

## STRUCTURE-ACTIVITY RELATIONSHIP OF LIPOPEPTIDE FROM OUTER MEMBRANE OF *ESCHERICHIA COLI* AND SYNTHESIS OF HIGHLY IMMUNOPOTENTING LIPOPEPTIDE DERIVATIVES WITH AN ACHIRAL LIPO-PART

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For outstanding the structure-activity relationship of lipopeptide derivatives, high biologically active lipopeptide derivatives with an achiral lipo-part were newly synthesized

**KEYWORDS** lipoprotein; lipopeptide derivative having an achiral lipo-part; mitogenic activity

It has been known that a lipopeptide from the outer membrane of *Escherichia coli* is an active mitogen and polyclonal activator for B lymphocytes.<sup>1-4)</sup> In the preceding paper,<sup>5-8)</sup> we reported a new synthesis of chiral lipopeptides, their derivatives(I) with higher activity than the native lipopeptide and the structure-activity relationship between number of amino acids and biological activity. Now we focused our attention on the lipo-part; to investigate the influence of the length and number of the aliphatic chain and its mitogenic activity, and also to find high biologically active lipopeptide derivatives with an achiral lipo-part, we have synthesized lipopeptide derivatives with one aliphatic chain linked to the propane skeleton 1,<sup>9)</sup> 2<sup>10)</sup> linked to the ethane 3,<sup>11)</sup> 4<sup>12)</sup> by an ether bond, linked to the propane skeleton 5,<sup>13)</sup> 6,<sup>14)</sup> 7<sup>15)</sup> by an ester bond and with two aliphatic chain linked to the propane or the ethane skeleton and cystein N-terminal 8,<sup>16)</sup> 9,<sup>17)</sup> 2-cysteinylmethyl glycerol type 10,<sup>18)</sup> 11,<sup>19)</sup> and 2-cysteinyl glycerol type 12<sup>20)</sup>(shown in Fig.2).

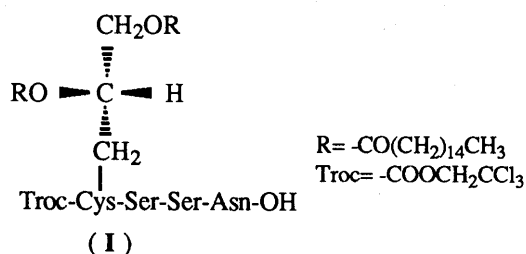


Fig. 1. Structure of Lipopeptide Derivative with High Activity

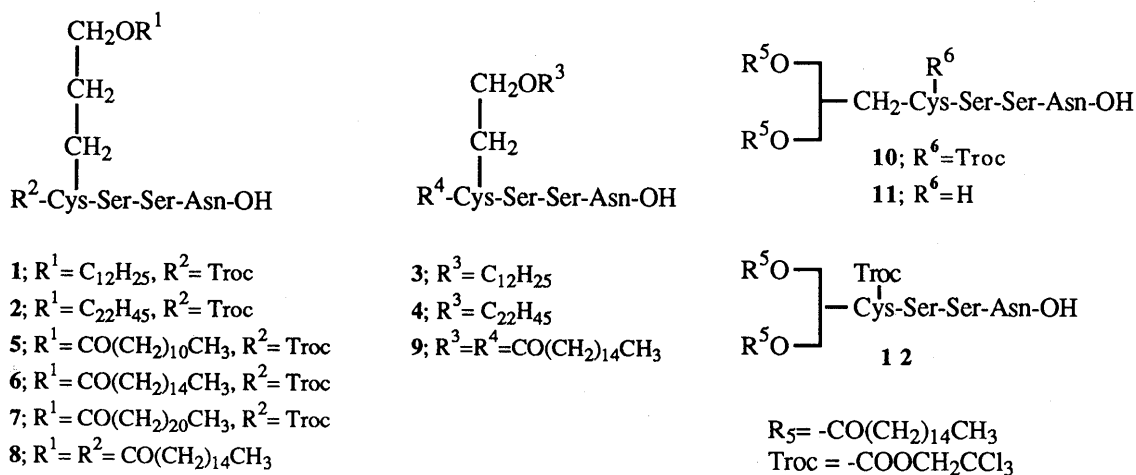


Fig. 2. Structure of Lipopeptide Derivatives

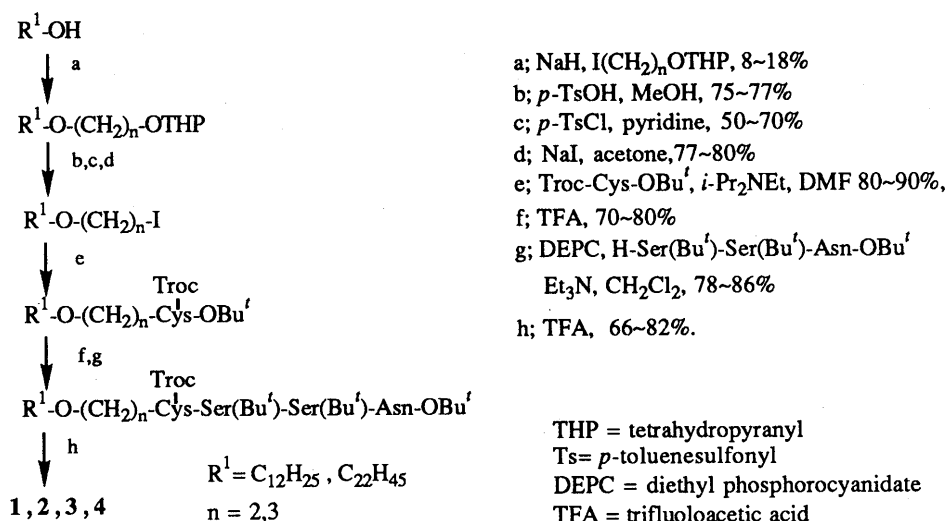


Chart 1. Synthesis of Ether Type Lipopeptide Derivatives

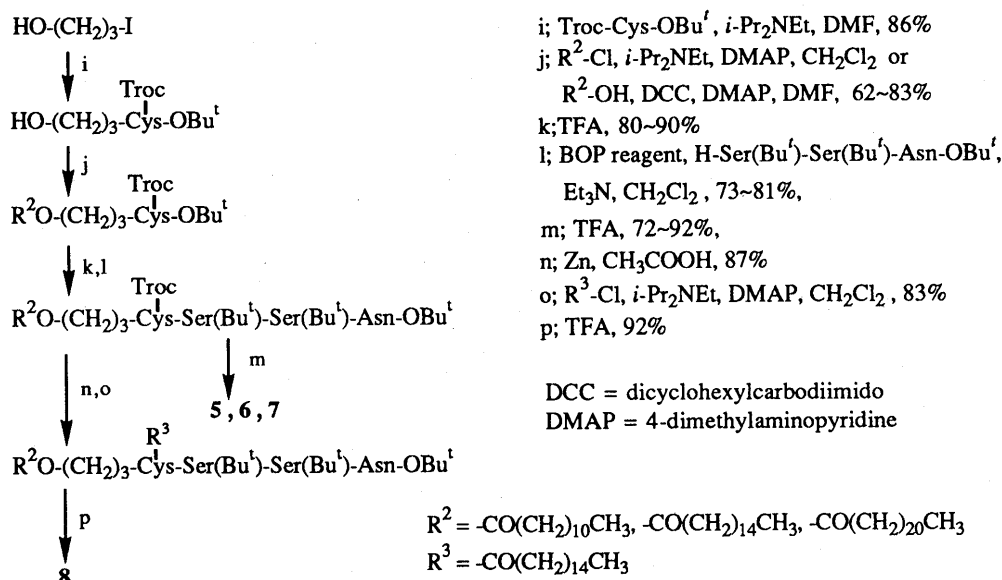
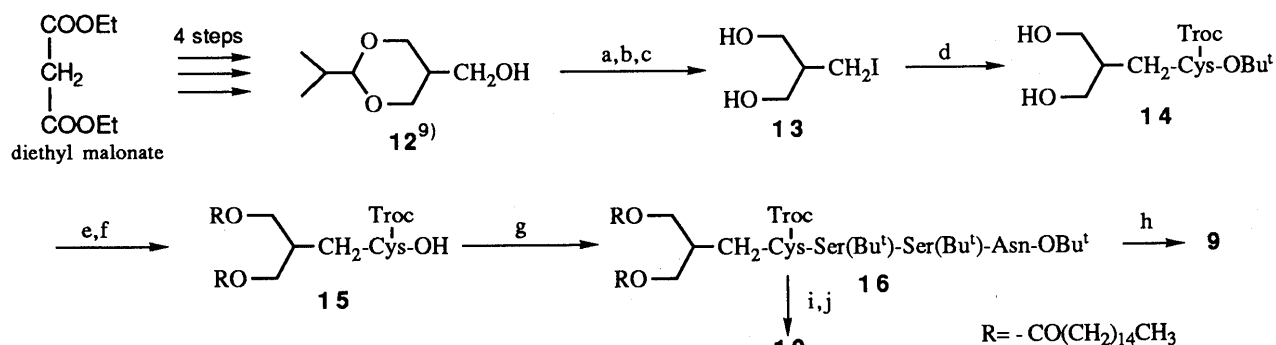
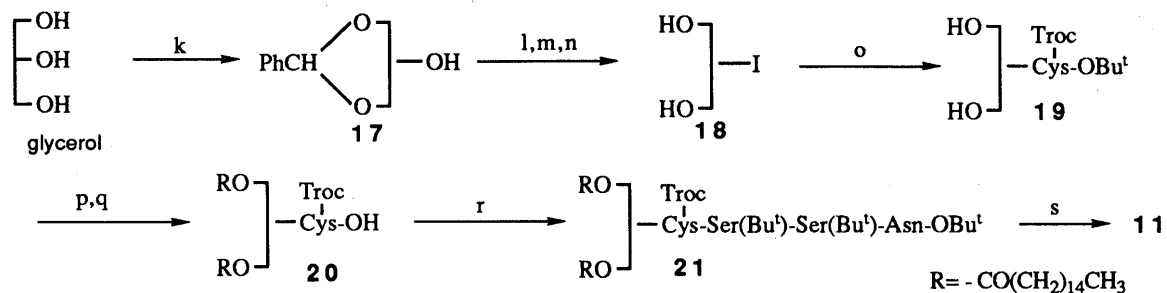


Chart 2. Synthesis of Ester Type Lipopeptide Derivatives



a; Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, TsCl, 60% b; MeOH, 1N HCl, 85% c; NaI, acetone, 40% d; Troc-Cys-OBu<sup>t</sup>, *i*-Pr<sub>2</sub>NEt, DMF, 86% e; CH<sub>3</sub>(CH<sub>2</sub>)<sub>14</sub>COCl, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, DMAP, 87% f; TFA, 64% g; BOP reagent, Et<sub>3</sub>N, H-Ser(Bu<sup>t</sup>)-Ser(Bu<sup>t</sup>)-Asn-OBu<sup>t</sup>, CH<sub>2</sub>Cl<sub>2</sub>, 56% h; TFA, 53% i; Zn, AcOH, 85% j; TFA, 80%.

Chart 3



k; PhCHO, benzene, sulfosalicylic acid, 18% l; Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, TsCl, 63% m; MeOH, 1N HCl, 82% n; NaI, acetone, 46% o; Troc-Cys-OBu<sup>t</sup>, *i*-Pr<sub>2</sub>NEt, DMF, 28% p; CH<sub>3</sub>(CH<sub>2</sub>)<sub>14</sub>COCl, DMAP, *i*-Pr<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 65% q; TFA, 81% r; BOP reagent, Et<sub>3</sub>N, H-Ser(Bu<sup>t</sup>)-Ser(Bu<sup>t</sup>)-Asn-OBu<sup>t</sup>, CH<sub>2</sub>Cl<sub>2</sub>, 65% s; TFA, 65%.

Chart 4

The mitogenic activity of all compounds 1~12 were measured and compared with the natural lipopeptide derivative<sup>22)</sup> (I). The activities of 1~9 were greatly reduced, and compound 10,11 did not show activity as high as that of compound (I), while compound 12 had the same degree of activity as compound (I). These results indicate that the lipopeptide derivatives with one aliphatic chain cannot show a high activity and that glyceryl part is necessary for lipopeptide derivatives to show a higher activity.

## REFERENCES AND NOTES

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- 9) mp 164~166°C, [α]<sub>D</sub><sup>22</sup> -5.4°(c 0.36, CHCl<sub>3</sub>), FABMS(*m/z*) 810(M+H)<sup>+</sup>.
- 10) mp 163~165°C, [α]<sub>D</sub><sup>22</sup> -8.4°(c 0.21, CHCl<sub>3</sub>), FABMS(*m/z*) 952(M+H)<sup>+</sup>.
- 11) mp 167~169°C, [α]<sub>D</sub><sup>22</sup> -15.3°(c 0.19, MeOH), FABMS(*m/z*) 796(M+H)<sup>+</sup>.
- 12) mp 168~170°C, [α]<sub>D</sub><sup>22</sup> -3.5°(c 0.22, CHCl<sub>3</sub>:MeOH=1;1), FABMS(*m/z*) 936(M+H)<sup>+</sup>.
- 13) mp 161~164°C, [α]<sub>D</sub><sup>22</sup> -3.8°(c 0.40, CHCl<sub>3</sub>), FABMS(*m/z*) 824(M+H)<sup>+</sup>.
- 14) mp 169~171°C, [α]<sub>D</sub><sup>22</sup> -4.2°(c 0.33, CHCl<sub>3</sub>), FABMS(*m/z*) 880(M+H)<sup>+</sup>.
- 15) mp 170~173°C, [α]<sub>D</sub><sup>22</sup> -4.3°(c 0.32, CHCl<sub>3</sub>), FABMS(*m/z*) 964(M+H)<sup>+</sup>.
- 16) mp 204~206°C, FABMS(*m/z*) 945(M+H)<sup>+</sup>.
- 17) mp 205~207°C, FABMS(*m/z*) 931(M+H)<sup>+</sup>.
- 18) mp 170~172°C, [α]<sub>D</sub><sup>22</sup> +10.4°(c 0.20, DMF), FABMS(*m/z*) 1149(M+H)<sup>+</sup>.
- 19) mp 238~240°C(dec), [α]<sub>D</sub><sup>22</sup> +7.0°(c 1.44, CHCl<sub>3</sub>), FABMS(*m/z*) 975(M+H)<sup>+</sup>.
- 20) mp 192~194°C, [α]<sub>D</sub><sup>22</sup> -10.0°(c 0.32, CHCl<sub>3</sub>), FABMS(*m/z*) 1135(M+H)<sup>+</sup>.
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- 22) The detailed paper will be published elsewhere.

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