Synthesis and Antifungal Activity of the Four Stereoisomers of Streptimidone, a Glutarimide Antibiotic from *Streptomyces rimosus* forma *paromomycinus*

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Four stereoisomers of streptimidone **(1)**, an antibiotic from *Streptomyces rimosus* forma *paromomycinus*, were synthesized from methyl (*S*)-3-hydroxy-2-methylpropanoate. The natural diastereomer **1** shows the strongest antimicrobial activity.

Introduction

Streptimidone has been isolated from various *Streptomyces* species,[1] and also from *Micromonospora coerulea.*[2] This compound belongs to the glutarimide antibiotics, and its absolute structure was deduced as shown in Figure 1 by a degradation study of the natural product.[3] Streptimidone has been shown to have strong antimicrobial activity against eukaryotic cells.[1b] Among glutarimide antibiotics, cycloheximide **(2)**, which is a well-known inhibitor of protein synthesis, shows inhibitory activity against the growth of toxic plant fungi.[4] However, the toxicity to the host plants limits its use as a plant chemotherapeutic agent. On the contrary, streptimidone inhibits the development of plant diseases such as Phytophthora blight on pepper, gray mold on cucumber leaves, and leaf blast on rice leaves, and does not show any phytotoxicity to the host plants.[2] Since this type of antibiotics are promising candidates for new pesticides, further chemical and biological studies of streptimidone are necessary. With a view to study structure-activity relationships, we have synthesized all four diastereomers of streptimidone and investigated their antimicrobial activity.

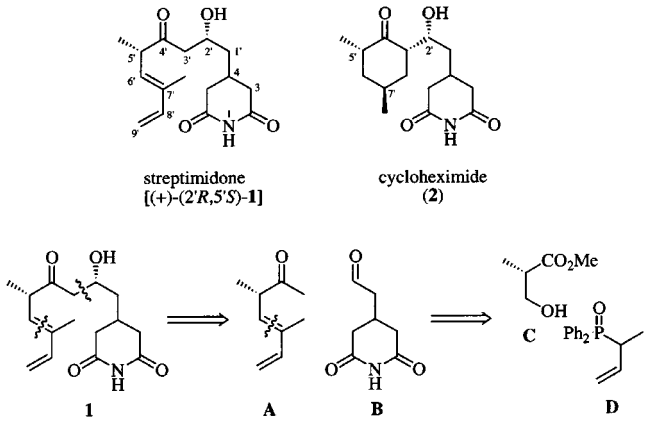

Figure 1. Streptimidone (**1**) and its retrosynthetic analysis

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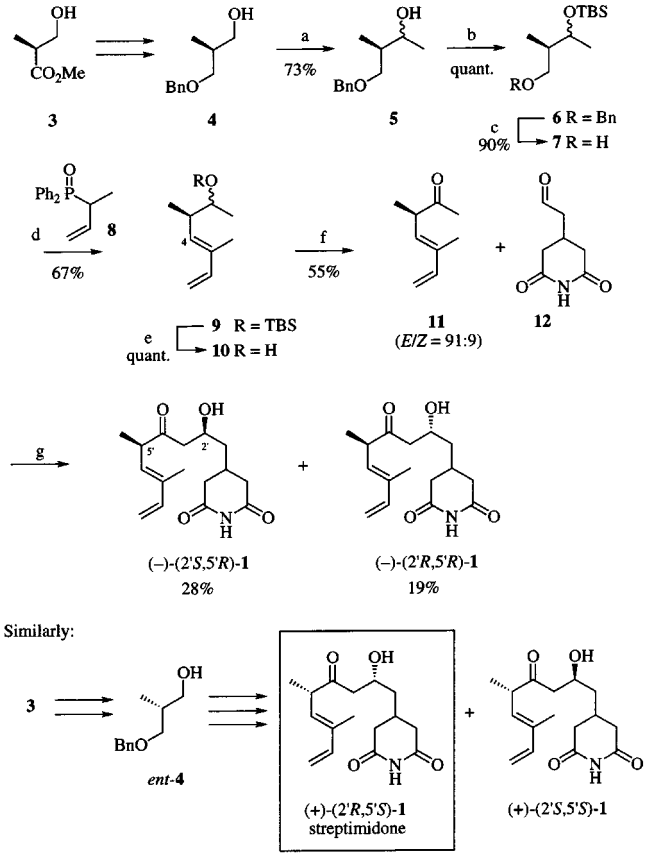
Results and Discussion

The retrosynthetic analysis of **1** is shown in Figure 1. Streptimidone could be formed as an aldol coupling product of ketone **A** and the known aldehyde **B.**[5] The ketone **A** could be prepared from the commercially available chiral building block **C** and phosphane oxide reagent **D.**[6] The synthesis of **1** and its diastereomers are summarized in Scheme 1. At first, we began the synthesis of an unnatural enantiomer of **1**. Methyl (*S*)-3-hydroxy-2-methylpropanoate **3** (= **C**, 99.88% *ee*) was converted into the known alcohol **4.**[7] The hydroxy group of **4** was oxidized to give the corresponding aldehyde which was treated with MeMgI to give **5**[8] in 73% yield. The so-formed secondary hydroxy group was protected with *tert*-butyldimethylsilyl (TBS) ether to give **6**;[9] removal of the benzyl group gave **7**. The primary hydroxy group was oxidized to give an aldehyde, which was then coupled with the phosphane oxide reagent **8** (= **D**)[6] to afford diene **9**. The TBS protecting group was removed, and the resulting hydroxy group was oxidized to give ketone **11** (= *ent*-**A**). The *E*/*Z* ratio of the 4-position was determined to be 91:9 by the ^{1}H NMR analysis of **11**. The regiochemistry was deduced from ^{1}H NMR chemical shifts: δ_{H-6} of (*E*)-**11** was 6.38, and δ_{H-6} of (*Z*)-**11** was 6.80; while the corresponding δ_{H-11} of the natural streptimidone was 6.33. Finally, aldol reaction of the lithium enolate derived from **11** with the known glutarimide part **12** (= **B**)[5] gave the unnatural enantiomer of streptimidone (−)-(2′*S*,5′*R*)-**1** and its 2′-epimer. These isomers were separated by preparative TLC, and purified by recrystallization. The selectivity of the key aldol reaction was poor (ca. 1.5:1). However, we did not try any alternative methods, because synthesis of all the diastereomers was necessary for the biological studies. The ^{1}H and ^{13}C NMR spectral data of (−)-(2′*S*,5′*R*)-**1** are identical with those reported for the natural product.[2] Only the ^{1}H NMR chemical shifts of the 3-position are different for (−)-(2′*S*,5′*R*)-**1** and the 2′-epimer. The ^{13}C NMR spectra are indistinguishable from each other. The IR spectra of the epimers are somewhat different when measured as KBr disks: there are three maximum peaks around the carbonyl region for the 2′-epimer, while only a broad single peak is observed for (−)-(2′*S*,5′*R*)-**1**. In $CHCl_3$ solution,

  1434−193X/00/1020−3459 $ 17.50+.50/0

the absorbances for the carbonyl groups of both compounds are observed as a single peak. The enantiomeric purity of (−)-**1** was determined to be 90% *ee* by a ^{1}H NMR analysis in the presence of the chiral shift reagent Eu(hfc)$_3$. The *E*/*Z* ratio at the 9′-position was 96:4. The selectivity of the aldol reaction and the rate of racemization at the 5′-position were in good agreement with those of Seebach's fundamental experiments.[10] The natural (+)-streptimidone and its 2′-epimer were prepared by a similar procedure as described for (−)-**1**. The optical rotation value of (+)-**1** {$[\alpha]_D^{22}$ = +220, ref.[2] $[\alpha]_D^{27}$ = +243} corresponds to the enantiomeric excess (90% *ee*) and the absolute configuration of (+)-**1** was reconfirmed by our synthesis. This is the first synthesis of streptimidone.



Scheme 1. Synthesis of **1**
Reagents: (a) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii) MeMgI, Et_2O. − (b) TBSCl, DMAP, Et_3N, DMF. − (c) 5% Pd-C, H_2, EtOH. − (d) i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; ii) **8**, *n*BuLi, THF, HMPA; then aldehyde. − (e) TBAF, THF. − (f) Dess−Martin periodinane, CH_2Cl_2. − (g) LiN(*i*Pr)$_2$, then **11**

The results of the antifungal activity of the four stereoisomers are shown in Table 1. The natural stereoisomer exhibits the strongest activity towards both *Saccharomyces cerevisiae* and *Cochliobolus miyabeanus*, and is almost equal to that of cycloheximide. (2′*R*,5′*R*)-**1** hardly inhibits the growth, and (2′*S*,5′*R*)- and (2′*S*,5′*S*)-**1** show moderate activity. The activity of (2′*S*,5′*R*)-**1** (90% *ee*) might be due to contamination with its enantiomer (2′*R*,5′*S*)-**1**, the natural form. These results indicate that the 2′*R*,5′*S* configuration, and especially 5′*S*, which is the same orientation as in cycloheximide, is necessary for the activity.

Table 1. Antifungal activity of **1**

Compounds	Inhibited zone (mm)					
	S. cerevisiae			*C. miyabeanus*		
	100 (μg/disk)	20	10	100	20	10
(+)-(2′*R*, 5′*S*)-**1** natural form	30	20	−	23	≈5	−
(+)-(2′*S*, 5′*S*)-**1**	14	≈5	−	≈5	−	−
(−)-(2′*S*, 5′*R*)-**1**	18	≈5	−	10	−	−
(−)-(2′*R*, 5′*R*)-**1**	−	−	−	≈5	−	−
Cycloheximide (**2**)	40	−	20	32	−	≈5

Conclusion

In conclusion, the first synthesis of streptimidone and its diastereomers was achieved and the natural 2′*R*,5′*S* configuration was found to be necessary for the antifungal activity.

Experimental Section

General Remarks: Melting points are uncorrected. − Optical rotations were recorded on a Jasco DIP-4. − IR spectra were measured on a Jasco IR-810 spectrometer. − MS spectra were recorded on a JEOL JMS HX-105. − NMR spectra were measured on a Varian JEOL GSX-270 spectrometer (270 MHz and 67.5 MHz, for ^{1}H and ^{13}C, respectively, in $CDCl_3$, TMS as an internal standard at 20 °C).

(2*RS*,3*R*)-4-Benzyloxy-3-methylbutan-2-ol (5): To a solution of oxalyl chloride (3.6 mL, 42 mmol) in CH_2Cl_2 (100 mL) was added dropwise a solution of DMSO (4.0 mL, 56 mmol) in CH_2Cl_2 (5 mL) at −78 °C under nitrogen. After stirring for 5 min, a solution of **4** (5.0 g, 28 mmol) in CH_2Cl_2 (5 mL) was added, and the resulting mixture was stirred for 15 min at −78 °C. Et_3N (19 mL) was then added, and the temperature was gradually raised to −10 °C. The reaction mixture was poured into ice/water and extracted with benzene/Et_2O (4:1). The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The crude aldehyde was used in the next step without further purification. IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, C=O).
To a solution of MeMgI, prepared from Mg (1.0 g, 42 mmol) and MeI (6.0 g, 42 mmol), was added the above-mentioned crude aldehyde in Et_2O (20 mL) at 10 °C, and the mixture was stirred for 50 min at 20 °C. The reaction was quenched with a saturated aqueous NH_4Cl solution and extracted with Et_2O. The extract was washed with water, saturated aqueous $NaHCO_3$ solution, and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1→7:1) gave **5** (3.9 g, 20 mmol, 73% from **4**). − IR (film): $\tilde{\nu}$ = 3430 cm^{-1} (s, O−H), 1455 (m), 1365 (m), 1095 (m), 740 (m). − ^{1}H NMR: δ = 0.85 and 0.92 (each d, ^1J = 6.8, 6.6 Hz, total 3 H), 1.15 and 1.17 (each d, ^1J = 6.6, 6.1 Hz, total 3 H), 1.85 (m, 1 H, 2-H), 3.4−3.8 (m, 3 H, 2- and 4-H), 4.51 and 4.52 (each s, total 2 H, CH_2Ph), 7.32 (m, 5 H, Ph). − $C_{12}H_{18}O_2$ (194.3): calcd. C 74.19, H 9.34; found C 73.83, H 9.44.

(2*R*,3*RS*)-1-Benzyloxy-3-*tert*-butyldimethylsilyloxy-2-methylbutane (6): A solution of **5** (4.0 g, 21 mmol), *tert*-butyldimethylsilyl chlor-

ide (TBSCl, 3.7 g, 25 mmol), 4-(dimethylamino)pyridine (DMAP, 0.85 g, 7.0 mmol), and Et_3N (3.6 mL, 26 mmol) in DMF (15 mL) was stirred for 10 h at 20 °C. The reaction mixture was poured into ice/water and extracted with Et_2O. The extract was washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **6** (6.5 g, 21 mmol, quant.). – IR (film): $\tilde{\nu}$ = 2890 cm^{-1} (w), 1460 (m), 1375 (m), 1250 (m). – ^1H NMR: δ = 0.02 and 0.04 (each s, total 6 H, Me_2Si), 0.87 (s, 9 H, *t*Bu), 0.95 (m, 3 H), 1.08 and 1.09 (each d, ^1J = 6.1, 6.4 Hz, total 3 H), 1.80 (m, 1 H, 2-H), 3.40 (m, 2 H, 1-H), 3.90 (m, 1 H, 3-H) 4.48 (s, 2 H, CH_2Ph), 7.32 (m, 5 H, Ph). – $C_{18}H_{32}O_2Si$ (308.5): calcd. C 70.07, H 10.45; found C 69.84, H 10.63.

(2*R*,3*RS*)-3-*tert*-Butyldimethylsilyloxy-2-methylbutan-1-ol (7): A suspension of **6** (6.9 g, 22 mmol) and 5% Pd-C (100 mg) in EtOH (65 mL) was stirred at 20 °C under H_2 for 12 h. The reaction mixture was filtered through a Celite pad and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **7** (4.3 g, 20 mmol, 90%). – IR (film): $\tilde{\nu}$ = 3380 cm^{-1} (s, O–H), 1460 (m), 1370 (m), 1250 (s). – ^1H NMR: δ = 0.08 and 0.09 (each s, total 6 H, Me_2Si), 0.75–1.00 (m, 12 H), 1.15 and 1.21 (each d, ^1J = 6.6, 6.4 Hz, total 3 H), 1.4–2.0 (m, 1 H, 2-H), 2.9 (br. s, 1 H, OH), 3.4–4.1 (m, 3 H). – $C_{11}H_{26}O_2Si$ (218.4): calcd. C 60.49, H 12.00; found C 60.51, H 11.94.

(3*E*,5*R*,6*RS*)-6-*tert*-Butyldimethylsilyloxy-3,5-dimethylhepta-1,3-diene (9): To a solution of oxalyl chloride (2.2 mL, 26 mmol) in CH_2Cl_2 (60 mL) was added dropwise a solution of DMSO (2.4 mL, 34 mmol) in CH_2Cl_2 (7 mL) at −78 °C under nitrogen. After stirring for 5 min, a solution of **7** (3.7 g, 17 mmol) in CH_2Cl_2 (7 mL) was added, and the resulting mixture was stirred for 15 min at −78 °C. Et_3N (19 mL) was then added, and the temperature was gradually raised to −10 °C. The reaction mixture was poured into ice/water and extracted with benzene/Et_2O (4:1). The extract was washed with water and brine, dried with $MgSO_4$, and concentrated in vacuo. The crude aldehyde was used in the next step without further purification. IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, C=O).
To a solution of (1-methylprop-2-enyl)diphenylphosphane oxide (**8**, 5.1 g, 20 mmol) in THF (65 mL) was added dropwise a solution of *n*BuLi (1.0 M in hexane, 20 mL, 20 mmol) at −70 °C under Ar. After the solution was stirred for 20 min, HMPA (7.2 g 40 mmol) in THF (7 mL) and the above-mentioned crude aldehyde (ca. 17 mmol) in THF (7 mL) were added successively, and the resulting mixture was stirred for 10 min. The reaction was quenched with ice/water and extracted with Et_2O. The extract was washed with water and saturated aqueous LiBr solution, dried with $MgSO_4$, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with Et_2O gave **9** (2.9 g, 11 mmol, 67% from **7**). – IR (film): $\tilde{\nu}$ = 1640 cm^{-1} (w, C=C), 1610 (w, C=C), 1460 (m), 1375 (m), 840 (w), 770 (w). – ^1H NMR: δ = 0.03 and 0.04 (each s, total 6 H, Me_2Si), 0.8–1.2 (m, 15 H), 1.74 (m, 3 H, 3-Me), 2.50 (m, 1 H, 5-H), 3.69 (m, 1 H, 6-H), 4.85–5.50 (m, 3 H), 6.38 (m, 1 H). – $C_{15}H_{30}OSi$ (254.5): calcd. C 70.80, H 11.88; found C 70.66, H 11.90.

(2*RS*,3*R*,4*E*)-3,5-Dimethylhepta-4,6-dien-2-ol (10): A solution of **9** (2.9 g, 11 mmol) in $(nBu)_4NF$ (TBAF, 1 M in THF, 20 mL, 20 mmol) was stirred for 12 h at 20 °C. The reaction mixture was poured into ice/water and extracted with Et_2O. The extract was washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **10** (1.5 g, 11 mmol, quant.). – IR (film): $\tilde{\nu}$ = 3370 cm^{-1} (s, O–H), 1640 (w, C=C), 1605 (w, C=C), 1450 (m), 1370 (m), 1090 (m), 1065 (m), 1040 (m), 990 (w), 930 (w), 895 (w). – ^1H NMR: δ = 0.99 and 1.02 (each d, ^1J = 6.6, 6.8 Hz, total 3 H), 1.14 and 1.18 (each d, ^1J = 6.4, 6.4 Hz, total 3 H), 1.6 (br. s, 1 H, OH), 1.78 and 1.79 (each d, ^1J = 1.0, 1.0 Hz, 5-Me, total 3 H), 2.55 (m, 1 H, 3-H), 3.8 (m, 1 H, 2-H), 4.9–5.5 (m, 3 H), 6.38 and 6.40 (each ddd, ^1J = 0.7, 11.5, 17.5 and 0.7, 11.5, 17.5 Hz, total 1 H). – $C_9H_{16}O$ (140.23): calcd. C 77.09, H 11.50; found C 76.78, H 11.42.

(3*R*,4*E*)-3,5-Dimethylhepta-4,6-dien-2-one (11): A solution of **10** (0.80 g, 5.7 mmol), Dess–Martin periodinane (3.6 g, 8.5 mmol) in CH_2Cl_2 (30 mL) was stirred for 40 min at 20 °C. The reaction mixture was diluted with Et_2O and washed with a saturated aqueous $Na_2S_2O_3$ solution, a saturated aqueous $NaHCO_3$ solution and water, dried with $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on preparative TLC (silica gel 0.75 mm thickness, 20 cm × 20 cm). Elution with hexane/CH_2Cl_2 (1:1) gave **11** (0.43 g, 3.1 mmol, 55%, *E*/*Z* = 91:9). This *E*/*Z* mixture was used in the next step without further purification because of its volatility and instability. For analysis, purification by $AgNO_3$-coated silica gel TLC gave pure (*E*)-**11**, $[\alpha]_D^{20}$ = −310 (*c* = 0.20, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 1720 cm^{-1} (s, C=O), 1640 (m, C=C), 1605 (w, C=C), 1450 (m), 1420 (m), 1170 (m), 1040 (m), 990 (w), 900 (w). – ^1H NMR: δ = 1.17 (d, ^1J = 6.8 Hz, 3 H), 1.84 (d, ^1J = 1.2 Hz, 3 H), 2.12 (s, 3 H, 1-H), 3.51 (qd, ^1J = 6.8, 9.7 Hz, 1 H, 3-H), 5.04 (d, ^1J = 10.7 Hz, 1 H), 5.19 (d, ^1J = 17.5 Hz, 1 H), 5.37 (ddd, ^1J = 0.7, 1.2, 9.7 Hz, 1 H), 6.38 (ddd, ^1J = 0.7, 10.7, 17.5 Hz, 1 H). – HR-EIMS: *m*/*z* (M^+) = 138.1014 (calcd. for $C_9H_{14}O$: 138.1044).

4-[(2′*S*,5′*R*,6′*E*)-2′-Hydroxy-5′,7′-dimethyl-4′-oxonona-6′,8′-dienyl]piperidine-2,6-dione [(−)-Streptimidone, (−)-(2′*S*, 5′*R*)-1] and (−)-(2′*R*, 5′*R*)-1: To a solution of $LiN(iPr)_2$ (ca. 1.85 mmol) in THF (20 mL) was added dropwise a solution of **11** (0.200 g, 1.45 mmol) in THF (2 mL) at −70 °C. After the mixture was stirred for 5 min at this temperature, aldehyde **12** (0.250 g, 1.59 mmol) in THF (3 mL) was added, and the resulting solution was stirred for 30 min. The reaction mixture was poured into a cooled solution of 5% AcOH in water and extracted with CH_2Cl_2. The extract was washed with water, a saturated aqueous $NaHCO_3$ solution, brine, and water, dried with Na_2SO_4, and concentrated in vacuo. The residue was chromatographed on preparative TLC [silica gel 0.75 mm thickness, 20 cm × 40 cm; elution with CH_2Cl_2/*i*PrOH (20:1)] to give (−)-(2′*S*, 5′*R*)-**1** (74 mg, 0.41 mmol, 28%) and its 2′*R*-epimer [(−)-(2′*R*, 5′*R*)-**1**, 49 mg, 0.27 mmol, 19%].

(−)-(2′*S*, 5′*R*)-1: m.p. 68.0–68.5 °C (*i*Pr_2O/acetone) (ref.[1] 72–73 °C); $[\alpha]_D^{22}$ = −230 (*c* = 0.30, $CHCl_3$) {ref.[1] $[\alpha]_D^{27}$ = +245 (*c* = 0.5, $CHCl_3$)}. – IR (KBr): $\tilde{\nu}$ = 3500 cm^{-1} (m), 3420 (m), 3200 (m), 3090 (m), 1700 (s, C=O), 1640 (w), 1600 (w), 1380 (m), 1280 (m), 1155 (m), 900 (w), 870 (w); ($CHCl_3$ soln.): $\tilde{\nu}$ = 3380 cm^{-1} (w), 1705 (br. s, C=O). – ^1H NMR: δ = 1.18 (d, *J* = 6.6 Hz, 3 H, 5′-Me), 1.32 (ddd, ^1J = 2.8, 8.8, 13.9 Hz, 1 H, 1′-H), 1.60 (ddd, ^1J = 4.8, 10.6, 13.9 Hz, 1 H, 1′-H), 1.83 (d, ^1J = 1.5 Hz, 3 H, 7′-Me), 2.30 (dd, ^1J = 5.6, 10.2 Hz, 1 H, 3-H), 2.34 (dd, ^1J = 5.6, 10.2 Hz, 1 H, 3-H), 2.48 (m, 1 H, 4-H), 2.55 (dd, ^1J = 4.0, 18.0 Hz, 1 H, 3′-H), 2.60 (dd, ^1J = 7.7, 18.0 Hz, 1 H, 3′-H), 2.77 (m, 2 H, 3-H), 3.24 (br. s, 1 H, OH), 3.50 (dq, ^1J = 6.6, 9.7 Hz, 1 H, 5′-H), 4.10 (m, 1 H, 2′-H), 5.08 (d, ^1J = 10.6 Hz, 1 H, 9′*Z*-H), 5.22 (d, ^1J = 17.5 Hz, 1 H, 9′*E*-H), 5.32 (d, ^1J = 9.7 Hz, 1 H, 6′-H), 6.36 (ddd, ^1J = 0.7, 10.6, 17.5 Hz, 1 H, 8′-H), 7.80 (br. s, 1 H, NH). – ^{13}C NMR: δ = 12.3, 16.2, 27.1, 37.1, 38.4, 40.8, 47.0, 47.4, 64.8, 113.1, 130.2, 136.8, 140.5, 172.3, 172.5, 212.2. – EIMS: *m*/*z* (%) = 293 (8) [M^+], 275 (4) [$M^+ - H_2O$], 198 (4) [$M^+ - C_7H_{11}$], 180 (19) [$M^+ - C_7H_{13}O$], 96 (36), 95 (100), 67 (38). – HR-EIMS: *m*/*z* =

293.1627 (M^+, calcd. for $C_{16}H_{23}NO_4$: 293.1626), 180.0651 ($M^+ - C_7H_{13}O$, calcd. for $C_9H_{10}NO_3$: 180.0660).

(−)-(2′*R*, 5′*R*)-1: m.p. 97.0−99.0 °C (*i*Pr_2O/acetone). − $[\alpha]_D^{22}$ = −68 (*c* = 0.10, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3460 cm^{-1} (m), 3210 (m), 3090 (m), 1720 (s, C=O), 1685 (w), 1665 (s, C=O), 1610 (w), 1390 (m), 1290 (m), 1160 (m), 890 (w), 870 (w); ($CHCl_3$ soln.): $\tilde{\nu}$ = 3360 cm^{-1} (w), 1700 (br. s, C=O). − ^{1}H NMR: δ = 1.18 (d, *J* = 6.6 Hz, 3 H, 5′-Me), 1.32 (ddd, *J* = 2.6, 8.8, 14.0 Hz, 1 H, 1′-H), 1.59 (ddd, ^1J = 4.9, 10.4, 14.0 Hz, 1 H, 1′-H), 1.83 (d, ^1J = 1.5 Hz, 3 H, 7′-Me), 2.32 (ddd, ^1J = 7.7, 10.0, 17.3 Hz, 2 H, 3-H), 2.49 (dd, ^1J = 9.2, 18.0 Hz, 1 H, 3′-H), 2.49 (m, 1H, 4-H), 2.65 (dd, ^1J = 2.6, 18.0 Hz, 1 H, 3′-H), 2.77 (m, 2 H, 3-H), 3.26 (br. s, 1 H, OH), 3.49 (dq, ^1J = 6.6, 9.9 Hz, 1 H, 5′-H), 4.10 (m, 1 H, 2′-H), 5.08 (d, ^1J = 10.6 Hz, 1 H, 9′*Z*-H), 5.22 (d, ^1J = 17.2 Hz 1 H, 9′*E*-H), 5.31 (dd, ^1J = 0.7, 9.9 Hz, 1 H, 6′-H), 6.36 (ddd, ^1J = 0.7, 10.6, 17.2 Hz, 1 H, 8′-H), 8.07 (br. s, 1 H, NH). − ^{13}C NMR: δ = 12.3, 16.1, 27.1, 37.1, 38.4, 40.7, 47.0, 47.4, 64.8, 113.2, 130.2, 136.8, 140.5, 172.2, 172.3, 212.2. − EIMS: *m*/*z* (%) = 293 (12) [M^+], 275 (5) [$M^+ - H_2O$], 198 (6) [$M^+ - C_7H_{11}$], 180 (21) [$M^+ - C_7H_{13}O$], 96 (43), 95 (100), 67 (36). − HR-EIMS: *m*/*z* = 293.1629 (M^+, calcd. for $C_{16}H_{23}NO_4$: 293.1626), 180.0646 ($M^+ - C_7H_{13}O$, calcd. for $C_9H_{10}NO_3$: 180.0660).

(+)-(2′*R*,5′*S*)-1 (Natural streptimidone) and (+)-(2′*S*,5′*S*)-1: These compounds were prepared from methyl (*S*)-3-hydroxy-2-methylpropanoate by a similar procedure as described for the other enantiomers.

(+)-(2′*R*, 5′*S*)-1: m.p. 65.0−66.5 °C (*i*Pr_2O/acetone). − $[\alpha]_D^{22}$ = +220 (*c* = 0.080, $CHCl_3$). − HR-EIMS: *m*/*z* = 275.1508 ($M^+ - H_2O$, calcd. for $C_{16}H_{21}NO_3$: 275.1520).

(+)-(2′*S*, 5′*S*)-1: m.p. 96.0−97.0 °C (*i*Pr_2O/acetone). − $[\alpha]_D^{22}$ = +59 (*c* = 0.10 $CHCl_3$). − HR-EIMS: *m*/*z* = 275.1499 ($M^+ - H_2O$, calcd. for $C_{16}H_{21}NO_3$: 275.1520).

Antifungal Activity: The antimicrobial activity of the synthesized analogs was determined by the conventional paper-disc method[11] against *Saccharomyces cerevisiae* (HUT7099) and *Cochliobolus miyabeanus* (IFO480). *S. cerevisiae* was cultured in a liquid malt medium at 28 °C for 48 h, and diluted 100-fold with 1.2% agar malt medium. *C. miyabeanus* was cultured on a slant potato medium at 28 °C for 1 week. After addition of sterilized water and shaking, the supernatants were diluted with 1.2% agar potato medium. The cultured broth of each strain was layered on a Petri dish, and 4 paper discs (8 mm, thin) containing each test sample were placed in position. After 48 h at 28 °C, the growth inhibitory zones around the discs were measured to give the results shown in Table 1.

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[1] [1a] R. P. Frohardt, H. W. Dion, Z. L. Jakubowski, A. Rydeer, J. C. French, Q. R. Bartz, *J. Am. Chem. Soc.* **1959**, *81*, 5500−5506. − [1b] M. S. Allen, A. M. Becker, R. W. Rickards, *Aust. J. Chem.* **1976**, *29*, 673−679.
[2] B. S. Kim, S. S. Moon, B. K. Hwang, *J. Agric. Food Chem.* **1999**, *47*, 3372−3380.
[3] A. M. Becker, R. W. Rickards, *Helv. Chim. Acta* **1976**, *59*, 2393−2401.
[4] J. H. Ford, W. Klomparens, C. L. Hamner, *Plant Dis. Rep.* **1958**, *42*, 680−695.
[5] Y. Egawa, M. Suzuki, T. Okuda, *Chem. Pharm. Bull.* **1963**, *11*, 589−596.
[6] J. Ukai, Y. Ikeda, N. Ikeda, H. Yamamoto, *Tetrahedron Lett.* **1983**, *24*, 4029−4033.
[7] H. Nagaoka, Y. Kishi, *Tetrahedron* **1981**, *37*, 3873−3888.
[8] All four diastereomers of **5** have been reported: L. J. Dolby, F. A. Meneghini, T. Koizumi, *J. Org. Chem.* **1968**, *33*, 3060−3066.
[9] The corresponding (*S*,*S*)-**6** isomer has been reported: K. Mori, T. Ebata, *Tetrahedron* **1986**, *42*, 4413−4420.
[10] D. Seebach, V. Ehrig, M. Teschner, *Liebigs Ann. Chem.* **1976**, 1357−1369.
[11] H. Kondo, T. Oritani, K. Yamashita, *Agric. Biol. Chem.* **1988**, 52, 129−133.

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