SYNTHESSES AND BIOLOGICAL ACTIVITIES OF THIOTETROMYCIN ANALOGS

Sir:

As reported in the previous paper, thiotetromycin (1) produced by Streptomyces sp. OM-674 contains a unique thiolactonic structure and shows selective activity against Bacteroides fragilis as well as inhibiting the proliferative response of T-cells stimulated with concanavalin A. In the course of structure-activity studies for the thiolactonic antibiotics, we have synthesized thiotetromycin analogs which possess a methyl and a benzyl group at C-4 of thiolactone. This paper describes the convergent synthesis of thiolactones, and their biological activities.

Ethyl 2-mercaptopropionate, possessing a methyl group to provide an alkyl residue at C-4 of the thiolactone, was chosen as starting material. The thiol group was protected as a thioether by treatment with methoxyethoxymethyl (MEM) chloride and triethylamine at room temperature (86% yield). Metalation of 6 with lithium diisopropylamide (LDA) in tetrahydrofuran at -78°C followed by alkylation with benzyl chloride gave 7 in 94% yield. Ester (7) was hydrolyzed with sodium hydroxide in ethanol and water at 50°C to give the corresponding acid, which was immediately treated with thionyl chloride at reflux to afford a 92% yield of the acid chloride (8). Reactions of 8 with sodio anions of methyl malonate and methyl acetoacetate afforded undesirable acylation products of the corresponding enols. The lithio anions of ethyl acetate, ethyl phenylacetate, and methyl 1-butylrate generated, instead by treatment with LDA in tetrahydrofuran at -78°C, gave rise to C-acylation products as 1:1 mixtures of diastereoisomers (except for 9b) in 55-72% yield. The SMEM group was cleaved by using mercuric acetate in aqueous acetic acid followed by hydrogen sulfide (61-80% yield). Hydrolysis of the

![Chart 1](image)

![Chart 2](image)
resulting thiols (10a, c) with sodium hydroxide, and then acidic workup gave the cyclized thiolactones (2, 4) in 80-85% yield. Thiolactonization of the mercapto acid (10d) was surprisingly difficult. Standard methods such as simple acid catalysis served only to destroy the substrate, however, the trifluoroacetic anhydride method did work to give rise to the enol trifluoroacetate (11) of the thiolactone, which could be removed easily by methanolysis at room temperature to yield a 82% yield of thiolactone (3). Introduction of the acyl group at C-2 of the thiolactone was performed by Lewis-acid catalyzed acylation. Treatment of 11 with acetyl chloride in the presence of BF3-etherate at 50°C followed by methanolysis at room temperature afforded a 46% yield of 5. The physicochemical properties of the thiolactones are summarized in Table 1.

Inhibitory activities of the synthesized thiolactones against B. fragilis and concanavalin A-stimulated T-cells are summarized in Table 2. Most of the thiolactones show weak activities against B. fragilis, however, thiolactones (4, 5) possess enhanced inhibitory activities against T-cells. These results suggest that electron-withdrawing groups at C-2 of the thiolactone play an important role in the inhibitory activity against T-cells stimulated with concanavalin A whereas the diene residue of thiotetromycin contributes to the antibiotic activity.

In order to further clarify the structure-activity relationship, synthetic studies of thiotetromycin analogs designed to functionalize the diene unit are currently in hand.

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### Table 1. Physicochemical properties of thiolactones (2-5).

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Mp (°C)</th>
<th>IR (cm⁻¹)</th>
<th>NMR (δ, ppm)</th>
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<td>2</td>
<td>107-108</td>
<td>1610</td>
<td>0.85 (3H, t, J=7 Hz)</td>
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<td>1.70 (3H, s)</td>
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<td>2.14 (2H, q, J=7 Hz)</td>
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<td></td>
<td>3.16 (2H, s)</td>
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<td>7.18 (5H, s)</td>
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<tr>
<td>3</td>
<td>119-120</td>
<td>1610</td>
<td>1.68 (3H, s)</td>
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<td></td>
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<td>3.18 (2H, s)</td>
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<td></td>
<td>7.26 (5H, s)</td>
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<tr>
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<td>1600</td>
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<td>7.29 (5H, s)</td>
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<td>7.1-7.5 (5H, m)</td>
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<td>5</td>
<td>163-164</td>
<td>1580d</td>
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<td>7.11 (5H, s)</td>
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### Table 2. Inhibitory activities against B. fragilis and concanavalin A stimulated T-cells.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>MIC (µg/ml)</th>
<th>ID₅₀ (µg/ml)</th>
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<tr>
<td>1</td>
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<td>2</td>
<td>50</td>
<td>155</td>
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<td>3</td>
<td>100</td>
<td>34</td>
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<tr>
<td>4</td>
<td>100</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>9</td>
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</tbody>
</table>

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*a* Elemental analysis of all compounds are in good agreement with the calculated value.

*b* Melting points are uncorrected.

*c* IR spectra were measured in CHCl₃ solution or KBr solution.

*d* Chemical shifts are reported in parts per million relative to internal Me₃Si shift =0 in CDCl₃ or (CD₃)₂CO solution.
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References

