

A formal synthesis of (+)-(S)-kurasoin B

Francisco Yuste,^{a,*} Virginia M. Mastranzo,^a Rubén Sánchez-Obregón,^a Benjamín Ortiz,^a
and José L. García Ruano^b

^a*Instituto de Química, Universidad Nacional Autónoma de México, Circuito Exterior, Cd. Universitaria, Coyoacán 04510, México D. F.*

^b*Departamento de Química Orgánica (C-I), Facultad de Ciencias, Universidad Autónoma de Madrid, Cantoblanco, 28049-Madrid, Spain*
E-mail: yustef@servidor.unam.mx

Abstract

A new diastereoselective synthesis of (S)-1-[(S)-oxiran-2-yl]-2-phenylethanone (**10**), a key intermediate in the synthesis of kurasoin B (**2**), has been accomplished in seven steps in an overall yield of 32%. The key synthetic step in the process is the diastereoselective reduction of the β -keto sulfoxide **6** derived from (S)-phenyllactic acid.

Keywords: Kurasoin B, diastereoselective synthesis, β -keto sulfoxides, DIBAH/ZnBr₂ reduction

Introduction

Kurasoins A (**1**) and B (**2**) are protein farnesyltransferase (PFTase) inhibitors isolated from the fermentation broth of the soil fungus *Paecilomyces sp.* FO-3684 (Figure 1).¹ These simple acyloin compounds are of interest because of their potential use as anti-cancer drugs. Kurasoins A and B both contain a 3-hydroxy-1-phenyl-2-butanone moiety to which 4-hydroxyphenyl and 3-indolyl substituents, respectively, are connected at C-4. The structures of **1** and **2** were determined by spectroscopic analysis and total synthesis of the racemates,² and asymmetric syntheses were used to establish the absolute configurations thereof.³ Since the stereochemistry of the hydroxy group is important for eliciting PFTase inhibition,^{3a} highly enantioselective syntheses of **1** and **2** are desirable. Three asymmetric syntheses of kurasoin B (**2**) have been reported. The first one employs a four-step approach starting from phenylacetaldehyde and uses a Sharpless asymmetric epoxidation in addition to a coupling reaction between indole and the epoxy ketone intermediate **10**, as key steps (6% overall yield).^{3a,b} The second route involves a Yb(OTf)₃-catalyzed coupling of indole with methyl glycidate.^{3c} More recently, a new synthesis of kurasoin B has appeared involving a Sharpless asymmetric dihydroxylation as the source of

chirality in the synthesis of **10** (50% yield) and a CH_3NO_2 -assisted or a $\text{Yb}(\text{OTf})_3$ -catalyzed regioselective coupling with indole.⁴

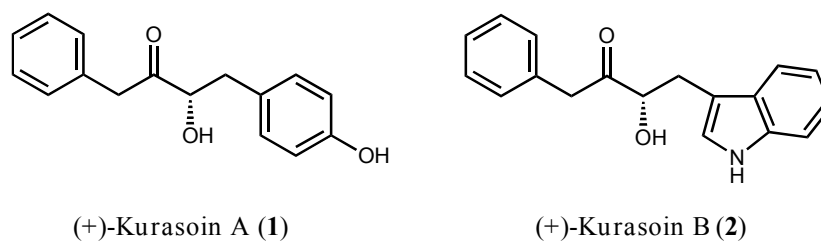


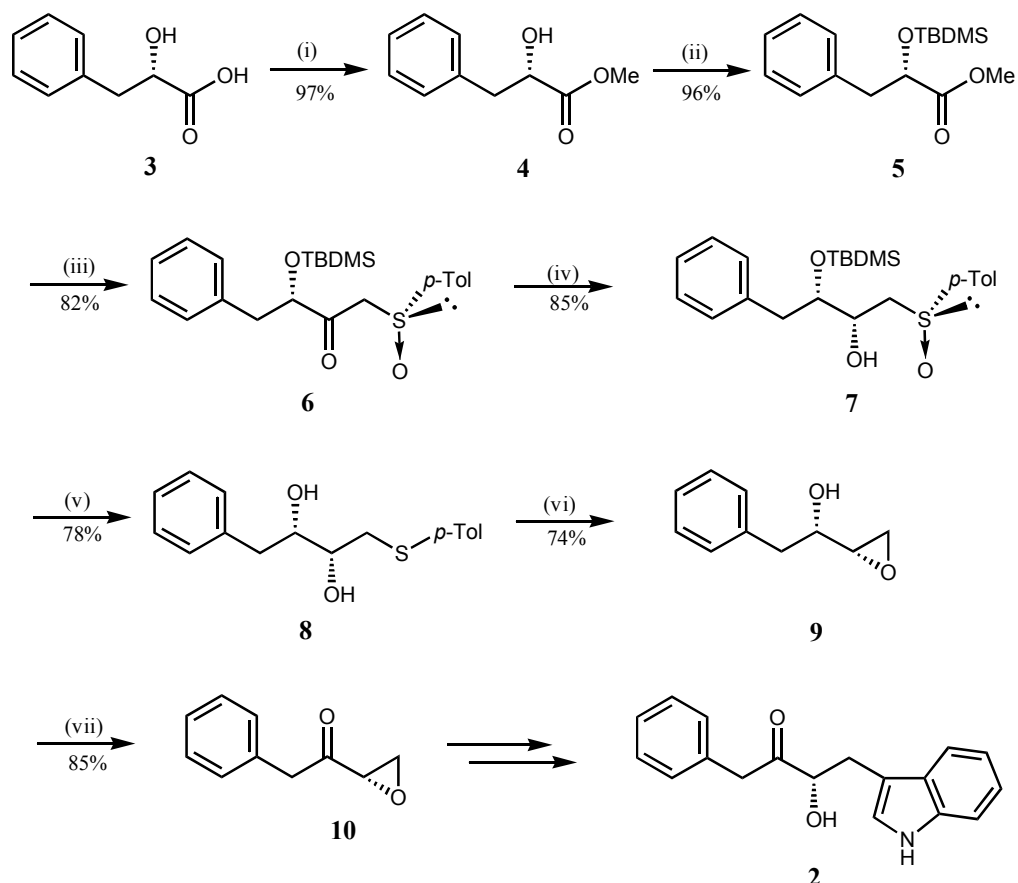
Figure 1

In recent years, the asymmetric synthesis of carbinols by nucleophilic addition to enantiomerically pure β -keto sulfoxides has been widely used.⁵ Alkylation⁶ and hydrocyanation⁷ reactions of these compounds with aluminum reagents have been described to prepare tertiary alcohols and cyanohydrins, respectively. However, the stereoselective reduction of β -keto sulfoxides has been the most extensively investigated and used reaction.^{5,8} The stereochemical outcome in the reduction of the β -keto sulfoxides can be controlled by the configuration of the sulfoxide, the reducing agent, and the absence or presence of a Lewis acid. The hydroxy sulfoxides resulting from these reactions can be transformed into epoxides,⁹ which can be subsequently opened with nucleophiles.¹⁰ As β -keto sulfoxides are easily obtained by reaction of esters with enantiomerically pure methyl *p*-tolyl sulfoxide,¹¹ we envisioned the synthesis of chiral epoxy ketone **10** making use of the above-mentioned reactions on (*S*)-phenyllactic acid **3**. Herein, we report the application of this process to the synthesis of **10**, a key intermediate in the synthesis of kurasoin B (**2**).

Results and Discussion

The overall synthetic sequence is depicted in Scheme 1. Methyl (*S*)-2-hydroxy-3-phenylpropanoate **4** was easily prepared in 97% yield by esterification of (*S*)-phenyllactic acid (**3**) with diazomethane. Then, the hydroxyl group of **4** was protected by using *tert*-butyldimethylsilyl chloride to give methyl ester **5** in 96% yield. The synthesis of β -keto sulfoxide **6** was performed, in 82% yield, by reaction of **5** with 2 equiv of the anion generated from enantiomerically pure (*R*)-(+)-methyl *p*-tolyl sulfoxide and LDA at -78°C , according to the procedure reported by Solladié.¹¹ The reduction of β -keto sulfoxide **6** with DIBAH in the presence of ZnBr_2 afforded, in a completely diastereoselective way, the hydroxy sulfoxide **7** (85% yield) having the *R* absolute configuration at the newly created C-2 stereogenic center. This result demonstrated that the well-established protocol to reduce β -keto sulfoxides, first

reported in 1985 by Solladié,¹² is working efficiently even in molecules with oxygenated centers α to the carbonyl group, which could compete with the sulfoxide in the diastereocontrol of the process.¹³ The synthesis of the epoxy alcohol **9** starting from β -sulfinyl alcohol **7** was performed following a well established synthetic sequence.¹² Thus, reduction of the sulfinyl group of **7** was accomplished with an aqueous HCl solution of TiCl_3 at room temperature. These reaction conditions simultaneously promoted the removal of the silyl protecting group furnishing the β -sulfenyl diol **8** in 78% yield. The reaction of sulfenyl derivative **8** with trimethyloxonium tetrafluoroborate in anhydrous CH_2Cl_2 , followed by aqueous K_2CO_3 (one-pot procedure) produced epoxy alcohol **9** in 74% yield. Finally, oxidation of **9** with the Dess-Martin periodinane reagent in CH_2Cl_2 at 0°C gave the intermediate epoxy ketone **10** in 85% yield.



Scheme 1. Reagents and conditions: (i) CH_2N_2 , Et_2O . (ii) TBDMSCl , imidazole, CH_3CN . (iii) (R)-(+)-methyl *p*-tolyl sulfoxide, LDA, THF, -78°C , 2h. (iv) DIBAH/ ZnBr_2 , THF, -78°C , 2h. (v) $\text{TiCl}_3/\text{HCl}/\text{EtOH}$. (vi) 1. $\text{Me}_3\text{OBF}_4/\text{CH}_2\text{Cl}_2$; 2. $\text{K}_2\text{CO}_3/\text{H}_2\text{O}$. (vii) Dess-Martin periodinane, CH_2Cl_2 , $0^\circ\text{C} \rightarrow 25^\circ\text{C}$, 1h.

In summary, a new diastereoselective synthesis of (*S*)-1-[(*S*)-oxiran-2-yl]-2-phenylethanone (**10**), a key intermediate in the synthesis of kurasoin B (**2**), has been accomplished in seven steps

in an overall yield of 32%. The key synthetic step in the process is the diastereoselective reduction of the β -keto sulfoxide **6** derived from (*S*)-phenyllactic acid.

Experimental Section

General Procedures. All moisture sensitive reactions were carried out in flame dried glassware under an argon atmosphere and monitored by TLC. Flash chromatography was performed with silica gel 60 (230-400 mesh ASTM). Melting points were determined in a Culatti melting point apparatus in open capillary tubes and are uncorrected. The optical rotations were measured at room temperature (20-23°C) using a Perkin-Elmer 343 polarimeter (concentration in g/100 mL). The NMR spectra were determined in CDCl₃ solutions unless otherwise indicated at 300 and 75.5 MHz for ¹H and ¹³C-NMR, respectively. *J* values are given in hertz. Mass spectra were measured at 70 eV and 190°C. All described compounds were over 97% pure by NMR analysis.

(*S*)-Methyl 2-hydroxy-3-phenylpropanoate (4). To a stirred solution of (*S*)-phenyllactic acid (**3**) (1.0 g, 6.0 mmol) in ether at 0°C an excess of cold ethereal solution of diazomethane was added. After 12 h at room temperature, the volatiles were evaporated. The crude product **4** was isolated as a white solid (1.05 g, 97%), mp 45-47 °C; [α]_D -8.5 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ 2.72 (br s, 1H), 2.96 (dd, 1H, *J* 6.6 and 14.1), 3.12 (dd, 1H, *J* 4.2 and 13.8), 3.77 (s, 3H), 4.46 (dd, 1H, *J* 4.5 and 6.6), 7.19-7.33 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ 40.5, 52.4, 71.3, 126.9, 128.4, 129.4, 136.3, 174.5.

(*S*)-Methyl 2-(*tert*-butyldimethylsilyloxy)-3-phenylpropanoate (5).¹⁴ To a solution of **4** (1.0 g, 5.8 mmol) in dry acetonitrile (4 mL) imidazole (2.4 g, 35.2 mmol) and *tert*-butyldimethylsilyl chloride (1.32 g, 8.8 mmol) were added and the resulting mixture was stirred at room temperature for 30 min. The reaction was quenched with water (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The extracts were dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography (hexane-ethyl acetate, 95:5) to give 1.65 g (96%) of **5** as colorless oil; [α]_D -33.2 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ -0.22 (s, 3H), -0.13 (s, 3H), 0.78 (s, 9H), 2.88 (dd, 1H, *J* 9.0 and 13.2), 3.07 (dd, 1H, *J* 3.9 and 13.2), 3.72 (s, 3H), 4.34 (dd, 1H, *J* 3.9 and 9.0), 7.18-7.31 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ -5.7, -5.5, 18.2, 25.5, 41.6, 51.8, 73.8, 126.6, 128.2, 129.8, 137.4, 173.6.

(3*S*,*Rs*)-3-(*tert*-Butyldimethylsilyloxy)-1-[(4-methylphenyl)sulfinyl]-4-phenylbutan-2-one (6). A solution of (*R*)-(+)-methyl *p*-tolyl sulfoxide (1.5 g, 10.2 mmol) in THF (10 mL) was added dropwise to a solution of LDA (10.2 mmol) in THF (25 mL) at -78 °C. The mixture was stirred at -78 °C for 1 h. Then, a solution of **5** (1.5 g, 5.1 mmol) in THF (5 mL) was added and the resulting mixture was stirred at -78 °C for 2 h. The reaction mixture was decomposed with saturated NH₄Cl (25 mL) and extracted with Et₂O (3 x 25 mL). The organic layer was washed with brine, dried and evaporated. The product was purified by flash chromatography (hexane-ethyl acetate, 80:20) to produce 1.74 g (82%) of **6** as an oil; [α]_D +100.6 (*c* 1.0, CHCl₃); ¹H

NMR (CDCl₃, 300 MHz): δ -0.31 (s, 3H), -0.20 (s, 3H), 0.79 (s, 9H), 2.41 (s, 3H), 2.81 (dd, 1H, *J* 8.4 and 13.5), 2.93 (dd, 1H, *J* 4.5 and 13.5), 3.83 and 4.08 (AB system, 2H, *J* 15.3), 4.21 (dd, 1H, *J* 4.5 and 8.4), 7.15-7.35 (m, 7H), 7.57 (half of an AA'BB' system, 2H); ¹³C NMR (CDCl₃, 75 MHz): δ -5.6, -5.4, 17.9, 21.4, 25.6, 40.4, 65.3, 80.0, 124.2, 126.9, 128.4, 129.9, 130.0, 136.2, 140.7, 142.0, 204.6. EIMS *m/z* 401 (2%, M⁺-15), 359 (55), 235 (34), 219 (100), 179 (10), 139 (25), 129 (16), 91 (13), 73 (49). HRMS (FAB⁺) *m/z* [M⁺+1] calcd. for: 417.1920. Found: 417.1917.

(2*R*,3*S*,*Rs*)-3-(*tert*-Butyldimethylsilyloxy)-1-[(4-methylphenyl)sulfinyl]-4-phenylbutan-2-ol**

(7). A solution of β -keto sulfoxide **6** (1.0 g, 2.4 mmol) in THF (10 mL) was added to a cooled solution of ZnBr₂ (0.59 g, 7.2 mmol) in THF (50 mL) at 0 °C and the resulting mixture was stirred at this temperature for 2 h. Then the solution was cooled at -78 °C and a 1.0 M solution of DIBAH in toluene (7.2 mL, 7.2 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 2 h and excess of DIBAH was decomposed by adding MeOH (10 mL). Once the solution reached room temperature, the volatiles were removed under vacuum, the residue was treated with saturated NH₄Cl (100 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The organic phase was washed with brine, dried and evaporated. The product was purified by flash chromatography (hexane-ethyl acetate, 2:1) to give 0.853 g (85%) of **7** as white crystals, mp 143-144 °C; [α]_D +35.0 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): δ -0.33 (s, 3H), -0.04 (s, 3H), 0.83 (s, 9H), 2.42 (s, 3H), 2.45 (dd, 1H, *J* 8.4 and 13.2), 2.98 (d, 2H, *J* 6.0), 3.00 (dd, 1H, *J* 4.8 and 13.2), 3.55 (d, 1H, *J* 4.5), 3.93 (m, 1H), 4.08 (m, 1H), 7.10-7.27 (m, 5H), 7.31 and 7.50 (AA'BB' system, 4H); ¹³C NMR (CDCl₃, 75 MHz): δ -5.2, -4.9, 17.9, 21.4, 25.8, 38.4, 58.8, 70.3, 75.5, 124.0, 126.2, 128.3, 129.8, 130.1, 138.3, 140.4, 141.9. EIMS *m/z* 419 (1%, M⁺+1), 361 (100), 261 (20), 235 (18), 183 (9), 139 (54), 91 (17), 73 (47). HRMS (FAB⁺) *m/z* [M⁺+1] calcd. for: 419.2076. Found: 419.2079.

(2*S*,3*R*)-4-[(4-methylphenyl)sulfenyl]-1-phenylbutane-2,3-diol (8). To a stirred solution of **7** (2.49 g, 5.95 mmol) in EtOH (25 mL) a 10% wt. solution of TiCl₃ (11.9 mmol, 2 equiv.) in 20-30% aqueous HCl was added at room temperature. After 3 h, the solution was cooled in an ice bath, treated with water (20 mL), 10% NaHCO₃ (20 mL) and extracted with ethyl acetate (3 x 40 mL). The organic phase was separated, washed with brine, dried and concentrated. The residue was purified by flash chromatography (hexane-ethyl acetate, 2:1) to give 1.337 g (78%) of **8** as white crystals, mp 108-110 °C; [α]_D +18.8 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): 2.31 (s, 3H), 2.84 (d, 2H, *J* 7.2), 3.01 (dd, 1H, *J* 8.1 and 13.8), 3.10 (dd, 1H, *J* 5.4 and 13.8), 3.84 (dd, 1H, *J* 3.0 and 6.3), 3.87 (dd, 1H, *J* 3.0 and 6.0), 7.07 (half of an AA'BB' system, 2H), 7.16-7.32 (m, 7H); ¹³C NMR (CDCl₃, 75 MHz): δ 21.0, 39.2, 40.4, 70.7, 73.4, 126.5, 128.6, 129.3, 129.9, 131.0, 137.0, 137.9 (2C).

(*S*)-1-[(*S*)-oxiran-2-yl]-2-phenylethanol (9). Trimethyloxonium tetrafluoroborate (0.52 g, 3.55 mmol) was added to a solution of **8** (0.93 g, 3.23 mmol) in CH₂Cl₂ (30 mL). The mixture was stirred at room temperature for 3 h and then a solution of K₂CO₃ (0.84 g, 6.44 mmol) in water (8 mL) was added. The resulting mixture was vigorously stirred for 24 h. The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The

combined organic layers were washed with brine, dried and concentrated. The residue was purified by flash chromatography (hexane-ethyl acetate, 2:1) to produce 0.392 g (74%) of **9** as a colorless oil; $[\alpha]_D +6.5$ (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 300 MHz): 2.30-2.60 (br s, 1H), 2.56 (dd, 1H, *J* 2.7 and 4.8), 2.71 (dd, 1H, *J* 3.9 and 4.8), 2.86 (dd, 1H, *J* 6.6 and 13.5), 2.94 (dd, 1H, *J* 7.2 and 13.5), 3.00 (ddd, 1H, *J* 2.7, 3.9 and 4.8), 3.66 (ddd, 1H, *J* 6.0, 6.9 and 12.3), 7.19-7.35 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ 40.8, 45.0, 54.7, 72.4, 126.5, 128.4, 129.3, 137.2; EIMS *m/z* 164 (2%, M⁺), 146 (17), 118 (14), 92 (100), 91 (90).

(S)-1-[(S)-oxiran-2-yl]-2-phenylethanone (10). To a cooled solution (0°C) of **9** (0.771 g, 4.70 mmol) in dry CH₂Cl₂ (60 mL) Dess-Martin periodinane (3.60 g, 8.48 mmol, 1.8 equiv) was added and the mixture was stirred at 0°C for 30 min and then at room temperature for additional 15 h. The reaction was cooled at 0°C and quenched by addition of saturated aqueous NaHCO₃ (60 ml), 10% aqueous Na₂S₂O₃ (60 ml) and Et₂O (60 mL). Then, the mixture was warmed at room temperature and stirred for 15 min. The layers were separated and the aqueous layer was extracted with Et₂O (2x30 mL). The combined organic extracts were dried and evaporated. The residue was purified by flash chromatography (hexane-ethyl acetate, 4:1) to produce 0.653 g (85%) of **10** as a colorless oil; $[\alpha]_D -47.5$ (*c* 1.14, CHCl₃) [Lit.^{3b} $[\alpha]_D -36.0$ (*c* 1.14, CHCl₃); Lit.⁴ $[\alpha]_D -36.4$ (*c* 1.5, CHCl₃)]; ¹H NMR (CDCl₃, 300 MHz): 2.87 (dd, 1H, *J* 2.7 and 6.0), 2.99 (dd, 1H, *J* 4.5 and 6.0), 3.49 (dd, 1H, *J* 2.4 and 4.5), 3.64 and 3.74 (AB system, 2H), 7.20-7.40 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz): δ 43.7, 46.2, 53.3, 127.2, 128.7, 129.5, 132.8, 204.6.

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