The Total Synthesis and Absolute Structure of Antifungal Antibiotics (-)-PF1163A and B

Sir:

Antifungal antibiotics (-)-PF1163A and B (1 and 2) were isolated from the fermentation broth of Penicillium sp. by the Meiji Seika Kaisha group. The structure of PF1163B (2) has been deduced by the chemical and X-ray crystallographic analyses. However, the absolute structure of PF1163A (1) including the relative configuration remained undetermined.

Herein, we report the total synthesis of (-)-PF1163A and B (1 and 2) to disclose their absolute structures unambiguously.

From the retrosynthetic perspective, (-)-PF1163B (2) is expected to be constructed reasonably from the unique amino acid 3 and the hydroxy acid 4 (R=H) (Chart 1). The latter may be prepared from optically active citronellol. Although we have synthesized both antipodes of 2 to determine the absolute configurations, only the synthesis of the natural product 2 is conveniently described from Boc-L-tyrosine (5) and (R)-citronellol (8) as follows.

Reaction of 5 with O-silylated hydroxyethyl bromide gave the ester 6, the phenol of which was simultaneously protected. N-Methylation of 6 followed by saponification produced the carboxylic acid 7 (Scheme 1 and Table 1). Ozonolysis of the double bond of 8 followed by Wittig olefination of the resulting aldehyde afforded the unsaturated ester 9. This was converted by reduction and oxidation into the aldehyde 10, which was submitted to the one-carbon elongation reaction to give the other aldehyde 11. Asymmetric synthesis of 13 from 11 was examined under several conditions with a variety of metals and allyl halides (Scheme 2). The best result was realized by the protocol reported by Hafner’s group using a chiral (S,S)-allyltitanium reagent 12, which was prepared from (S,S)-tartrate. The desired (9S)-alcohol 13 was produced in 72% yield with 6:1 selectivity for the (6R,9S)-diastereomer. As direct ozonolysis of 13 gave the corresponding aldehyde in low yield, the hydroxy group was protected to give 14 by diethylisopropyl silyl group. This protecting group has been developed in our laboratories to be removed under reduction conditions using hydrogen and Pd(OH)₂ in MeOH. Ozonolysis of 14 afforded the aldehyde 15, which was submitted to the Wittig reaction followed by reduction with de-O-silylation to afford the hydroxy ester 16.

With both segments 7 and 16 in hand, we turned to the esterification and cyclization.

Conversion of 7 with β-naphthoyl chloride to the mixed anhydride was followed by reaction with 16 to give the ester 17 in high yield. After removal of all protecting groups, the resulting amino acid was cyclized by bis(2-oxo-3-oxazolidinyl)phosphinic chloride (Bop-Cl) to (-)-PF1163B (2), which was identical with the natural antibiotic in all respects. The ¹H-NMR spectrum exhibited similarly broad signals and was superimposable on that of the natural product.

Next, (-)-PF1163A (1) was synthesized following similar synthetic strategies (Scheme 3).

However, in 1, even relative configurations remained...
undetermined. We anticipated that all configurations except at C-11 of the hydroxy acid moiety would be the same as those of 2 and, consequently, synthesized first the C-11 diastereomers (20 and 20') of the hydroxy acid from the key aldehyde 15 to determine the absolute configuration.

Enantioselective allyltitanation of 15 with the (R,R)-Ti-complex 18\(^3\) gave preferentially the (l\(^{\text{ll}}\))-alcohol 19, while reaction with (S,S)-Ti-complex 12 gave the diastereomeric (l\(^{\text{ll}}\))-alcohol 19' as mentioned before. Silylation of 19 to give the O-TBS derivative followed by treatment with H\(_2\) and Pd(OH)\(_2\) in MeOH afforded the saturated hydroxy ester 20 with selective removal of the O-diethylisopropylsilyl group\(^4\). The diastereomer 20' was obtained from 19' in the same way. Treatment of 20 with isopropenyl methyl ether gave no acetonated derivative, while 20' gave the acetonide 21, indicating that 20 and 20' have the anti- and syn-diols, respectively. Finally, 20 proved to be suitable for the synthesis of (-)-1163A (1), because the methyl ester 22, which was derived from 20 by methanolation, was identical with the naturally derived sample\(^2\). These results showed that the hydroxy acid moiety of 1 has the (6R,9S,11\(^{\text{ll}}\))-configuration.

Esterification of 7 with 20 was accomplished under the conditions described using β-naphthoyl chloride\(^5\) to give the ester 23, from which all protecting groups were removed by 95% TFA. The resulting amino acid having two hydroxy groups was submitted to cyclization\(^6\) with preferential formation of the amido bond to give exclusively (-)-PF1163A (1) without formation of any lactones. The \(^1\)H-NMR spectrum of 1 was completely superimposable on that of the natural product, although all the signals were very broad as reported in the previous paper\(^1,2\).

Finally, the product 1 was identical with the natural antibiotic in all respects, completing the total synthesis and configurational analysis.
Table 1-1. Physico-chemical properties of products.

<table>
<thead>
<tr>
<th>No.</th>
<th>$\lbrack \alpha \rbrack_D$</th>
<th>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-91</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>2</td>
<td>-115</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>6</td>
<td>+6.7</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>7</td>
<td>-25</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>9</td>
<td>+6.1</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>10</td>
<td>+3.9</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>11</td>
<td>+0.8</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>13</td>
<td>-3.3</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>14</td>
<td>-7.3</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>15</td>
<td>+10</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>16</td>
<td>+1.4</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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<tr>
<td>17</td>
<td>-15</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>19</td>
<td>+20</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>20</td>
<td>+18</td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl3; $\delta$ ppm; J Hz)</td>
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</table>
Table 1-2. Physico-chemical properties of products.

<table>
<thead>
<tr>
<th>No.</th>
<th>[α]D</th>
<th>$^1$H-NMR (300, 400, 500 or 600MHz; CDCl₃; δ ppm; J Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22</td>
<td>+16</td>
<td>0.87 (3H, d, J=7.0 Hz), 0.94 (3H, t, J=7.0 Hz), 1.05 - 1.67 (15H, m), 1.61 (2H, dd, J=5.5, 5.5 Hz), 2.00 - 2.50 (2H, br), 2.31 (2H, t, J=7.5 Hz), 3.67 (3H, s), 3.91 (1H, m), 3.96 (1H, m), 0.01 &amp; 0.03 (6H, s), 0.10 (6H, s), 0.80 - 0.92 (6H, m), 0.88 (9H, s), 0.91 (9H, s), 1.31 &amp; 1.36 (9H, s), 1.44 (9H, s), 1.00 - 1.70 (17H, m), 2.20 (2H, t, J=8.0 Hz), 2.70 &amp; 2.76 (3H, s), 2.84 &amp; 3.21 (2H, m), 3.66 (1H, m), 3.95 (2H, m), 3.99 (2H, m), 4.71 &amp; 4.96 (1H, m), 4.93 (1H, m), 6.81 &amp; 6.82 (2H, d, J=8.5 Hz), 7.07 &amp; 7.11 (2H, d, J=8.5 Hz)</td>
</tr>
<tr>
<td>23</td>
<td>-5.2</td>
<td>(c 0.85, MeOH)</td>
</tr>
</tbody>
</table>

Scheme 2

11 \[ \text{MgBr} \] \[ \rightarrow \] \[ 9S \] \[ \text{Me} \] \[ \text{CO}_2\text{Bu} \] \[ 13 : R = H \] \[ \text{O}_3 \text{ then Ph}_3\text{P} / \text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 15\text{min} \] \[ 71\% \]

12 \[ / \text{EtO}, -78^\circ\text{C}, 2\text{hr} \] \[ 72\% \]

15 \[ \text{Me} \] \[ \text{CO}_2\text{Bu} \] \[ 1) \text{PPh}_3\text{Br}^{-} \text{see BuLi/THF} -78^\circ\text{C}, 4\text{hr} \] \[ 2) \text{H}_2, \text{Pd(OH)}_2 / \text{MeOH, rt, 15hr} \] \[ 69\% \]

16

7 + 16 \[ \text{TEA/THF, rt then DMAP / PhMe, rt, 3hr} \] \[ 95\% \]

1) 95%TFA / CH₂Cl₂, rt, 2hr
2) Bop-Cl, TEA / CH₂Cl₂, 0°C, 48hr

62%
Acknowledgment

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References


