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TOTAL SYNTHESES OF KURASOINS A AND B, NOVEL PROTEIN FARNESYLTRANSFERASE INHIBITORS, AND ABSOLUTE STRUCTURES OF KURASOINS A AND B

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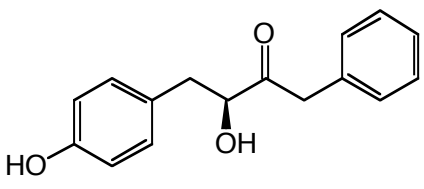
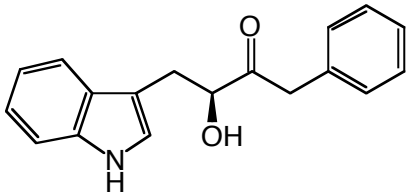
Abstract - Asymmetric total syntheses of kurasoins A (**1**) and B (**2**), recently discovered protein farnesyltransferase (PFTase) inhibitors, have been achieved in seven steps from 2-(4-hydroxyphenyl)ethanol *via* the stereospecific alkylation of the chiral epoxide ((-)-**7**) and in four steps from phenylacetaldehyde *via* the coupling reaction of the chiral epoxide ((-)-**13**) with indole, respectively. The synthesis defined the (3*S*) absolute configuration of **1** and **2**. The stereochemistry of the hydroxy group is important for eliciting PFTase inhibition.

Ras proteins have been shown to be post-translationally farnesylated on a specific carboxy-terminal cysteine by protein farnesyltransferase (PFTase).[1] One of the interests in PFTase inhibitors is their potential use as anti-cancer drugs. 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.[2] (Figure 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 μM, respectively.

The structures of **1** and **2** were initially deduced *via* extentive spectroscopic analyses and total syntheses of the racemates.[3] However, the absolute configurations of **1** and **2** remained unknown. Herein we describe concise asymmetric constructions of **1** and **2**, as well as the elucidation of their natural absolute configurations.



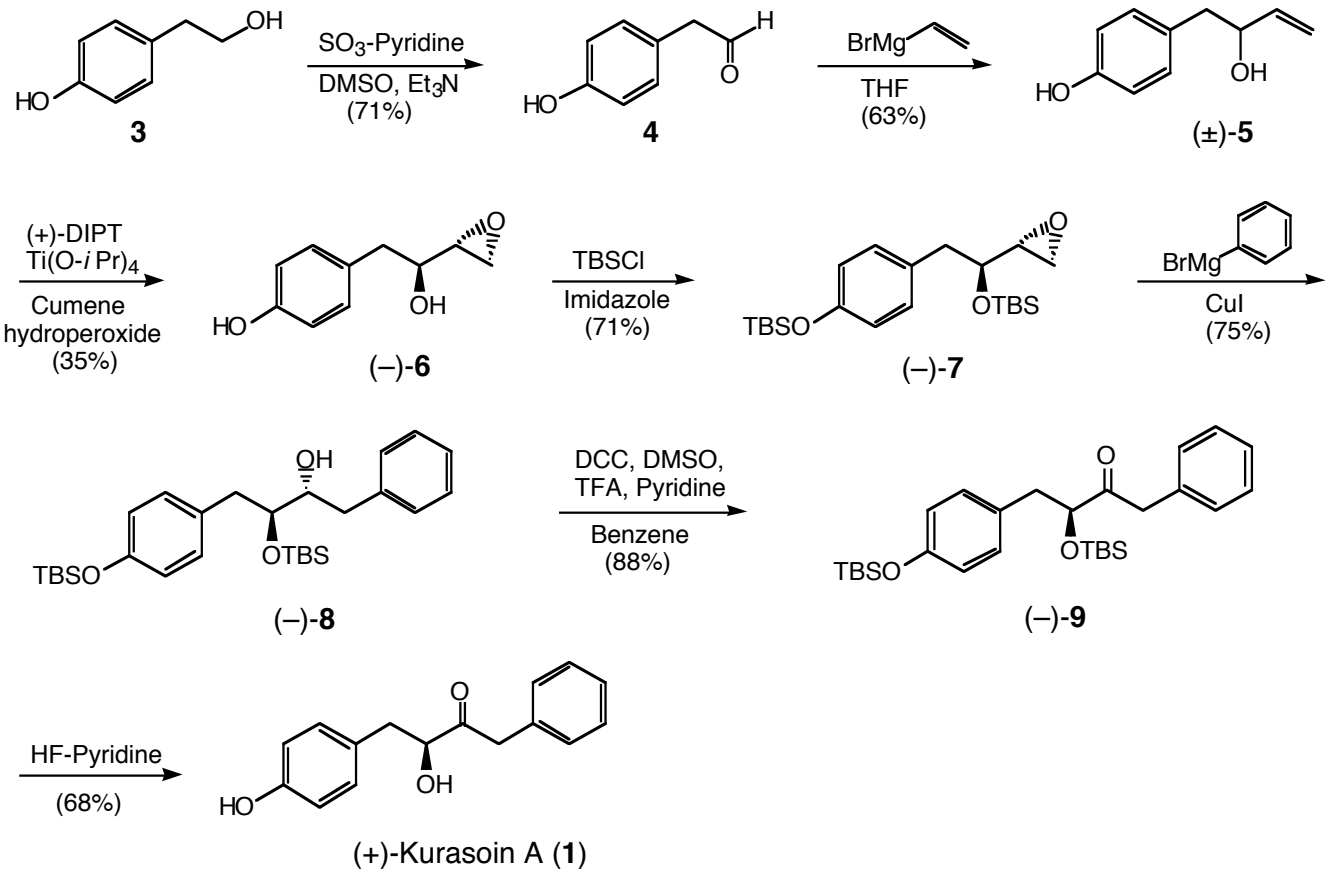
(+)-Kurasoin A (**1**)



(+)-Kurasoin B (**2**)

Figure 1 Structures of (+)-kurasoins A (**1**) and B (**2**)

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

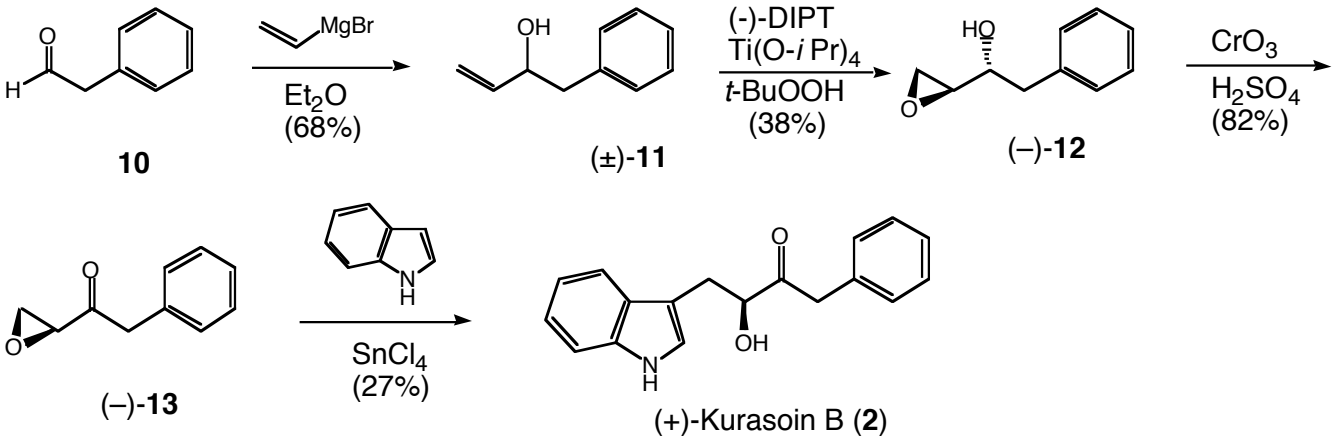


Scheme 1 Synthesis of (+)-kurasoin A (**1**)

Use of (–)-DIPT for asymmetric epoxidation of (±)-**5** subsequently produced 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.[7] The antipodes were separated and individually

characterized. The natural-**1** was identical to 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) with a 68% yield. Kinetic resolution of (±)-**11** *via* Sharpless asymmetric epoxidation[5] [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] then gave the desired epoxy alcohol ((–)-**12**) with a 38% yield (76% of theory) and >90% ee, as determined by NMR analysis of the derived (+)-MTPA ester,[6] and recovered **11** at a 45% yield. Then, (–)-**12** was oxidized (CrO_3, H_2SO_4) to furnish epoxy ketone ((–)-**13**) at an 82% yield. Stereospecific alkylation of indole (2.0 equiv) with epoxide ((–)-**13**) (1.4 equiv $SnCl_4$, CCl_4, 0°C)[8] afforded (+)-kurasoin B (**2**) at a 27% yield. The synthetic material was identical to natural **2** in all respects (TLC, ^{1}H and ^{13}C NMR, IR, HRMS and UV), and optical rotation [synthetic (+)-**2** , $[\alpha]_D^{22}$ +31° (*c*=0.33, chloroform); natural (+)-**2**[1] , $[\alpha]_D^{22}$ +22° (*c*=0.1, chloroform)] was obteined, too. The synthesis also established that the absolute configuration of kurasoin B is (3*S*).



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

Use of (–)-DIPT for asymmetric epoxidation of (±)-**11** subsequently produced the (–) enantiomer of **2** [$[\alpha]_D^{22}$ –30° (*c*=0.4, chloroform)]. We also analyzed racemic kurasoin B [(±)-**2**], synthetic (+)-**2**, (–)-**2** and natural (+)-**2** *via* HPLC with a scalemic stationary phase.[9] The antipodes were separated and individually characterized. The natural **2** was identical to synthetic (+)-**2**.

The completion of these syntheses supported that kurasoins 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.

The PFTase inhibitory activity was next measured for the kurasoins and related compounds. As shown in Figure 2, the IC_{50} values of **(+)-1** and **2** against PFTase were 59 μM and 65 μM, respectively. On the other hand, related compounds (**(–)-2**, **(±)-2**, **(+)-14**, **(±)-14**[10], **15**[11] and **16**) were >790~120 μM at the same condition. These results indicated that the stereochemistry of the hydroxy group is important for eliciting potent PFTase inhibition.

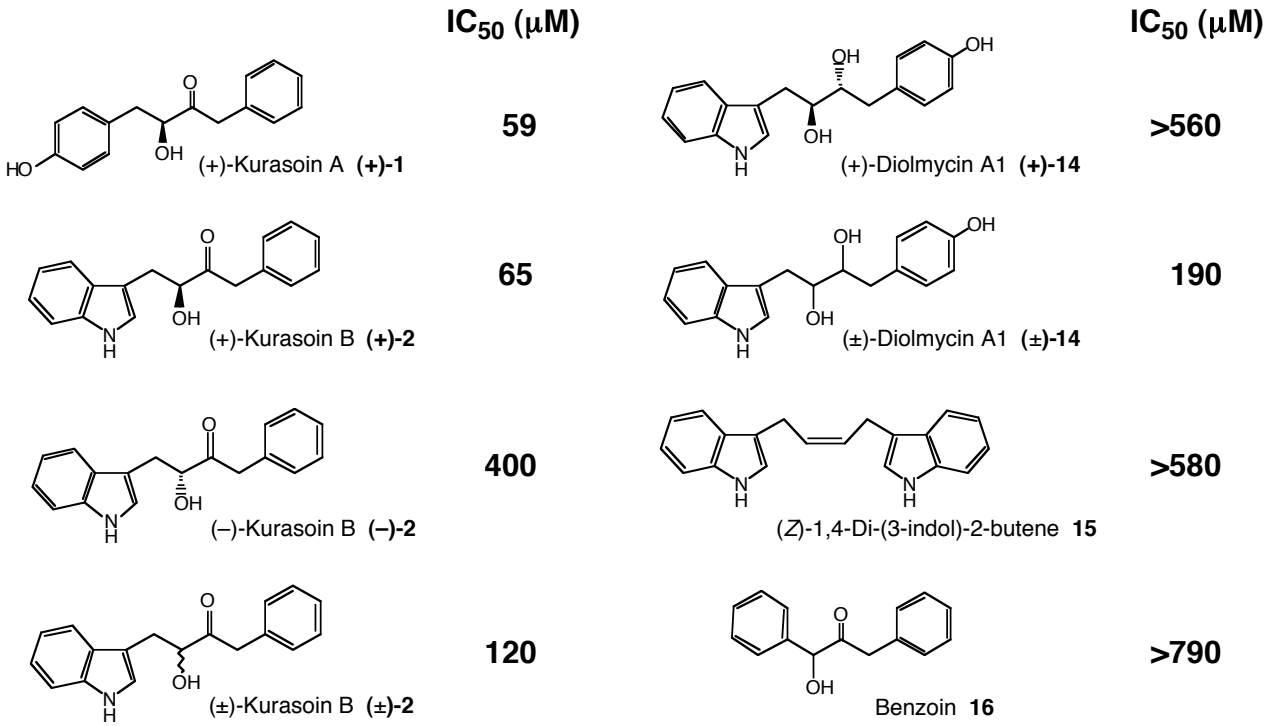


Figure 2 Protein farnesyltransferase (PFTase) inhibitory activities of the kurasoins and related compounds

EXPERIMENTAL

Except as stated otherwise, reactions were carried out under an argon atmosphere with freshly distilled solvents, magnetic stirring, and monitoring by thin layer chromatography (TLC) with 0.25mm precoated silica gel plates (E. Merck). Column chromatography was performed with silica gel (partical size 0.040-0.063 mm, E. Merck). Melting points were measured using a Yanagimoto micro melting point apparatus and were uncorrected. IR spectra were recorded on a Horiba FT-210 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on JEOL-270 and Varian XL-400 spectrometers. Chemical shifts for $CDCl_3$ are reported relative to TMS. ^{1}H NMR data collected in methanol-d_4 are reported relative to the methanol peak at 3.31 ppm. MS specta were obtained with a JMS-D100 or JMS-D300 instrument. Optical rotations were measured with a JASCO DIP-370 digital polarimeter.

4-Hydroxyphenylacetaldehyde (4): To the solution of **3** (5.0 g, 36 mmol) in DMSO (40 mL) was added triethyl amine (10 mL) and fully stirred, pyridine-sulfur trioxide (11.6 g, 72.9 mmol) in DMSO (40 mL) was slowly dripped into that mixture. After 1 h, the reaction mixture was diluted with water (200 mL) at 0°C, extracted with CH_2Cl_2 (200 mL x 3), dried over anhydrous Na_2SO_4 and concentrated. The oil residue was purified by column chromatography (solvent, Hexane : EtOAc = 5 : 1) to give **4** (3.47 g, 71%): colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 9.71 (t, J = 2.4 Hz, 1H), 7.06 (d, J = 8.6 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 5.81 (s, 1H), 3.63 (d, J = 2.4 Hz, 2H). Anal. Calcd for $C_8H_8O_2$-3/5H_2O: C, 65.40; H, 6.27. Found: C, 65.41; H, 6.13.

2-Hydroxy-1-(4'-hydroxyphenyl)-3-butene (5): To the vinylmagnesium bromide solution (19.4 mL, 19.4

mmol, 1.0 M in THF), **4** (2.2 g, 16.2 mmol) in THF (30 mL) was added dropwise at -76˚C. After 25 min at -76˚C, the reaction mixture was quenched with sat. aq. NH_4Cl and water. The mixture was then extracted with EtOAc (20 ml x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (solvent Hexane : EtOAc = 4 : 1) to give **5** (1.14 g, 63%): colorless oil; IR (KBr) 3367 (s), 1614 (m), 1515 (s), 1448 (m), 1240 (s), 993 (m), 819 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.05 (d, *J* = 8.6 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 6.17 (s, 1H), 5.92 (m, 1H), 5.19 (m, 2H), 4.31 (m, *J* = 5.6 Hz, 1H), 2.76 (m, 2H), 2.14 (s, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.5, 139.7, 130.6 (2 C), 129.2, 115.4 (2 C), 115.3, 74.0, 42.7; HRMS(EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0832. Anal. Calcd for $C_{10}H_{12}O_2$-1/8H_2O: C, 72.16; H, 7.42. Found: C, 72.19; H, 7.40.

(2*S*,3*R*)-3,4-Epoxy-2-hydroxy-1-(4'-hydroxyphenyl)butane ((-)-(6)): To the mixture of 4 Å molecular sieves (1.5 g) in CH_2Cl_2 (10 mL) and tetraisopropyl orthotitanate (1.98 g, 6.95 mmol), (+)-diisopropyl-L-tartrate (1.95 g, 8.34 mmol) was added dropwise at -5˚C. After 30 min at -20˚C, 80 % cumene hydroperoxide (529 mg, 3.48 mmol) was added dropwise. After 10 min **5** (1.14 g, 6.95 mmol, in 10 mL of CH_2Cl_2) was added dropwise and stirring was performed for 2 days at -20 ˚C. Then the reaction mixture was quenched with ether (5 mL) and sat. aq. Na_2SO_4 (5 mL), and warmed to rt; stirring was performed for 2 h. The mixture was filtered. The filtrate was concentrated. The residue was purified by column chromatography (solvent Hexane : EtOAc 10 : 1) to give **6** (438 mg, 35%): white solid; m.p. 121-126 ˚C; $[\alpha]^{23}_D$ -8˚ (*c* 1.0, CH_3OH); IR (KBr) 3268 (s), 2931 (m), 1594 (m), 1517 (s), 837 (s) cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.04 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 4.81 (m, 1H), 3.62 (m, 1H), 2.88 (m, 2H), 2.71 (m, 2H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 156.8, 131.5 (2 C), 130.1, 116.0 (2 C), 72.8, 55.3, 45.5, 40.6; HRMS(EI) calcd for $C_{10}H_{12}O_3$ 180.0786, found 180.0783. Anal. Calcd for $C_{10}H_{12}O_3$-1/5H_2O: C, 65.35; H, 6.80. Found: C, 65.31; H, 6.65.

(2*S*,3*R*)-3,4-Epoxy-2,4'-di-*t*-butyldimethylsiloxy-1-phenylbutane ((-)-(7)): The solution of **6** (362 mg, 2.01 mmol), imidazole (684 mg, 10.1 mmol), and TBDMSCl (756.5 mg, 5.0 mmol) in DMF (5 mL) was stirred for 3 h at rt. Then, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (10 mL) and water (10 mL), extracted with EtOAc (20 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (solvent CH_2Cl_2) to give **7** (578.6 mg, 71%): colorless oil; $[\alpha]^{23}_D$ -10˚ (*c* 1.0, CH_3OH); IR (KBr) 2956 (s), 2929 (s), 2858 (s), 1610 (w), 1510 (w), 1255 (s), 916 (s), 838 (s), 779 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.69 (m, 1H), 2.79 (m, 5H), 0.98 (s, 9H), 0.80 (s, 9H), 0.17 (s, 6H), -0.08 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.1, 130.8, 130.7 (2 C), 119.8 (2 C), 72.8, 54.4, 45.1, 41.0, 25.8 (6 C), 18.2, 18.1, -4.5 (2 C), -4.7 (2 C); HRMS(FAB) calcd for $C_{22}H_{40}O_3NaSi_2$ 431.2414, found 431.2464. Anal. Calcd for $C_{22}H_{40}O_3Si_2$-3/4H_2O: C, 62.58; H, 9.90. Found: C, 62.68; H, 9.56.

(2*S*,3*R*)-2,4'-Di-*t*-butyldimethylsiloxy-3-hydroxy-1,4-diphenylbutane ((-)-(8)): To the

solution of copper iodide (93.3 mg, 0.49 mmol) in THF (1 mL), phenylmagnesium bromide (1.47 ml, 1.47 mmol, 1.0 M in THF) was added dropwise at -40 ˚C. After 5 min, **7** (200 mg, 0.49 mmol) in THF (0.5 mL) was added dropwise. The reaction mixture was stirred for 30 min at -40 ˚C. Then, the mixture was quenched with sat. aq. NH_4Cl and water, extracted with EtOAc (10 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by PTLC (solvent CH_2Cl_2) to give **8** (177.2 mg, 75 %): colorless oil; $[\alpha]^{24}_D$ -31˚ (*c* 1.0, CH_2Cl_2); IR (KBr) 3440 (s), 2954 (s), 2929 (s), 2858 (s), 1510 (s), 1257 (s), 916 (s), 837 (s), 779 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28 (m, 5H), 7.01 (d, *J* = 8.6 Hz, 2H), 6.75 (d, *J* = 8.6 Hz, 2H), 3.86 (m, 1H), 3.77 (m, 1H), 2.71 (m, 4H), 2.21 (s, 1H), 0.98 (s, 9H), 0.82 (s, 9H), 0.17 (s, 6H), -0.13 (s, 3H), -0.41 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 154.0, 138.6, 131.7, 130.7 (2 C), 129.2 (2 C), 128.5 (2 C), 126.4, 119.9 (2 C), 76.2, 75.6, 38.5, 36.7, 25.9 (3 C), 25.7 (3 C), 18.2, 18.0, -4.5 (2 C), -4.9 (2 C); HRMS(FAB) calcd for $C_{28}H_{46}O_3NaSi_2$ 509.2883, found 509.2883.

(2*S*)-2,4'-Di-*t*-butyldimethylsiloxy-1,4-diphenyl-3-butanone ((-)-(9)): The mixture of **8** (135.8 mg, 0.28 mmol), benzene (2.8 mL), DMSO (418 μL), dicyclohexylcarbodiimide (173.2 mg, 0.84 mmol), trifluoroacetic acid (10.8 μL, 0.14 mmol) and pyridine (22.6 μL, 0.28 mmol) was stirred for 3 h at rt. Then, the reaction mixture was quenched with water, extracted with EtOAc (20 ml x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by PTLC (solvent CH_2Cl_2) to give **9** (118 mg, 88%): colorless oil; $[\alpha]^{23}_D$ -33˚ (*c* 1.0, CH_3OH); IR (KBr) 2956 (s), 2929 (s), 2285 (s), 1724 (s), 1608 (m), 1510 (s), 1471 (m), 1125 (s), 1103 (s), 1089 (s), 916 (s), 837 (s), 779 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.15 (m, 5H), 7.00 (d, *J* = 8.3 Hz, 2H), 6.59 (d, *J* = 8.3 Hz, 2H), 4.23 (dd, *J* = 7.9, 4.0 Hz, 1H), 3.74 (d, *J* = 15.6 Hz, 1H), 3.65 (d, *J* = 15.6 Hz, 1H), 2.83 (dd, *J* = 13.5, 3.6 Hz, 1H), 2.70 (dd, *J* = 13.5, 7.9 Hz, 1H), 0.93 (s, 9H), 0.83 (s, 9H), 0.13 (s, 6H), -0.11 (s, 3H), -0.28 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 210.7, 154.5, 133.9, 130.9 (2 C), 129.8, 129.7 (2 C), 128.4 (2 C), 126.8, 120.0 (2 C), 79.9, 44.5, 40.7, 25.8 (3 C), 25.7 (3 C), 18.2, 18.0, -4.49 (4 C); HRMS(FAB) calcd for $C_{28}H_{44}O_3NaSi_2$ 507.2727, found 507.2729.

(+)-Kurasoin A ((+)-(1)): The solution of **9** (28.8 mg, 0.06 mmol) in THF (1.2 mL) was treated with a mixture of hydrogen fluoride-pyridine(70 %) (0.25 mL, 0.34 mmol), pyridine (0.12 mL), and THF (0.27 mL) at 0˚C. The mixture was allowed to warm to rt and was stirred for 20 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and water, extracted with EtOAc (10 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by PTLC (solvent CH_2Cl_2) to give **1** (10.4 mg, 68 %): needle, mp 121-123 ˚C; $[\alpha]^{22}_D$ +9˚ (*c* 1.0, CH_3OH); IR (KBr) 3419 (s), 1710 (s), 1515 (s), 1124 (m), 1049 (s) cm^{-1}; ^1H NMR (270 MHz, CD_3OD) δ 7.19 (m, 5H), 7.04 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.3 Hz, 2H), 4.35 (dd, *J* = 7.6, 4.9 Hz, 1H), 3.71 (d, *J* = 16.7 Hz, 1H), 3.63 (d, *J* = 16.7 Hz, 1H), 2.97 (dd, *J* = 14.0, 4.9 Hz, 1H), 2.76 (dd, *J* = 14.0, 7.6 Hz, 1H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 212.2, 157.2, 135.5, 131.6 (2 C), 130.9 (2 C), 129.4 (2 C), 129.3, 127.7, 116.1 (2 C), 78.8, 46.6, 40.2; HRMS(FAB) calcd for $C_{16}H_{17}O_3$ 257.1178, found 257.1192.

2-Hydroxy-1-phenyl-3-butene (11): To the vinylmagnesium bromide solution (24.0 mL, 24.0 mmol, 1.0 M in THF), **10** (2.6 g, 21.8 mmol) in ether (16 mL) was added dropwise at -78°C. The reaction mixture was stirred for 20 min at -78°C. Then, the reaction mixture was quenched with sat. aq. NH_4Cl (15 mL), extracted with EtOAc (25 mL x 3), and the combined extracts were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (solvent, Hexane : EtOAc = 5 : 1) to give **11** (2.2 g, 68%): colorless oil; IR (KBr) 3430 (s), 2980 (m), 1497 (w), 1030 (m), 764 (m), 700 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.94 (m, 1H), 5.20 (m, 2H), 4.36 (m, 1H), 2.85 (m, 2H); MS(EI) *m/z* 148 $[M]^+$. Anal. Calcd for $C_{10}H_{12}O$-1/10H_2O: C, 80.07; H, 8.20. Found: C, 80.07; H, 8.11.

(2*S*,3*S*)-3,4-Epoxy-2-hydroxy-1-phenylbutane ((-)-(12)): To the mixture of 4 Å molecular sieves (3.5 g) in CH_2Cl_2 (40 mL) and tetraisopropyl orthotitanate (2.30 g, 8.11 mmol), (-)-diisopropyl-L-tartrate (2.28 g, 9.73 mmol) was added dropwise at -5°C. After 30 min at -20°C, *t*-butyl hydroperoxide solution (0.81 mL, 4.05 mmol, 5.0 M in decane) was added dropwise. After 10 min, **11** (1.20 g, 8.11 mmol, in 20 mL CH_2Cl_2) was added dropwise and stirring was performed for 2 days at -20°C. Then, the reaction mixture was quenched with ether (9 mL) and sat. aq. Na_2SO_4 (6 mL) and warmed to ambient temperature; stirring was performed for 2 h. The mixture was filtered. The filtrate was concentrated. The residue was purified by column chromatography (solvent, Hexane : EtOAc = 4 : 1) to give **12** (505 mg, 38%): colorless oil; $[\alpha]^{24}_D$ -7° (*c* 0.87, $CHCl_3$); IR (KBr) 3430 (s), 1497 (m), 1454 (m), 1084 (m), 746 (m), 702 (s) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.02 (m, 1H), 3.06 (m, 1H), 2.92 (m, 2H), 2.79 (m, 2H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 137.2, 129.4 (2 C), 128.5 (2 C), 126.7, 69.8, 54.0, 43.9, 40.1; HRMS(EI) calcd for $C_{10}H_{12}O_2$ 164.0837, found 164.0835. Anal. Calcd for $C_{10}H_{12}O_2$-2/5H_2O: C, 70.07; H, 7.53. Found: C, 69.79; H, 7.30.

(3*R*)-3,4-Epoxy-1-phenyl-2-butanone ((-)-(13)): To an ambient temperature solution of **12** (450 mg, 2.74 mmol) in acetone (20 mL) Jones reagent (5.8 mL; 2.66 g of CrO_3 in 2.3 mL of conc. H_2SO_4 and 10 mL of H_2O) was added, and the solution was stirred for 25 min, then quenched with *iso*-propyl alcohol. This mixture was extracted with CH_2Cl_2 (60 mL x 2), and the combined extracts were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (solvent, Hexane : EtOAc = 6 : 1) to give **13** (365 mg, 82%): colorless oil; $[\alpha]^{24}_D$ -36° (*c* 1.14, $CHCl_3$); IR (KBr) 3032 (w), 1720 (s), 1497 (m), 1454 (m), 866 (m), 733 (m), 700 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.24 (m, 5H), 3.74 (d, *J* = 15.5 Hz, 1H), 3.64 (d, *J* = 15.5 Hz, 1H), 3.45 (m, 1H), 2.94 (m, 1H), 2.83 (m, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 204.6, 132.8, 129.5 (2 C), 128.7 (2 C), 127.2, 53.2, 46.3, 43.7; HRMS(EI) calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0667.

(+)-Kurasoin B ((+)-(2)): A solution of **13** (360 mg, 2.22 mmol) and indole (389 mg, 3.33 mmol) in CCl_4 (6.0 mL) was cooled to -5°C and treated with Tin(IV) chloride solution (744 μL, 0.74 mmol, 1.0 M in CH_2Cl_2). The reaction mixture was stirred for 30 min and then quenched with sat. aq. Na_2CO_3 solution (10 mL) and stirred for 1 h. This mixture was extracted with $CHCl_3$ (20 mL x 3), and the combined extracts

were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (solvent, $CHCl_3$: MeOH = 50 : 1) and repurified by PTLC (solvent, $CHCl_3$: MeOH = 20 : 1) to give **2** (167 mg, 27%): brown oil; $[\alpha]^{24}_D$ +31° (*c* 0.33, $CHCl_3$); IR (KBr) 3405 (s), 1713 (s), 1456 (m), 744 (s), 702 (m) cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.23 (m, 8H), 4.60 (m, 1H), 3.81 (d, *J* = 16.2 Hz, 1H), 3.74 (d, *J* = 16.2 Hz, 1H), 3.33 (dd, *J* = 14.5, 4.9 Hz, 1H), 3.16 (dd, *J* = 14.5, 7.1 Hz, 1H); ^{13}C NMR (67.5 MHz, CD_3OD) δ 212.8, 138.0, 135.4, 130.8, 129.3 (2 C), 128.9, 127.7 (2 C), 124.7, 122.4, 119.8, 119.6, 112.3, 110.9, 77.8, 46.1, 31.1; HRMS(EI) calcd for $C_{18}H_{17}O_2N$ 279.1259, found 279.1276.

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