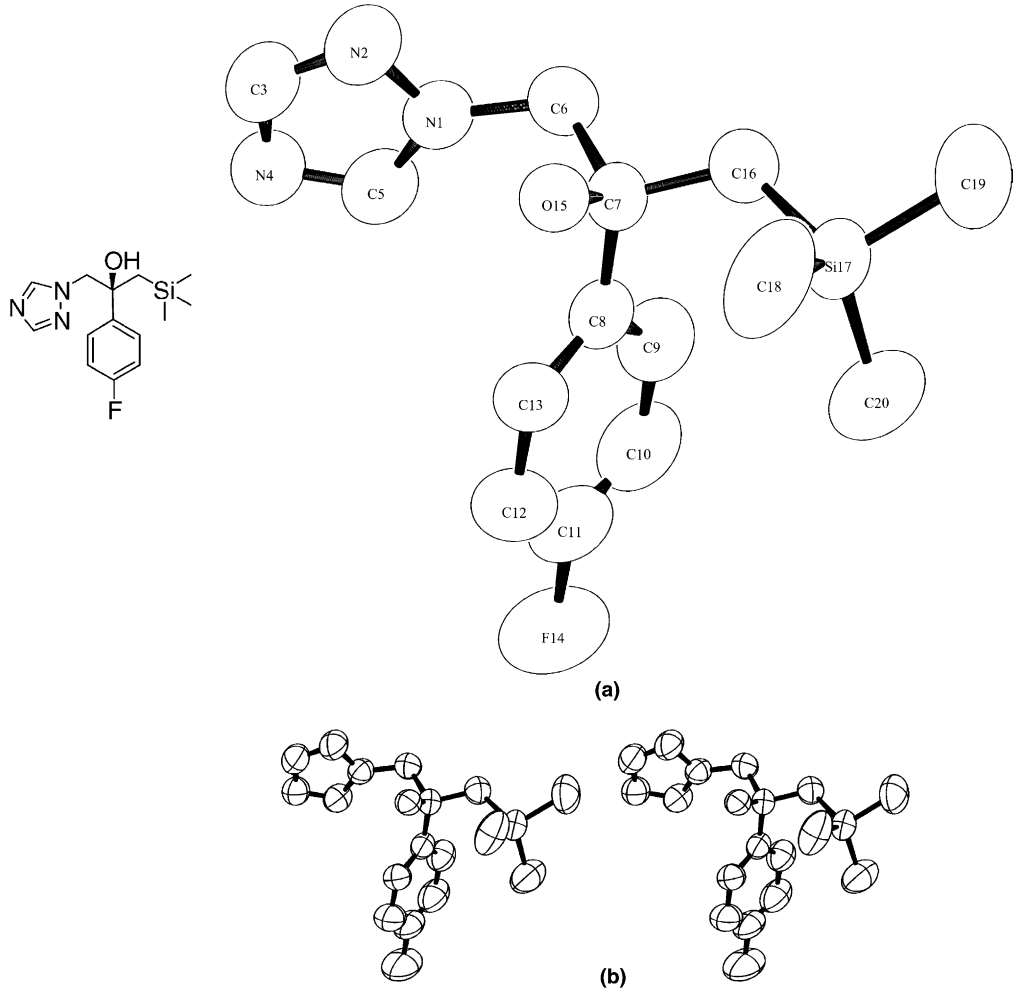


Figure 2. (a) Molecular structure of **1**(+) with atomic numbering and (b) stereoscopic view of **1**(+).

Table 1. Fungicidal activities of enantiomers

Compd no	*Rhizoctonia solani* IC_{50} (ppm)	Sheath blight (g/10a)	*Pyricularia oryzae* IC_{50} (ppm)	Rice blast (g/10a)
1(−)	0.016	25	0.95	100
1	0.042	25	1.25	100
1(+)	0.54	>100	33.5	>100

The atomic labeling and thermal ellipsoids of **1**(+) are shown in Figure 2. The configuration of **1**(+) was determined by observing and calculating the $F(+)/F(-)$ ratios of Bijvoet pairs with the mean F value of each independent reflection. The data are available as supporting information. Based on the results, the stereochemistry of **1**(+) was determined to be *S* as that shown in Figure 2. The crystal was stabilized by intramolecular hydrogen bonding between O15 and N4.

4. Fungicidal activities and discussion

The in vitro and in vivo antifungal activities of **1**(−), **1**(+) and racemic **1** are shown in Table 1. The enantiomer **1**(−) was more potent than racemic **1** against both *Pyricularia oryzae* and *Rhizoctonia solani* in vitro. In contrast, the other enantiomer **1**(+) showed over 10-fold less activity than **1**(−) against both pathogens in vivo.

In the test of the fungicidal activity for rice blast and sheath blight by submerged application, **1**(−) showed almost the same efficacy as **1**. On the other hand, **1**(+) showed no efficacy at the same treatment dose.

Azole fungicides such as imidazole and triazole have been shown to inhibit the fungal biosynthesis of ergosterol, an important constituent of the fungal cell membrane. A crucial step in ergosterol biosynthesis is the 14C-demethylation of lanosterol, mediated by the cytochrome P450 monooxygenase enzyme.[12]

These results agree with the earlier contention that the *R*-absolute configuration is the only enantiomer that can fit sterically over the lanosterol skeleton and effectively inhibit cytochrome P450 14C-demethylase.

5. Conclusion

We found a novel and efficient method to prepare silicon-containing triazolyl derivatives **1** via a Grignard reaction with phenylglyoxylate. The optically active enantiomers **1**(−) and **1**(+) were synthesized by following exactly the same procedure used to prepare the racemic **1** with the use of (1*R*,2*S*)- and (1*S*,2*R*)-*trans*-2-phenylcyclohexanols as a chiral auxiliary. The absolute configuration of enantiomer **1**(+) was determined by X-ray crystallographic analysis. Comparison of the antifungal activity of the enantiomers revealed that the (−)-enantiomer with the *R*-absolute configuration was far more potent than the (+)-enantiomer.

6. Experimental

All melting points (mp) were uncorrected. IR was recorded on a Perkin Elmer 1600 spectrometer and ^{1}H NMR spectra were recorded on a Varian Gemini 200 spectrometer using tetramethylsilane as an internal standard. MS were obtained on a JEOL JMS-D300 spectrometer and a VG Auto Spec M mass spectrometer. TLC was performed on a plate precoated with a 0.25 mm-thick layer of silica gel (E. Merck), and the spots were made visible by ultraviolet (UV) irradiation or by spraying with a solution made of 25 g ammonium molybdate and 1 g ceric sulfate in 500 mL of 10% sulfuric acid followed by heating. Silica gel (350–250 mesh, Yamamura Chemical Laboratories Co., Ltd) was used for column chromatography and preparative TLC was carried out on a plate precoated with a 2 mm-thick layer of silica gel (E. Merck). The following abbreviations are used hereafter: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; dt, doublet of triplet; q, quartet; m, multiplet. Optical rotations were determined on a JASCO DIP-370 digital polarimeter at 27 °C at the sodium D-line; the concentrations are reported g/100 mL.

6.1. 2-Phenylcyclohexyl 2-(4-fluorophenyl)glyoxylate (9)

Oxalyl chloride (40.0 g, 0.31 mol) was added to a solution of 2-(4-fluorophenyl)glyoxylic acid (13.1 g, 78.0 mmol) in dichloromethane (100 mL) and stirred at room temperature for 3 h. After evaporation the solvent and dissolving the residue with acetonitrile (100 mL), the solution was added to a solution of *trans*-2-phenylcyclohexanol (3.1 g, 17.6 mmol) in acetonitrile (50 mL), stirred for 3 h at room temperature, poured into ice, and extracted with ethyl acetate. The organic layer was washed with diluted hydrochloric acid, aqueous solution of sodium hydrogencarbonate, and water, and dried over magnesium sulfate. The solvent was evaporated to give an oily residue, which was purified by column chromatography (ethyl acetate–hexane, 1:10, v/v) to afford **3** (4.4 g, 77%) as colorless crystals (recrystallized from diisopropyl ether), mp 66 °C. IR (KBr) cm^{-1}: 3007, 2858, 1961, 1919, 1750, 1681, 1593, 1494, 1448, 1300, 1225. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.30–2.31 (8H, m), 2.76 (1H, dt, $J = 3.9$, 10.7 Hz), 5.41 (1H, dt, $J = 4.6$, 10.7 Hz), 6.90 (2H, t, $J = 8.5$ Hz), 7.16–7.40 (7H, m). MS m/z: 326 (M^+), 214, 160. Anal. Calcd for $C_{20}H_{19}FO_3$: C, 73.60; H, 5.87; F, 5.82. Found: C, 73.64; H, 5.94; F, 5.74.

The same procedure was used to prepare optically active enantiomers **9**(−) and **9**(+) with NMR and MS spectra identical to those of **9**.

9(−) 91%, $[\alpha]_D^{27}$ −9.3 (*c* 3.75, $CHCl_3$); **9**(+) 88%, $[\alpha]_D^{27}$ +12.0° (*c* 2.75, $CHCl_3$).

The following compound **7** was prepared similarly.

6.2. (−)-8-Phenylmenthyl 2-(4-fluorophenyl)glyoxylate (7)

82%, mp 121–122 °C. IR (KBr) cm^{-1}: 2900, 2853, 1954, 1898, 1700, 1678, 1597, 1500, 1445, 1416, 1330, 1225. ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (3H, d, $J = 8.6$ Hz), 0.85–1.72 (7H, m), 1.30 (3H, s), 1.37 (3H, s), 2.08 (1H, dt, $J = 4.8$, 12.0 Hz), 5.01 (1H, dt, $J = 4.8$, 12.0 Hz), 6.84–7.28 (7H, m), 8.01 (2H, dd, $J = 5.7$, 10.0 Hz). MS *m*/*z*: 382 (M^+), 330, 193, 165. Anal. Calcd for $C_{24}H_{27}FO_3$: C, 75.37; H, 7.12; F, 4.97. Found: C, 75.51; H, 7.21; F, 4.98.

6.3. 2-Phenylcyclohexyl 2-(4-fluorophenyl)-2-hydroxy-3-trimethylsilylpropionate (10)

A solution of trimethylsilylmethylmagnesium chloride in diethyl ether (4.1 mL, 4.1 mmol) was added dropwise to a solution of **9** (890 mg, 2.7 mmol) in diethyl ether (5 mL) at −70 °C and stirred for 1 h at the same temperature. The reaction mixture was poured into ice and extracted with ethyl acetate. The organic layer was washed with aqueous solution of ammonium chloride and dried over magnesium sulfate. The solvent was evaporated to give **10** (1.1 g, 98%) as diastereomixture (4:1).

The same procedure was used to prepare diastereomixtures of **10**(−) and **10**(+) with NMR and MS spectra identical to those of **10**. Diastereomixture **10**(−) (3.5:1) was obtained in 90% yield and diastereomixture **10**(+) (3.4:1) was obtained in 97% yield.

The following compound **8** was prepared similarly.

6.4. (−)-8-Phenylmenthyl 2-(4-fluorophenyl)-2-hydroxy-3-trimethylsilylpropionate (8)

70%, oil. IR (neat) cm^{-1}: 3564, 3501, 2950, 2872, 1715, 1603, 1504, 1445, 1371, 1248, 1207, 1159, 1086, 1009. ^1H NMR (200 MHz, $CDCl_3$): δ −0.10 (9H, s), 0.82 (3H, d, $J = 7.1$ Hz), 0.70–2.15 (7H, m), 0.97 (3H, s), 1.06 (3H, s), 4.79 (1H, dt, $J = 4.7$, 11.8 Hz), 6.95 (2H, t, $J = 8.5$ Hz), 7.20–7.54 (7H, m). MS *m*/*z*: 470 (M^+), 211, 121. Anal. Calcd for $C_{28}H_{39}FO_3Si$: C, 71.45; H, 8.35; F, 4.04. Found: C, 71.12; H, 8.37; F, 4.13.

6.5. Resolution of (1′*R**,2′*S**,2*R**)-2-phenylcyclohexyl 2-(4-fluorophenyl)-2-hydroxy-3-trimethylsilylpropionate (10)

Diastereomixture **10** (1.18 g, 2.8 mmol) was dissolved in hot ethanol (10 mL). After cooling, the resulting precipitates were collected by filtration to give a solid (765 mg, 1.8 mmol). This solid was dissolved in ethanol (7 mL) and recrystallized from the solution to afford a single diastereomer **10** (531 mg, 1.3 mmol) in 46%. Mp 101 °C. IR (KBr) cm^{-1}: 3477, 2950, 2862, 1713, 1602, 1506, 1450, 1381, 1250, 1197, 1113, 1092, 1016. ^1H NMR (200 MHz, $CDCl_3$): δ −0.13 (9H, s), 1.20–1.60 (7H, m), 1.70–1.95 (3H, m), 2.20–2.35 (1H, m), 2.69 (1H, dt, $J = 3.7$, 10.9 Hz), 3.67 (1H, s), 4.96 (1H, dt, $J = 4.4$, 10.9 Hz), 6.68 (2H, t, $J = 8.6$ Hz), 6.95–7.14 (7H, m). MS *m*/*z*: 414 (M^+), 211, 195, 121. Anal. Calcd for $C_{24}H_{31}FO_3Si$: C, 69.53; H, 7.54. Found: C, 69.82; H, 7.41.

The same procedure was used to prepare optically active diastereomers **10**(−) and **10**(+) with NMR and MS spectra identical to those of **10**.

6.6. (1′*R*,2′*S*,2*R*)-2-Phenylcyclohexyl 2-(4-fluorophenyl)-2-hydroxy-3-trimethylsilylpropionate 10(−)

50%, $[\alpha]_D^{27}$ −61.3 (*c* 3.15, $CHCl_3$). Recrystallization from ethanol solution gave colorless plates. The crystal used has approximate dimensions of 0.5 × 0.2 × 0.2 mm. Data were collected on a diffractometer, Rigaku AFC7R, and corrected for Lorentz and polarization factors. Absorption correction was not applied. The structure was determined by a direct method with the program SIR 92.[13] The parameters refined include the coordinates and anisotropic thermal parameters for all nonhydrogen atoms. Most of the hydrogen atoms were found in the difference map and the remaining hydrogen atoms were calculated at ideal positions and refined in terms of isotropic temperature factors. The final cycle of full-matrix least-squares refinement was based on 1921 observed reflections ($F \geqslant 2\sigma(F)$) and converged with $R = 0.035$ and $Rw = 0.043$. A Chebychev weighting scheme was used.[14] Crystal data and conditions of data collection are summarized in Table 2. Tables of atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are available as supporting information.

6.7. (1′*S*,2′*R*,2*S*)-2-Phenylcyclohexyl 2-(4-fluorophenyl)-2-hydroxy-3-trimethylsilylpropionate 10(+)

63%, $[\alpha]_D^{27}$ +64.4 (*c* 2.05, $CHCl_3$).

6.8. 2-(4-Fluorophenyl)-3-trimethylsilylpropan-1,2-diol (11)

Lithium aluminum hydride (75 mg, 2.0 mmol) was added to a solution of **10** (414 mg, 1.0 mmol) in tetrahydrofuran (40 mL). After stirring for 1 h at 0 °C, the mixture was diluted with ethyl acetate (10 mL), methanol (10 mL), and water (1 mL) in succession and filtered through celite. The filtrate was concentrated to give a solid and purified by column chromatography (ethyl acetate–hexane, 1:4, v/v) to afford **11** (170 mg, 70%) as colorless crystals (recrystallized from diisopropyl ether), mp 50 °C. IR (KBr) cm^{-1}: 3306, 2950, 2897, 2360, 1894, 1722, 1604, 1504, 1425, 1228, 1161, 1075, 1015. ^1H NMR (200 MHz, $CDCl_3$): δ −0.17 (9H, s), 1.14 (1H, d,

Table 2. Summary of crystal data and intensity collections for **10**(−)

Formula	$C_{24}H_{31}O_3FSi$
Formula weight	414.6
Crystal color	Colorless
Crystal description	Prismatic
Crystal system	Monoclinic
Space group	C2
a (Å)	24.589(3)
b (Å)	6.934(1)
c (Å)	17.211(2)
β (deg)	126.394(8)
V (Å^3)	2362.3(6)
Z	4
Dc (g/cm^3)	1.166
Absorption coef (cm^{-1})	1.112
Temperature (°C)	25
Radiation	Cu Kα ($\lambda = 1.5418$)
2*θ* range of reflections for cell determination (deg)	50–59
Scan mode	ω–2θ
26 range of data collection (deg)	2–136
No of unique reflections	2345
No of reflections used for refinement ($F \geqslant 2\sigma(F)$)	1921
R	0.035
Rw	0.043

$J = 14.7$ Hz), 1.27 (1H, d, $J = 14.7$ Hz), 1.85 (1H, b s), 2.70 (1H, b s), 2.58 (1H, d, $J = 11$ Hz), 3.73 (1H, d, $J = 11.0$ Hz), 7.03 (2H, t, $J = 8.9$ Hz), 7.39 (2H, dd, $J = 5.5$, 8.9 Hz). MS *m/z*: 224 (M^+-18), 211, 195, 121. Anal. Calcd for $C_{12}H_{19}FO_2Si$: C, 59.47; H, 7.90. Found: C, 59.24; H, 7.73.

The same procedure was used to prepare optically active enantiomers **11**(−) and **11**(+) with NMR and MS spectra identical to those of **11**. Enantiomers **11**(−) and **11**(+) were obtained in 43%, $[\alpha]_D^{27}$ +4.7 (*c* 4.05, $CHCl_3$) and 45%, $[\alpha]_D^{27}$ −3.2 (*c* 3.10, $CHCl_3$) yields, respectively.

6.9. 2-(4-Fluorophenyl)-1-methanesulfonyloxy-3-trimethylsilylpropan-2-ol (12)

Methanesulfonyloxy chloride (720 mg, 6.3 mmol) was added to a solution of **11** (1.26 g, 5.2 mmol) in pyridine (15 mL) at 0 °C. After stirring for 2 h at the same temperature, the reaction mixture was poured into ice and extracted with ethyl acetate. The organic layer was washed with aqueous solution of ammonium chloride and dried over magnesium sulfate. The solvent was evaporated to give a solid, which was purified by column chromatography (ethyl acetate–hexane, 1:4, v/v) to afford **12** (1.5 g, 90%) as colorless crystals (recrystallized from diisopropyl ether), mp 115–116 °C. IR (KBr) cm^{-1}: 3493, 2950, 2895, 1908, 1722, 1736, 1605, 1510, 1425, 1340, 1248, 1159, 1097, 1064. ^{1}H NMR (200 MHz, $CDCl_3$): δ −0.17 (9H, s), 1.24 (1H, d, $J = 14.8$ Hz), 1.38 (1H, d, $J = 14.8$ Hz), 2.47 (1H, s), 2.91 (3H, s), 4.27 (2H, s), 7.05 (2H, t, $J = 8.8$ Hz), 7.41 (2H, dd, $J = 5.2$, 8.8 Hz). MS *m/z*: 320 (M^+), 211, 195, 121. Anal. Calcd for $C_{13}H_{21}FO_4SSi$: C, 48.73; H, 6.61; F, 5.93; S, 10.01. Found: C, 48.58; H, 6.53; F, 5.86; S, 9.86.

The same procedure was used to prepare optically active enantiomers **12**(−) and **12**(+) with NMR and MS spectra identical to those of **12**. Enantiomers **12**(−) and **12**(+) were obtained in 90% and 84% yields, respectively.

6.10. (*RS*)-2-(4-Fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-trimethylsilylpropan-2-ol (1)

A mixture of **12** (1.43 g, 4.46 mmol) and 1*H*-1,2,4-triazole sodium salt (900 mg, 8.9 mmol) in *N*,*N*-dimethylformamide (20 mL) was heated to 80 °C for 2 h. The reaction mixture was poured into ice and extracted with ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate. The solvent was evaporated to give a solid, which was purified by column chromatography (ethyl acetate–hexane, 1:1, v/v) to afford **1** (529 mg, 40%) as colorless crystals. The NMR and MS spectra of **1** were identical to these reported in the literature.[1]

The same procedure was used to prepare optically active enantiomers **1**(−) and **1**(+) with NMR and MS spectra identical to those of **1**.

6.11. (*R*)-2-(4-Fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-trimethylsilylpropan-2-ol 1(−)

40%, $[\alpha]_D^{27}$ −70.5 (*c* 3.75, $CHCl_3$).

6.12. (*S*)-2-(4-Fluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-3-trimethylsilylpropan-2-ol 1(+)

27%, $[\alpha]_D^{27}$ +70.1 (*c* 3.62, $CHCl_3$). Recrystallization from diisopropyl ether solution gave colorless plates. The crystal used has approximate dimensions of $0.3 \times 0.3 \times 0.2$ mm. Diffraction experiments and structure determination were carried out using the method and procedures described for **10**(−). The absolute configuration of **1**(+) was determined based on anomalous scattering effects of the silicon atom. The final refinement converged at $R = 0.050$ and $Rw = 0.063$. Crystal data and conditions of data collection are summarized in Table 3. Tables of atomic coordinates, thermal parameters, bond distances, bond angles, and torsion angles are available as supporting information.

6.13. Antifungal activity

IC_{50}s (50% inhibitory concentration) of the compounds were determined by an agar dilution method using potato dextrose agar medium (PDA). The agar medium (10 mL) was poured into petri dishes containing 0.1 mL of serial dilutions of the test compounds dissolved in dimethyl sulfoxide containing 10% Tween 20 and was solidified.

The 4 mm mycelial disks of *P. oryzae* or *R. solani* were then placed in center of the PDA plates, and measured the mycelial growth rate between 24 and 48 h at 25 °C to determine the IC_{50}s for these fungi.

Table 3. Summary of crystal data and intensity collections for **1**(+)

Formula	$C_{14}H_{20}N_3FOSi$
Formula weight	293.4
Crystal color	Colorless
Crystal description	Prismatic
Crystal system	Orthorhombic
Space group	$P2_1P2_1$
a (Å)	11.666(2)
b (Å)	12.784(1)
c (Å)	10.933(1)
V (Å^3)	1630.5(3)
Z	4
Dc (g/cm^3)	1.195
Absorption coef (cm^{-1})	1.365
Temperature (°C)	25
Radiation	Cu Kα ($\lambda = 1.5418$)
2θ range of reflections for cell determination (deg)	45–49
Scan mode	ω–2θ
26 range of data collection (deg)	2–100
No of unique reflections	3672
No of reflections used for refinement ($F \geqslant 2\sigma(F)$)	3628
R	0.050
Rw	0.063

6.14. Preventive activity against rice blast by submerged application

Rice seedlings (variety Sachikaze) at the three-leaf stage were flooded to a depth of 1 cm with water in pots and then exposed to the test compound by mixing it into the water. After keeping the seedlings in a greenhouse for 7 days, the rice seedlings were sprayed with a spore suspension of the fungus *P. oryzae* and then kept in a moist chamber (relative humidity: 100%) for 7 days at 25–27 °C. The number of grams per 10 acres required to eradicate rice blast was determined after 7 days. The results are shown in Table 1.

6.15. Preventive activity against rice sheath blight by submerged application

Rice seedlings (variety Sachikaze) at the three-leaf stage were flooded to a depth of 1 cm with water in pots and then exposed to the test compound by mixing it into the water. After keeping the seedlings in a greenhouse for 7 days, 4–5 oat grains cultured with *R. solani* were placed around the base of each seedling. The seedlings were then kept in a moist chamber (relative humidity: 100%) for 7 days at 25–27 °C. The number of grams per 10 acres required to eradicate rice sheath blight was determined after 7 days. The results are shown in Table 1.

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References and notes

1. Itoh, H.; Yoneda, R.; Tobitsuka, J.; Matsuhisa, T.; Kajino, H.; Ohta, H.; Hayashi, N.; Takahi, Y.; Tsuda, M.; Takeshiba, H. *Chem. Pharm. Bull.* **2000**, *48*, 1148.
2. Itoh, H.; Kajino, H.; Tsukiyama, T.; Tobitsuka, J.; Ohta, H.; Takahi, Y.; Tsuda, M.; Takeshiba, H. *Bioorg. Med. Chem.* **2002**, *10*, 4029.
3. Itoh, H.; Kajino, H.; Tsukiyama, T.; Takeshiba, H.; *Ann. Rep. Sankyo Res.* **2003**, *55*, 119.
4. Carelli, A.; Farina, G.; Gozzo, F.; Merlini, L.; Kelly, S. L. *Pestic. Sci.* **1992**, *35*, 167.
5. Konosu, T.; Miyaoka, T.; Tajima, Y.; Oida, S. *Chem. Pharm. Bull.* **1991**, *39*, 2241.
6. Miyauchi, H.; Nakamura, T.; Ohashi, N. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 2625.
7. Gala, D.; DiBenedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P. *Tetrahedron Lett.* **1996**, *37*, 611.
8. Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 987.
9. Whitesell, J. K.; Deyo, D.; Bhattacharya, A. *J. Chem. Soc., Chem. Commun.* **1983**, 802.
10. Whitesell, J. K.; Chen, H. H.; Laurence, R. M. *J. Org. Chem.* **1985**, *50*, 4663.
11. Peter, E.; Helmut, B. *Angew. Chem.* **1992**, *104*, 1254.
12. Aoyama, Y.; Yoshida, Y.; Sato, R. *J. Biol. Chem.* **1984**, *259*, 1661.
13. Altomar, A.; Burla, M. C.; Camalli, M.; Cascarrano, M.; Giacovazzo, C.; Guagliardi, A.; Polodori, G. SIR92 a Program for Automatic Solution of Crystal Structures by Direct Methods. *J. Appl. Cryst.* **1994**, *27*, 435.
14. Carruthers, J. R.; Watkin, D. J. A Weighting Scheme for Least-Squares Structure Refinement. *Acta Crsyt.* **1979**, *A35*, 698–699.