# Syntheses and Absolute Structures of Novel Protein Farnesyltransferase Inhibitors, Kurasoins A and B

Sir:

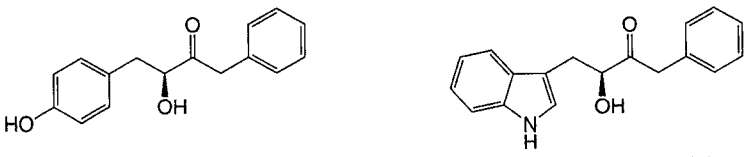
Our search for new protein farnesyltransferase inhibitors recently led to the isolation of kurasoins A (**1**) and B (**2**) from a fermentation broth of *Paecilomyces* sp. FO-3684.[1] Kurasoins A (**1**) and B (**2**) proved to inhibit farnesyltransferase in a dose-dependent manner. The $IC_{50}$ values of **1** and **2** against protein farnesyltransferase were 59.0 and 58.7 $\mu$M, respectively.

The structures of **1** and **2** were initially deduced *via* extentive spectroscopic analyses and total syntheses of the racemates.[2] However, the absolute configurations of **1** and **2** remained unknown. Herein we describe a concise asymmetric construction of **1** and **2**, as well as the elucidation of their natural absolute configurations.

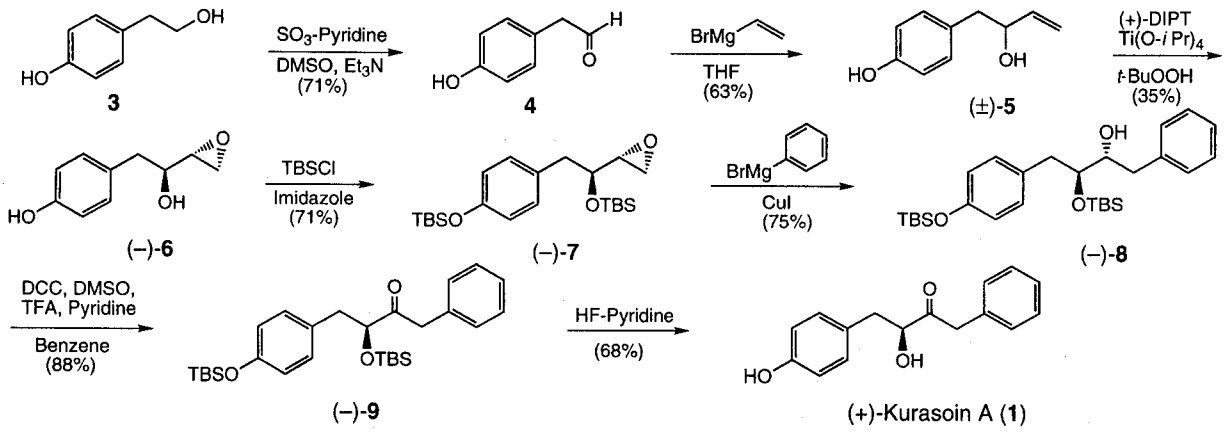
Concerning the total synthesis of kurasoin A (**1**), as our point of departure, Doering-Parikh oxidation[3] of 2-(4-hydroxyphenyl)ethanol (**3**) (pyridine-$SO_3$, DMSO, $Et_3N$) furnished hydroxy aldehyde **4** (Scheme 1), which in turn was added vinylmagnesium bromide to obtain the racemic allylic alcohol **5** (45% overall yield). Kinetic resolution of (±)-**5** *via* Sharpless asymmetric epoxidation[4] [1.2 equiv (+)-DIPT, 1.0 equiv Ti(O-*i*-Pr)$_4$, 0.5 equiv *t*-butyl hydroperoxide, $CH_2Cl_2$, −20°C, 2 days] gave the desired epoxy alcohol (−)-**6**† in 35% yield (70% of theory) and >90% ee, as determined by NMR analysis of the derived (+)-MTPA ester.[5] Protection of (−)-**6** by TBSCl and imidazole afforded (−)-**7**† in 71% yield. Stereospecific alkylation of epoxide (−)-**7** with phenylmagnesium bromide in the presence of CuI afforded the (−)-**8**† in 75% yield. Moffat oxidation (DCC, TFA, pyridine, DMSO, benzene) of (−)-**8** furnished (−)-**9**† (88%). Finally, removal of the TBS group (HF-pyridine) generated (+)-kurasoin A (**1**) (68%). The synthetic material was identical with natural **1** in all respects (TLC, $^1$H and $^{13}$C NMR, IR, HRMS and UV), furthermore, optical rotation [synthetic (+)-**1**, $[\alpha]_D^{22}$ +9° ($c$=1.0, MeOH); natural (+)-**1**[1], $[\alpha]_D^{22}$ +7° ($c$=0.1, MeOH)]. The synthesis established that the absolute configulation of kurasoin A is (3*S*).

Use of (−)-DIPT for asymmetric epoxidation of (±)-**5**

Fig. 1. Structures of kurasoins A (**1**) and B (**2**).

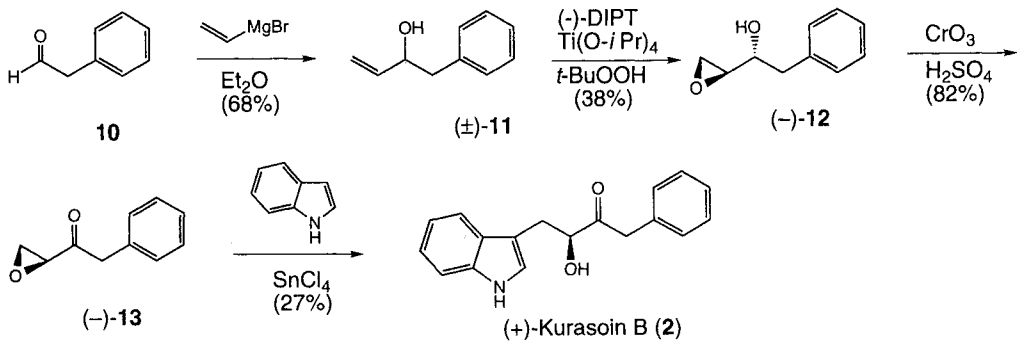



Scheme 1. Synthesis of (+)-kurasoin A (**1**).




† All synthetic compounds were purified by flash chromatography on silica gel. The structure assigned to each new compound is in accord with its infrared, 270 MHz $^1$H NMR, and 67.5 MHz $^{13}$C NMR spectra, as well as appropriate parent ion identification by high resolution mass spectrometry.

Scheme 2. Synthesis of (+)-kurasoin B (**2**).




subsequently furnished the (−) enantiomer of **1** [$[\alpha]_D^{22}$ −6.0° ($c$=1.0, MeOH)]. We next analyzed racemic kurasoin A [(±)-**1**], synthetic (+)-**1**, (−)-**1** and natural (+)-**1** *via* HPLC with a scalemic stationary phase. The antipodes were separated and individually characterized. The natural-**1** was identical with synthetic (+)-**1**.††

On the other hand, for the total synthesis of kurasoin B (**2**), as our point of departure, addition of vinylmagnesium bromide to phenylacetaldehyde (**10**) afforded the racemic allylic alcohol **11** (Scheme 2) in 68% yield. Kinetic resolution of (±)-**11** *via* Sharpless asymmetric epoxidation[4] [1.2 equiv (−)-DIPT, 1.0 equiv Ti(O-*i*-Pr)$_4$, 0.5 equiv *t*-butyl hydroperoxide, $CH_2Cl_2$, −20°C, 2 days] gave the desired epoxy alcohol (−)-**12**† in 38% yield (76% of theory) and >90% ee, as determined by NMR analysis of the derived (+)-MTPA ester,[5] and recovered **11** in 45% yield. Then, (−)-**12** was oxidized ($CrO_3$, $H_2SO_4$) to furnish epoxy ketone (−)-**13**† in 82% yield. Stereospecific alkylation of indole (2.0 equiv) with epoxide (−)-**13** (1.4 equiv $SnCl_4$, $CCl_4$, 0°C)[6] afforded (+)-kurasoin B (**2**) in 27% yield. The synthetic material was identical with natural **2** in all respects (TLC, $^1$H and $^{13}$C NMR, IR, HRMS and UV), furthermore, optical rotation [synthetic (+)-**2**, $[\alpha]_D^{22}$ +31° ($c$=0.33, chloroform); natural (+)-**2**[1], $[\alpha]_D^{22}$ +22° ($c$=0.1, chloroform)]. The synthesis also established that the absolute configulation of kurasoin B is (3*S*).

Use of (−)-DIPT for asymmetric epoxidation of (±)-**11** subsequently furnish the (−) enantiomer of **2** [$[\alpha]_D^{22}$ −15° ($c$=0.4, chloroform)]. We also analyzed racemic kurasoin B [(±)-**2**], synthetic (+)-**2**, (−)-**2** and natural (+)-**2** *via* HPLC with a scalemic stationary phase. The antipodes were separated and individually characterized. The natural-**2** was identical with synthetic (+)-**2**.

The completion of these syntheses supported that kurasoin A (**1**), and B (**2**) are (3*S*)-3-hydroxy-4-(*p*-hydroxyphenyl)-1-phenyl-2-butanone, and (3*S*)-3-hydroxy-4-(3-indolyl)-1-phenyl-2-butanone.[2]

In summary, we have prepared (+) and (−)-kurasoin A (**1**) and (+) and (−)-kurasoin B (**2**) in sufficient quantities to permit more detail biological evaluation. Further studies of the kurasoins are in progress.

Acknowledgments

We wish to thank Ms. AKIKO NAKAGAWA and Ms. CHIKAKO SAKABE, School of Pharmaceutical Sciences, Kitasato University, for measurements of mass spectra. This work was supported in part by a grant from Ministry of Education, Science and Culture of Japan and Japan Keirin Association.

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(Received February 12, 1997)

## References

1) UCHIDA, R.; K. SHIOMI, J. INOKOSHI, R. MASUMA, T. KAWAKUBO, H. TANAKA, Y. IWAI & S. ŌMURA: Kurasoins A and B, new protein farnesyltransferase inhibitors

†† Chiralcel OJ i.d. 4.6 × 250 mm column; mobile phase, *n*-hexane - 2-propyl alcohol (85 : 15); Flow rate, 1.0 ml/minute; Detection, UV at 275 nm.

produced by *Paecilomyces* sp. FO-3684. I. Producing strain, fermentation, isolation, and biological activities. J. Antibiotics 49: 932~934, 1996

2) UCHIDA, R.; K. SHIOMI, T. SUNAZUKA, J. INOKOSHI, A. NISHIZAWA, T. HIROSE, H. TANAKA, Y. IWAI & S. ŌMURA: Kurasoins A and B, new protein farnesyltransferase inhibitors produced by *Paecilomyces* sp. FO-3684. II. Structure elucidation and total synthesis. J. Antibiotics 49: 886~889, 1996

3) PARIKH, J. R. & W. V. DOERING: Sulfur trioxide in the oxidation of alcohols by dimethyl sulfoxide. J. Am. Chem. Soc. 89: 5505~5507, 1967

4) GAO, Y.; R. M. HANSON, J. M. KLUNDER, S. Y. KO, H. MASAMUNE & K. B. SHARPLESS: Catalytic asymmetric epoxidation and kinetic resolution: Modified procedures including in situ derivatization. J. Am. Chem. Soc. 109: 5765~5780, 1987

5) DALE, J. A.; D. L. DULL & H. S. MOSHER: α-Methoxy-α-trifluoromethylphenylacetic acid, a versatile reagent for the determination of enantiomeric composition of alcohols and amines. J. Org. Chem. 35: 3519~3521, 1970

6) SUNAZUKA, T.; N. TABATA, T. NAGAMITSU, H. TOMODA & S. ŌMURA: Asymmetric synthesis of the anticoccidial antibiotic diolmycin A1. Determination of absolute stereochemistry. Tetrahedron Lett. 42: 6659~6660, 1993