The structures of new protein farnesyltransferase inhibitors, kurasoins A and B, were elucidated by NMR study. Kurasoins A and B are acyloin compounds having in common a 3-hydroxy-1-phenyl-2-butanone moiety, to which β-hydroxyphenyl and 3-indolyl moieties respectively, are connected at C-4. The structures were confirmed by total synthesis.

In the course of screening for inhibitors of protein farnesyltransferase, we have found some new compounds, kurasoins A and B (1 and 2, Fig. 1), from the cultured broth of Paecilomyces sp. FO-3684. In this paper, the structure elucidation and total synthesis of 1 and 2 are described.

Structure Elucidation of Kurasoin A (1)

Chemical shifts in the 1H and 13C NMR of 1 and 2 observed in methanol-d4 are shown in Tables 1. The HMQC experiments revealed the connectivity of each proton and carbon.

HR-FAB-MS of 1 revealed its molecular formula, C16H16O3. Compound 1 showed two methylene, one oxymethine, nine aromatic methine, one carbonyl, and three quaternary carbon signals in the DEPT spectra. Nine protons at the low field of 1H NMR in 1 were assigned as one monosubstituted and one disubstituted benzene by the WH COSY (Fig. 2). The XH-XH COSY also indicated that the remaining protons were assigned to be -CH2-CH-O- and isolated CH2. The result of the HMBC experiment are shown in Fig. 2. The long-range couplings of 4-H2 (δ 2.77, 2.97)/C-1'' (δ 129.3), 4-H2/C-2'' (6') (δ 131.6), and 2'' (6'')-H (δ 7.04)/C-4 (δ 40.2) revealed that C-4 connected to C-1''. The couplings of 3-H (δ 4.35)/C-2 (δ 121.3) and 4-H2/C-2 indicated the arrangement of C-2—C-3—C-4. Also the couplings of 2'(6')-H (δ 7.10)/C-1 (δ 46.6), 1-H2 (δ 3.63, 3.71)/C-1' (δ 135.5), and 1-H2/C-2'(6') (δ 130.9) revealed that C-1 was connected to C-1' of monosubstituted benzene. Three oxygens were suggested to be connected to C-2, C-3 (δ 78.8), and C-4'' (δ 157.2) on the basis of their chemical shifts. The remaining atoms were two hydrogens, which were suggested to be active hydrogens as they were not observed in methanol-d4. Therefore they were assumed to be hydroxy protons of 3-OH and 4''-OH and remaining C-1 and C-2 were considered to be connected. This connectivity was supported by the long-range coupling between 1-H2 and C-2. Finally the structure of 1 was elucidated as 3-hydroxy-4-(β-hydroxyphenyl)-1-phenyl-2-butanone by its total synthesis.

The 1H and 13C NMR signal intensities of C-1 gradually declined in methanol-d4 solution. It may be due to the enolization of the ketone of C-2, enabling deuterium exchanges of methylene protons of 1-H2.

Structure Elucidation of Kurasoins B (2)

The molecular formula of 2 was elucidated by HR-FAB-MS as C18H17NO2. The 1H and 13C NMR spectra (Table 1) of 1 and 2 resembled in their high field
Table 1. The \(^1\)H and \(^{13}\)C NMR data of 1 and 2.

<table>
<thead>
<tr>
<th>Position</th>
<th>(^{13})C</th>
<th>(^1)H</th>
<th>(^{13})C</th>
<th>(^1)H</th>
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<tr>
<td>1</td>
<td>46.1 t</td>
<td>3.63 d (1H, J=16.7 Hz), 3.71 d (1H, J=16.7 Hz)</td>
<td>46.1 t</td>
<td>3.55 d (1H, J=16.8 Hz), 3.63 d (1H, J=16.8 Hz)</td>
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<tr>
<td>2</td>
<td>212.3 s</td>
<td>7.88 s</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>40.2 t</td>
<td>2.77 dd (1H, J=7.6, 14.0 Hz), 2.97 dd (1H, J=4.9, 14.0 Hz)</td>
<td>31.1 t</td>
<td>3.10 dd (1H, J=5.7, 14.6 Hz), 3.20 dd (1H, J=6.8, 14.6 Hz)</td>
</tr>
<tr>
<td>4</td>
<td>135.5 s</td>
<td>3.65 d (1H, J=16.8 Hz), 3.63 d (1H, J=16.8 Hz)</td>
<td>135.4 s</td>
<td>3.55 d (1H, J=16.7 Hz), 3.63 d (1H, J=16.7 Hz)</td>
</tr>
<tr>
<td>1'</td>
<td>130.3 d</td>
<td>7.10 d (2H, J=6.5 Hz)</td>
<td>129.3 d</td>
<td>7.21 d (2H)</td>
</tr>
<tr>
<td>3', 5'</td>
<td>129.4 d</td>
<td>7.28 dd (2H, J=6.5, 7.5 Hz)</td>
<td>129.3 d</td>
<td>7.21 d (2H)</td>
</tr>
<tr>
<td>4'</td>
<td>127.8 d</td>
<td>7.24 d (1H, J=7.5 Hz)</td>
<td>127.7 d</td>
<td>7.20 m (1H)</td>
</tr>
<tr>
<td>1''</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2'' (6'')</td>
<td>131.6 d</td>
<td>7.04 d (2H, J=8.5 Hz)</td>
<td>124.7 d</td>
<td>7.09 s (1H)</td>
</tr>
<tr>
<td>3'' (5'')</td>
<td>116.1 d</td>
<td>6.71 d (2H, J=8.5 Hz)</td>
<td>110.9 s</td>
<td></td>
</tr>
</tbody>
</table>

The MeOH-d\(_4\) signals (3.31 ppm of \(^1\)H and 49.0 ppm of \(^{13}\)C) were used as references. The coupling constants (Hz) are in parentheses.

regions. Common structure of kurasoins, 3-hydroxy-1-phenyl-2-butanone, and 3-substituted indole was revealed \(^1\)H-\(^1\)H COSY and HMBC (Fig. 2). The long-range couplings of 3-H (\(\delta 4.52\))/C-3'' (\(\delta 110.9\)), 4-H\(_2\) (\(\delta 3.10, 3.20\))/C-2'' (\(\delta 124.7\)), 4-H\(_2\)/C-3', 4-H\(_2\)/C-3a'' (\(\delta 128.9\)), and 2''-H (\(\delta 7.09\))/C-4 (\(\delta 31.1\)) indicated the connection of C-4 and C-3''. Thus the structure of 2 was elucidated as 3-hydroxy-4-(3-indolyl)-1-phenyl-2-butanone and it was confirmed by total synthesis described below.

Both 1 and 2 are acyloin compounds and have a 3-hydroxy-1-phenyl-2-butanone moiety in common. The absolute configurations of 1 and 2 were shown to be both S by the asymmetric synthesis of (+)-1 and (+)-2. The asymmetric synthesis of kurasoins will be reported elsewhere.

Total Synthesis of Kurasoins

The deduced structures of 1 and 2 were confirmed by synthesis. The synthesis of 1 and 2 were accomplished as outlined in Scheme 1.

\((\pm)-p\)-Hydroxyphenyllactic acid (3) as a starting material was converted to the methyl ester (4) in the treatment with hydrogen chloride gas in methanol in 75% yield. Treatment of 4 with the aluminum amide reagent derived from N,O-dimethylhydroxylamine hydrochloride and AlMe\(_3\), according to the procedure of WEINREB\(^{21}\), gave effectively the desired transamination
of 4 to the N-methoxy-N-methylamide (5) in 67% yield. Compound 5 was treated with benzylmagnesium chloride to obtain the (+)-kurasoin A (1) in 65% yield.

(+)-Indollactic acid (6) was treated in a similar manner to that described for the preparation of (+)-1 to obtain (±)-kurasoin B (2) in 15% overall yield. Synthetic (+)-1 and (±)-2 were identical in 1H and 13C NMR, IR, and mass spectra with natural 1 and 2.

The first total synthesis of (±)-1 and (±)-2 confirmed the deduced structures.

**Experimental**

NMR spectra were obtained with JEOL JNM-EX270 and Varian Unity 400 spectrometers. Mass spectrometry was conducted on a JEOL JMS-AX505 HA spectrometer. IR spectra were recorded on a Horiba FT-210 Fourier transform infrared spectrometer.

**Total Synthesis of Kurasoin A**

(+)-p-Hydroxyphenyllactic Acid Methyl Ester (4)
A solution of (+)-p-hydroxyphenyllactic acid (3, 100 mg, 0.05 mmol) in MeOH (3 ml) was treated with a rapid stream of dry HCl gas until the solution boiled. The solution, saturated with HCl, was then cooled to room temperature and stirred for 1 hour.

The resulting mixture was evaporated to give a yellow solid, which was purified by preparative silica gel chromatography (CHCl₃-MeOH, 10:1) to obtain (±)-p-hydroxyphenyllactic acid methyl ester (4, 80.2 mg, 75%). EIMS m/z 196 (M⁺). HR-EI-MS calcd for C₁₀H₁₂O₄, 196.0735; found, 196.0729. IR (KBr) cm⁻¹ 1740, 2950, 3400. 1H NMR (CDCl₃) δ 2.83 (1H, dd, J = 6.6, 14.0 Hz), 2.99 (1H, dd, J = 4.3, 14.0 Hz), 3.71 (3H, s), 4.37 (1H, m), 6.64 (2H, d, J = 8.5 Hz), 6.97 (2H, d, J = 8.5 Hz).

13C NMR (CDCl₃) δ 41.5, 54.4, 73.3, 117.3, 129.8, 132.5, 156.6, 176.6.

(+)-2-Hydroxy-3-(p-hydroxyphenyl)-N-methoxy-N-methylpropanamide (5)
To a suspension of N,O-dimethylhydroxylamine hydrochloride (196 mg, 2.01 mmol) in CH₂Cl₂ (3.1 ml) was added dropwise 2.0 M trimethylaluminum in hexane (1.0 ml, 2.01 mmol) with concomitant evolution of gas. The resulting homogeneous solution was stirred for 15 minutes at room temperature.

A solution of 4 (55 mg, 0.34 mmol) in CH₂Cl₂ (2 ml) was added dropwise to the aluminum amide solution at room temperature. The resulting solution was stirred at room temperature for 4 hours. The reaction mixture was quenched by 0.5 N HCl solution (5 ml), and the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford a yellow oil, which was purified by preparative silica gel chromatography (CHCl₃-MeOH, 10:1) to obtain (±)-2-hydroxy-3-(p-hydroxyphenyl)-N-methoxy-N-methylpropanamide (5, 43 mg, 67%). EIMS m/z 225 (M⁺). HR-EI-MS calcd for C₁₄H₁₅NO₄, 225.1000; found, 225.1006. IR (KBr) cm⁻¹ 1650, 2940, 3340. 1H NMR (CDCl₃) δ 2.74 (1H, dd, J = 6.9, 13.9 Hz), 2.93 (1H, dd, J = 3.6, 13.9 Hz), 3.17 (3H, s), 3.66 (3H, s), 4.56 (1H, m), 6.59 (2H, d, J = 8.6 Hz), 6.96 (2H, d, J = 8.6 Hz). 13C NMR (CDCl₃) δ 32.5, 39.9, 61.4, 69.8, 115.3, 128.4, 130.5, 154.8, 174.1.

(+)-3-Hydroxy-4-(p-hydroxyphenyl)-1-phenyl-2-butanone (1)
To a solution of 5 (17.9 mg, 0.08 mmol) in THF (10.8 ml) at 0°C was added dropwise 2.0 M benzylmagnesium chloride in THF (200 µl, 0.40 mmol). After 4.5 hours, the reaction mixture was quenched by 5% HCl-MeOH (2 ml) and was warmed to room temperature. The mixture was poured into 10 ml each of CH₂Cl₂ and H₂O, and the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2 x 10 ml). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated in vacuo to afford a yellow oil, which was purified by preparative silica gel chromatography (hexane-EtOAc, 1:1) to obtain (±)-3-hydroxy-4-(p-hydroxyphenyl)-1-phenyl-2-butanone (1, 13.2 mg, 65%). EIMS m/z 256 (M⁺). HR-EI-MS calcd for C₁₆H₁₆O₃, 256.1099; found, 256.1072. IR (KBr) cm⁻¹ 1710, 2920.

**Total Synthesis of Kurasoin B**

(+)-Indollactic Acid Methyl Ester (7)
A solution of (+)-indollactic acid (6, 200 mg, 0.98 mmol) in MeOH (6 ml) was treated with a rapid stream of dry HCl gas until the solution boiled for 30 minutes. The solution, saturated with HCl, was then cooled to room temperature and evaporated to give a yellow oil, which was purified by flash chromatography (hexane-
EtOAc, 3:1) to obtain (±)-indollactic acid methyl ester (7, 128.1mg, 60%). EI-MS m/z 219 (M+). HR-EI-MS calcd for C_{12}H_{13}NO_3, 219.0895; found, 219.0882. IR (KBr) cm^{-1} 1730, 3360, 3400. 1^H NMR (CDCl_3) δ 3.11 (1H, dd, J=6.1, 14.7 Hz), 3.23 (1H, dd, J=4.9, 14.7 Hz), 3.64 (3H, s), 4.45 (1H, q), 7.03~7.19 (4H, m), 7.27 (1H, d, J=7.9 Hz), 7.54 (1H, d, J=7.5 Hz). 13C NMR (CDCl_3) δ 30.2, 52.4, 70.8, 110.0, 111.1, 118.8, 119.5, 122.1, 123.1, 127.5, 136.1, 174.8. 

(±)-2-Hydroxy-3-(3-indolyl)-N-methoxy-N-methylpropanamide (8)

Compound 7 (102.3mg, 0.47mmol) was treated with N',O-dimethylhydroxylamine hydrochloride and trimethylaluminum in a similar manner to that described for the preparation of 5 to obtain (±)-2-hydroxy-3-(3-indolyl)-N-methoxy-N-methylpropanamide (8, 59.4mg, 51%). EI-MS m/z 248 (M+). HR-EI-MS calcd for C_{13}H_{16}N_2O_3, 248.1161; found, 248.1152. IR (KBr) cm^{-1} 1650, 3350, 3400. 1^H NMR (CDCl_3) δ 2.99 (1H, dd, J=7.1, 14.9 Hz), 3.14 (3H, s), 3.31 (1H, dd, J=8.3, 14.9 Hz), 3.67 (3H, s), 4.61~4.62 (1H, m), 7.03~7.19 (4H, m), 7.28 (1H, d, J=6.6 Hz), 7.53 (1H, d, J=7.6 Hz). 13C NMR (CDCl_3) δ 30.5, 32.5, 53.4, 61.4, 69.0, 111.1, 118.5, 119.3, 121.9, 123.1, 127.7, 136.0, 174.2. 

(±)-3-Hydroxy-4-(3-indolyl)-1-phenyl-2-butanone (2)

Compound 8 (51.8mg, 0.21mmol) was treated with benzylmagnesium chloride in a similar manner to that described for the preparation of 1 to obtain the (±)-3-hydroxy-4-(3-indolyl)-1-phenyl-2-butanone (2, 28.6mg, 49%). EI-MS m/z 279 (M+). HR-EI-MS calcd for C_{18}H_{17}NO_2, 279.1259; found, 279.1271. IR (KBr) cm^{-1} 1710, 2920.

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References