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Synthesis of Streptovitacin-C_2 Isomers

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(2*R**,4*S**,6*S**,α*S**)- and (2*R*,4*R*,6*R*,α*S*)-Streptovitacin-C_2 (STV-C_2) (**1a** and **1b**) were synthesized by an aldol condensation of (2*R**,4*S**)- or (2*R*,4*R*)-2,4-dimethyl-2-trimethylsiloxy-1-cyclohexanone (**15a** or **15b**) with 4-(2-oxoethyl)-2,6-piperidinedione (**16**), which was followed by desilylation of the products. The stereochemistry of the synthesized STV-C_2 isomers (**1a** and **1b**) was elucidated by NMR. STV-C_2 isomers (**1a** and **1b**) did not show strong antimicrobial activity against *Saccharomyces cerevisiae* and *Pyricularia oryzae*.

STV-C_2 (**1**), STV-B (**2**) and STV-A (**3**),[1] the hydroxylated analogs of cycloheximide (**4**), are known as antitumor agents isolated from the cultured broth of *Streptomyces griseus*. Their chemical structures (Fig. 1) have been elucidated by Herr *et. al.*,[2] but their stereochemistry was unresolved and their synthesis had not been achieved. In our previous reports.[3,4] a marked difference of antimicrobial activity among the stereoisomers of cycloheximide was shown. In order to examine the effect of a hydroxyl group introduced on the 2,4-dimethyl-1-cyclohexanone (2,4-DMC) ring of **4** against antimicrobial activity, we synthesized the stereoisomers of STV-C_2 (**1**). In this paper, we report the synthesis and

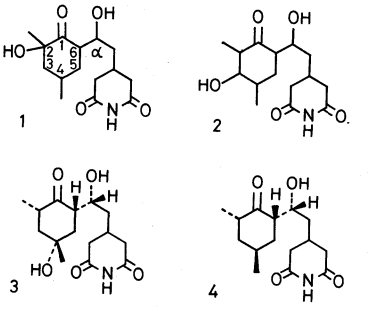
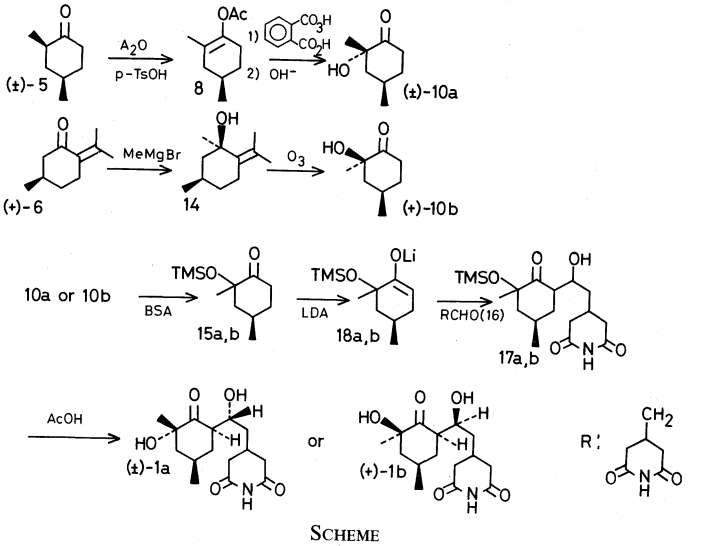


FIG. 1.



SCHEME

TABLE I. ^{13}CNMR DATA OF THE SYNTHETIC PRODUCTS

Compound	Chemical Shift (ppm)		
	C-2-Methyl-carbon	C-4-Methyl-carbon	C-α-Carbon
(±)-**10a**	24.4	21.0	—
(+)-**10b**	25.9	21.2	—
11a[a]	14.7 (*eq*)	—	—
11b[a]	16.8 (*ax*)	—	—
12[b]	14.0 (*eq*)	21.1 (*eq*)	68.9 (*threo*)
13[b]	17.6 (*ax*)	21.5 (*eq*)	68.7 (*threo*)
(±)-**17a**	23.4	20.8	68.9
(−)-**17b**	24.1	20.5	69.0
(±)-**1a**	23.8	20.9	69.0
(+)-**1b**	25.9	21.2	66.3

[a] Reported data, see ref. 6.
[b] See refs. 3 and 4.

antimicrobial activity of STV-C_2 isomers.

The synthesis of STV-C_2 isomers was performed by an aldol condensation of *cis*- and *trans*-dimethyl hydroxyketones (**10a** and **10b**) with the aldehyde **16**. The ketone **10a** was synthesized from (±)-*cis*-2,4-DMC (**5**) as follows. Catalytic hydrogenation of 2,4-dimethylphenol (**7**) and subsequent oxidation of the resulting 2,4-dimethyl-1-cyclohexanols gave (±)-*cis*-2,4-DMC (**5**),[5] which was then converted to its enol-acetate **8**. Epoxidation of **8** with monoperphthalic acid, which was followed by alkaline hydrolysis, gave a stereoisomeric mixture of 2-hydroxy-2,4-DMC (**9**), which consisted of *cis*-dimethylhydroxyketone (**10a**, 7%) and *trans*-dimethylhydroxyketone (**10b**, 93%) by GLC analysis. The structure of these products was elucidated by their ^{13}C-NMR data (Table I). The C-2-*equatorial* methyl carbons of *cis*-4-*t*-butyl-2-methyl-1-cyclohexanone (**11a**) and isocycloheximide (**12**) showed higher field shifts than those of the C-2-*axial*-methyl carbons of *trans*-4-*t*-butyl-2-methyl-1-cyclohexanone (**11b**) and naramycin B (**13**). Because the C-2 methyl carbon (24.4 ppm) of **10a** shifted to a higher field than that of **10b** (25.9 ppm), and the C-4-methyl carbons of **10a** and **10b** (21.0 and 21.2 ppm) were identical to the C-4-*equatorial* methyl carbons of isocycloheximide (**12**) and naramycin B(**13**) (21.1 and 21.5 ppm), it was concluded that **10a** and **10b** were the *cis*- and *trans*-dimethyl form respectiviely. Therefore, it became apparent that the synthesis of the hydroxyketones *via* epoxidation of the enol-acetate **8** gave the *cis*-dimethyl hydroxyketone **10a** as the main product. Furthermore, *trans*-dimethyl hydroxyketone **10b** was prepared from (*R*)-(+)-pulegone (**6**). Grignard reaction of **6** with methylmagnesium bromide gave the alcohol **14**, whose ozonolysis gave the *trans*-dimethyl hydroxyketone **10b** as an almost pure product. Treatment of each hydroxyketone (±)-**10a** and (+)-**10b** with *N,O*-bis(trimethylsilyl)-acetamide (BSA) gave the corresponding trimethylsilyl ethers (±)-**15a** and (+)-**15b** respectiviely. Lithium enolate **18a** of (±)-**15a** was reacted with the aldehyde **16** to give a silylated *threo*-STV-C_2 isomer ((±)-**17a**) in almost pure form, and deprotection of the product gave a *threo*-(±)-STV-C_2 isomer (**1a**), mp 169~170°C. Condensation of lithium enolate **18b** of another silyl-ether (+)-**15b** with the aldehyde **16** gave the silylated *threo*-STV-C_2 (−)-**17b** in pure form, and subsequent deprotection of the product gave a (+)-*erythro*-STV-C_2 isomer (**1b**), $[\theta]_{max}$: + 6.2×10^3 (λ_{max}: 291 nm). The stereochemistry of the STV-C_2 isomers was elucidated by comparing their ^{13}C-NMR data with those of cycloheximide isomers. Because the chemical shifts of methyl carbons of the hydroxyketone **10a** (24.4 and 21.0 ppm) were very similar to those of the final product **1a** (23.8 and 20.9 ppm), the configuration of the methyl groups of **10a** and **1a** was presumed to be the same. Similarly, the chemical shifts of the methyl carbons of the hydroxyketone **10b** (25.9 and 21.2 ppm) were identical with those of **1b**. In addition, the conformation of the side chains of **1a** and **1b** at C-6 was assumed to be *equatorial* rather than *axial* owing to steric repulsion between the C-2-*axial* substituents and C-6 side chain. C-α-signals of the isomers (**17a**, **17b**, **1a** and **1b**) were good indicators for the determination of relative stereochemistry between C-6 and C-α. In our previous reports,[3,4] it was revealed that the C-α methyl signals of the *threo* isomers

TABLE II. ANTIMICROBIAL ACTIVITY OF THE SYNTHETIC STV-C_2 ISOMERS

Compound	Concentration (μg/disc)	Inhibited zone (mm)			
		S. cerevisiae (HUT 7099)		*P. oryzae* (Ken 62-89)	
		48 hr	72 hr	48 hr	72 hr
Cycloheximide (**4**)	1	27.0	25.0	12.0	11.0
	10	36.0	35.0	25.0	24.0
	100	43.0	43.0	35.0	34.0
(±)-STV-C_2(**1a**)	100	—	—	—	—
(+)-STV-C_2 (**1b**)	100	—	—	—	—

appeared at near 69.0 ppm, and that those of the *erythro* isomers appeared at near 66.5 ppm. From these data (Table I), (±)-**17a**, (−)-**17b** and (±)-**1a** were concluded to be the *threo* form, and also (+)-**1b** to be the *erythro* form. ^{1}H-NMR data also supported this conclusion, the signals of the C-α-proton of (±)-**17a**, (−)-**17b** and (±)-**1a** showing the multiplet characteristic of such *threo* isomers as isocycloheximide (**12**)[4] or naramycin B (**13**),[3] and that of (+)-**1b** showing d-d-d coupling (10.7, 2.4, 2.4 Hz)[7] that is characteristic of such *erythro* isomers as cycloheximide (**4**).[3] The synthesized isomers **1a** and **1b** did not coincide with natural STV-C_2 in their mp and IR spectra;[8] but as the ^{1}H and ^{13}C-NMR spectra of natural STV-C_2 have not yet been reported, further synthesis of the other isomers is necessary to determine the stereochemistry of natural STV-C_2 (**1**).

The antimicrobial activity of the synthesized STV-C_2 isomers against *Saccharomyces cerevisiae* and *Pyricularia oryzae* was examined to give the results shown in Table II. (±)STV-C_2 (**1a**), C-2-hydroxylated isocycloheximide and (+)-STV-C_2 (**1b**), C-2-hydroxylated naramycin B, did not show strong antimicrobial activity. It was concluded that the introduction of a hydroxy group into the C-2 position of cycloheximide isomers decreased the antimicrobial activity.

EXPERIMENTAL

All boiling points and melting points are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a JEOL JNM FX-100 spectrometer, and IR spectra were recorded on a JASCO IR-810 infrared spectrometer. Optical rotations were measured on a JASCO DIP-4 spectrometer, and circular dichroism (CD) spectra were measured on a Dichrograph Mark III-J spectrometer. Gas chromatographic analyses were performed on a JEOL JGC-1100 instrument with a thermal conductance detector and stainless steel column (2 m × 3 mm) packed with 20% DEGS on Chromosorb W or 5% Lac 2R-446 on Chromosorb W. High pressure liquid chromatography (HPLC) was performed at 254 nm on a JASCO TRIROTAR instrument with a UV spectrometer, using a stainless steel column (4.6 mm × 250 mm) packed with silica-gel (SS-05) and a solvent system of methylene chloride/isopropyl alcohol = 98/2 or 95/5 at a flow rate of 1 ml/min. MPLC was performed on the same instrument, using a glass column packed with a silica-gel (Lichroprep Si 60, 40 ~ 63 μm) and the same solvent system.

1) Preparation of (±)-(*2R*,4S**)-*2,4-dimethyl-2-hydroxy-1-cyclohexanone* (**10a**). A mixture of (±)-*cis*-2,4-DMC (**5**, 40 g), acetic anhydride (60 ml) and a catalytic amount of *p*-toluenesulfonic acid was refluxed for 10 hr. The reaction mixture was poured into aq. $NaHCO_3$ and extracted with *n*-hexane. The organic layer was washed with brine, and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 44 g (an 81.5% yield) of (±)-2,4-dimethyl-1-cyclohexen-1-yl acetate (**8**), which almost consisted of a single product (t_R: 26.5 min) by GLC analysis (column, 20% DEGS on Chromosorb W; temp., 85°C; He flow rate, 15 ml/min). **8**: bp 83 ~ 86°C (15 mmHg); IR ν_{max}^{film} cm^{-1}: 2870, 1760 (C=O), 1450, 1370, 1230, 1210, 1120. To an ether solution (50 ml) of the enol acetate (**8**, 15 g), 73% of monoperphthalic acid in ether (300 ml) was added and the mixture stirred at room temperature for 18 hr. The reaction mixture was successively washed with 20% aq.

$NaHSO_3$, aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Evaporation of the solvent, followed by distillation under reduced pressure, gave a product (10.1 g, 61% yield), bp 110~120°C (15 mmHg); IR ν_{max}^{film} cm^{-1}: 2870, 1750 (C=O), 1450, 1370, 1250, 1230, 1090, 1050. This product (6 g) was hydrolyzed by refluxing with methanolic potassium hydroxide, and after diluting with water, the reaction mixture was extracted with ether. The organic layer was successively washed with dil. HCl, aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Evaporation of the solvent, followed by distillation under reduced pressure, gave an isomeric mixture (1.5 g, 32.5% yield) of *cis*- and *trans*-dimethylhydroxyketones (**10a** and **10b**), which consisted of 93% of **10a** (t_R: 7 min) and 7% of **10b** (t_R: 4 min) by GLC analysis (column, 5% Lac 2R-446 on Chromosorb W; temp., 140°C; He flow rate, 20 ml/min). The mixture was separated into each component by silica-gel column chromatography (solvent system, benzene/MeOH=20/1). **10a**: IR ν_{max}^{film} cm^{-1}: 3400 (OH), 2920, 1720 (C=O), 1460, 1380, 1250, 1170, 1120, 1100, 1050; ^{1}H-NMR ($CDCl_3$) δ: 0.96 (3H, d, J=6.3 Hz, CH_3), 1.25 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 21.0, 24.4, 27.0, 35.3, 36.8, 49.2, 74.9, 212.3. **10b**: IR ν_{max}^{film} cm^{-1}: 3400 (OH), 2950, 2930, 1730 (C=O), 1460, 1370, 1250, 1190, 1140, 1070, 990, 840, 750; ^{1}H-NMR ($CDCl_3$) δ: 1.0 (3H, d, J=5.9 Hz, CH_3), 1.42 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 21.2, 25.9, 29.8, 35.7, 36.9, 50.1, 75.8, 214.6; MS *m/z*: 142 (M^+, 17%), 124 (2%), 98 (46%), 85 (100%), 71 (62%), 58 (52%).

2) Preparation of (+)-(*2R,4R*)-*2,4-dimethyl-2-hydroxy-1-cyclohexanone* (**10b**). To a solution of methylmagnesium bromide in ether, which was prepared from 4.6 g of magnesium and an equimolar amount of methyl bromide, 23 g of (*R*)-(+)-pulegone (**6**) was gradually added between −10°C and −5°C, and strirring was continued for 2 hr at room temperature. The mixture was hydrolyzed with saturated aq. NH_4Cl and then extracted with ether. The organic layer was washed with aq. $NaHCO_3$ and brine, and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave an oily residue, which was chromatographed on alumina (200 g) with hexane and ether. Evaporation of the ether fraction gave an oil (4.2 g, 16.6% yield), which consisted only of **14** (t_R: 7 min) by GLC analysis (column, 5% 2R-446 on Chromosorb W; temp., 120°C; He flow rate, 20 ml/min). **14**: bp 78~80°C (4 mmHg); IR ν_{max}^{film} cm^{-1}: 3400 (OH), 1480, 1370, 1150, 1120, 1050, 1020. A solution of **14** in chloroform (70 ml) was ozonized and the ozonide was decomposed overnight with 2.2 g of dimethylsulfide. Evaporation of the excess dimethylsulfide, which was followed by distillation under reduced pressure, gave the (+)-(*2R,4R*)-dimethylhydroxyketone **10b** (1.87 g, 52% yield), bp 85~87°C (15 mmHg), $[\alpha]_D^{22}$ +105.5 (c=1.2, $CHCl_3$). MS *m/z*: 142 (M^+, 11%), 124 (2%), 98 (50%), 85 (100%), 71 (59%), 58 (63%). GLC analysis with a column of 5% Lac 2R-446 on Chromosorb W (temp., 110°C; He flow rate, 16 ml/min) showed that **10b** consisted of only one component (t_R: 4 min). The spectral data of (+)-**10b** were identical with those of (±)-**10b**.

3) Synthesis of (±)-(*2R*,4S*,6S*,αS**)-*STV-C*$_2$ (**1a**). (±)-*cis*-Dimethylhydroxyketone (**10a**, 1 g) and *N,O*-bistrimethylsilylacetamide (4.4 ml) were dissolved in 20 ml of dry dimethylformamide, and the mixture was refluxed for 24 hr. Hexane was added to the reaction mixture, and the separated hexane layer was washed with brine and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave a residual oil, which was chromatographed over alumina. Elution with hexane gave 781 mg of the trimethylsilyl derivative **15a**, bp 107~109°C (15 mmHg); IR ν_{max}^{film} cm^{-1}: 2950, 2925, 2870, 1725 (C=O), 1460, 1420, 1380, 1250, 1170, 1120, 1060, 990, 930, 880, 840, 750; ^{1}H-NMR ($CDCl_3$)δ: 0.11 (9H, s, CH_3), 0.91 (3H, d, J=6.6 Hz, CH_3), 1.27 (3H, s, CH_3); ^{13}C-NMR ($CDCl_3$) δ: 1.99, 20.9, 23.7, 27.0, 36.2, 37.2, 51.4, 75.8, 212.4. To a stirred solution of LDA (lithium diisopropylamide) in 50 ml of dry tetrahydrofuran, which was prepared from 2.2 mmol of *n*-butyllithium and 2.2 mmol of diisopropylamine, were added 473 mg (2.2 mmol) of the silylated ketone **15** and then 350 mg (2.2 mmol) of the aldehyde **16** at −70°C. After stirring for 1.5 hr, the mixture was poured into ice-cooled 2% aq. acetic acid and extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 596 mg of an oil, which was fractionated by MPLC (solvent system, CH_2Cl_2/iso-PrOH=98/2; flow rate, 2 ml/min) to give an aldol fraction (197 mg). The fraction mainly consisted of **17a** by HPLC analysis (solvent system, same as MPLC; flow rate, 1 ml/min; t_R: 8.8 min). Fractionation by MPLC gave the pure aldol **17a** (89 mg, 11% yield); IR ν_{max}^{film} cm^{-1}: 3500 (OH), 3220, 3110, 2950, 2925, 2875, 1700 (C=O), 1380, 1250, 1170, 1150, 1060, 980, 950, 890, 840; ^{1}H-NMR ($CDCl_3$) δ: 0.12 (9H, s), 0.92 (3H, d, J=6.8 Hz CH_3), 1.28 (3H, s, CH_3), 3.8 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 2.0, 20.8 (q), 23.4 (q), 26.4, 27.1, 37.1, 38.6, 39.4, 50.4, 51.4, 68.9 (d), 78.3, 172.5, 216.0. After heating the aldol **17a** in 5 ml of 30% aq. acetic acid–tetrahydrofuran (1:1) at 80°C for 24 hr, the reaction mixture was poured into aq. $NaHCO_3$ and extracted with ethyl acetate. The extract was washed with brine and dried over anhyd. $MgSO_4$. Evaporation of the solvent gave an oil, which was fractionated by MPLC (solvent system, CH_2Cl_2/iso-PrOH=98/2; flow rate, 2 ml/min) to give the aldol (±)-(*2R*,4S*,6S*,αS**)-STV-C_2 (**1a**, 9 mg), for which an HPLC analysis showed only one peak (t_R: 7.4 min, solvent system, CH_2Cl_2/iso-PrOH=95/5; flow rate, 1 ml/min). (±)-**1a**: mp 169~170°C; IR ν_{max}^{film} cm^{-1}: 3400 (OH), 3225, 3100, 2950, 1720 (CO–N), 1680 (1–C=O), 1450, 1370, 1270, 1150, 1080, 860; ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, d, J=6.6 Hz, CH_3), 1.26 (3H, s, CH_3), 3.8 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 20.9, 23.8, 26.6,

27.1, 37.1, 38.5, 38.7, 39.1, 49.7, 50.6, 69.0, 75.8, 172.5, 172.6, 215.8; *Anal.* Found: C, 60.02; H, 8.52; N, 4.62. Calcd. for $C_{15}H_{23}O_4N$: C, 60.58; H, 7.69; N, 4.71%.

4) Synthesis of (+)-(2R,4R,6R,αR)STV-C_2 (**1b**). (+)-*trans*-Dimethylhydroxyketone (**10b**, 1 g), which was prepared from (R)-(+)-pulegone (**6**) and *N,S*-bis(trimethylsilyl)acetamide (4.5 ml), was dissolved in 20 ml of dry dimethylformamide, and the solution was refluxed for 24 hr. After treating the reaction mixture with the treatment for **15a**, 846 mg of the trimethylsilyl derivative (+)-**15b** was obtained. (+)-**15b**: bp 101~103°C (15 mmHg); IR ν_{max}^{film} cm^{-1}: 2950, 2925, 1730 (C=O), 1460, 1370, 1250, 1190, 1140, 1060, 990, 940, 900, 840; $[\alpha]_D^{22}$ +112.7° (c=1.5, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.12 (9H, s), 0.98 (3H, d, J=5.9 Hz, CH_3), 1.41 (3H, s, CH_3); ^{13}C-NMR δ: 2.7, 21.3, 26.9, 30.1, 35.5, 38.3, 52.0, 79.7, 211.5. To a stirred solution of LDA in 50 ml of tetrahydrafuran, which was prepared from 1.2 mmol of *n*-butyllithium and 1.2 mmol of diisopropylamine, were added 264 mg (1.2 mmol) of (+)-**15b** and then 195 mg (1.2 mmol) of the aldehyde **16** at −70°C. After stirring for 1.5 hr, the reaction mixture was poured into ice-cooled 2% aq. acetic acid and extracted with CH_2Cl_2. The extract was washed with aq. $NaHCO_3$ and brine, and then dried over anhyd. $MgSO_4$. Evaporation of the solvent gave 328 mg of an oil, which as fractionated by MPLC (solvent system, CH_2Cl_2/iso-PrOH=98/2; flow rate, 2 ml/min) to give the aldol fraction (72 mg, 16.2% yield), which only consisted of **17b** (t_R: 10 min) by HPLC analysis (solvent system, same as MPLC; flow rate, 1 ml/min). (−)-**17b**: mp 117~119°C; IR ν_{max}^{film} cm^{-1}: 3500 (OH), 3200, 3100, 2950, 1720 (C=O), 1380, 1250, 1160, 1070, 1000, 950, 880, 840, 750; ^{1}H-NMR ($CDCl_3$) δ: 0.12 (9H, s), 1.29 (3H, d, J=6.8 Hz, CH_3), 1.29 (3H, s, CH_3), 3.8 (1H, m); ^{13}C-NMR ($CDCl_3$) δ: 2.0, 20.5 (q), 24.1 (q), 26.6, 27.1, 37.0, 37.4, 38.6, 38.7, 47.0, 48.1, 69.0 (d), 79.1, 172.5, 172.6, 215.9; $[\alpha]_D^{20}$ −49.8° (c=1.1, $CHCl_3$); MS m/z: 369 (M^+, 2%), 341 (43%), 199 (30%), 157 (100%), 147 (35%). The aldol (−)-**17b** was dissolved in 4 ml of a mixture of 30% aq. acetic acid and tetrahydrofuran (1:1), and refluxed at 80°C for 24 hr. The reaction mixture was poured into aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent left an oil, which was purified by MPLC (solvent system, CH_2Cl_2/iso-PrOH=98/2; flow rate, 2 ml/min) to give 4 mg of (+)-(2*R*,4*R*,6*R*,α*S*)-STV-C_2 (**1b**), for which the HPLC analysis (solvent system, CH_2Cl_2/iso-PrOH=95/5; flow rate, 1 ml/min) showed only one peak (t_R: 6 min). (+)-**1b**: IR ν_{max}^{film} cm^{-1}: 3425 (OH), 3300, 3125, 2950, 1720 (1-C=O, CO-N), 1400, 1280, 1160, 1120, 1040; ^{1}H-NMR ($CDCl_3$) δ: 1.0 (3H, d, J=5.9 Hz, CH_3), 1.42 (3H, s, CH_3), 4.2 (1H, d-d-d, J=10.7, 2.4, 2.4 Hz); ^{13}C-NMR ($CDCl_3$) δ: 21.2, 25.9, 27.6, 28.4, 35.0, 37.1, 38.1, 38.4, 50.3, 50.4, 66.1, 75.2, 171.9, 172.1, 216.8; CD ($c=4\times10^{-4}$, MeOH) $[\theta]_{max}$: $+6.2\times10^3$ (λ_{max}: 291 nm); MS m/z: 298 (M^++1, 1%), 280 (1%), 251 (30%), 194 (100%), 193 (73%), 135 (22%), 112 (37%).

5) Antimicrobial assay of STV-C_2 isomers (±)-**1a** *and* (+)-**1b** *against Saccharomyces cerevisiae* (*HUT 7099*) *and Pyricularia oryzae* (*Ken 62-89*). The antimicrobial activity of (±)-**1a** and (+)-**1b** was determined by the conventional paper disc method as has been described in the previous papers.[3,4] The results are summarized in Table III.

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