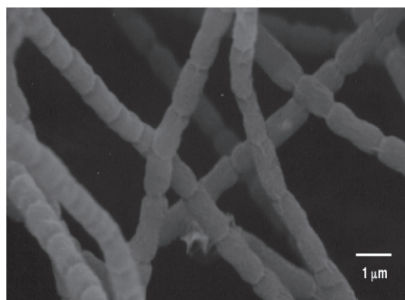


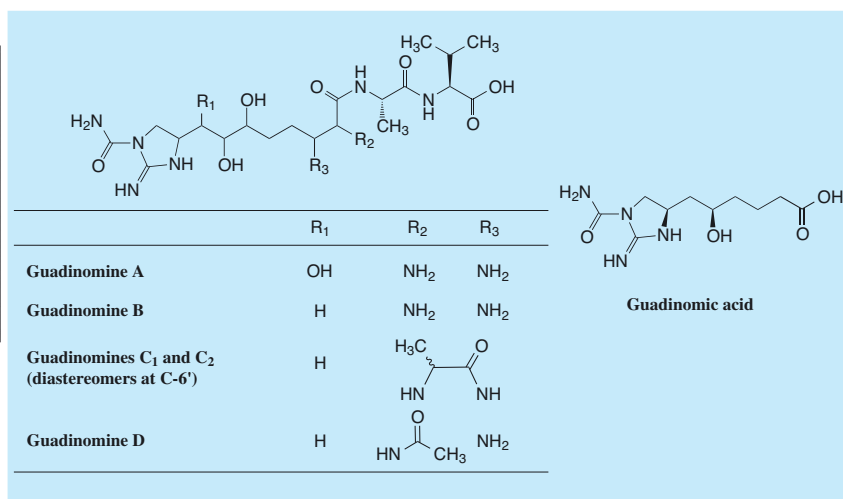
# Guadinomine

## 1. Discovery, producing organism and structures<sup>1,2)</sup>

Guadinomines were found from the culture broth of the actinomycete strain K01-0509 as inhibitors of Type III secretion system (TTSS), which is a common virulence system present in many gram-negative bacteria. Guadinomines A-D consist of a carbamoylated cyclic guanidinyll moiety, an alkyl chain moiety and an L-Ala-L-Val moiety in common. While guadinomic acid is a smaller molecule consisting of a carbamoylated cyclic guanidinyll moiety and a hydroxyl hexanoate moiety.<sup>2)</sup> The total synthesis of guadinomic acid and guadinomines B and C<sub>2</sub> have been reported by Ōmura's group<sup>3,5,6)</sup> (See Appendix-I).



*Streptomyces* sp. K01-0509  
Bar: 1 μm

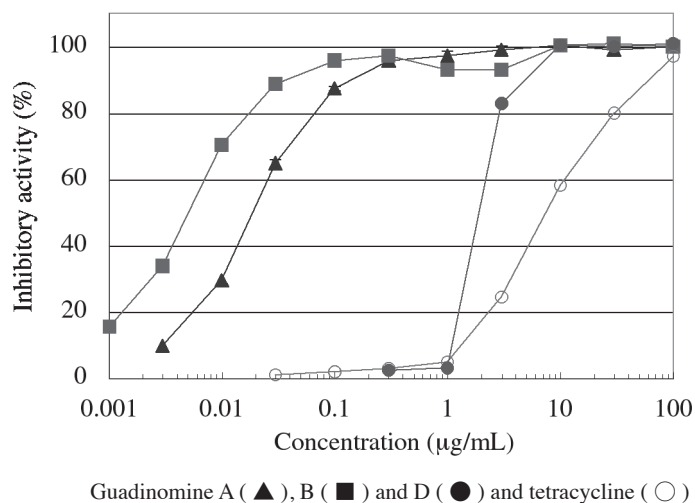


## 2. Physical data (Guadinomine A)

White powder. C<sub>20</sub>H<sub>38</sub>N<sub>8</sub>O<sub>8</sub>; mol wt 518.56. Sol. in H<sub>2</sub>O, MeOH. Insol. in EtOAc, CHCl<sub>3</sub>.

## 3. Biological activity<sup>1)</sup>

1) Guadinomines A and B showed potent inhibition of TTSS-induced hemolysis with IC<sub>50</sub> values of 0.02 and 0.007 μg/ml, respectively. Guadinomine D showed moderate activity (IC<sub>50</sub>: 8.5 μg/ml), but guadinomines C<sub>1</sub>, C<sub>2</sub> and guadinomic acid exhibited no activity.



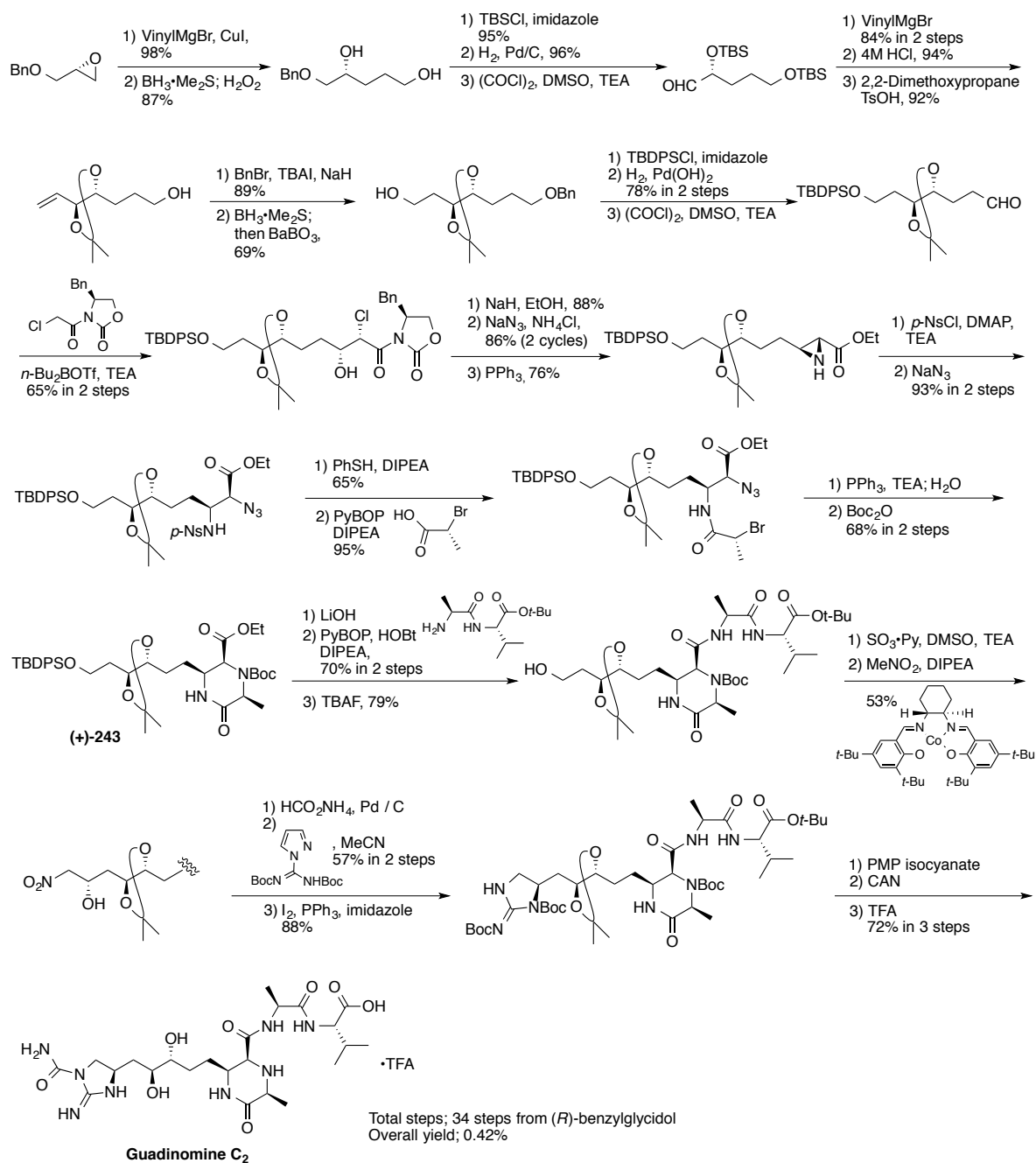
2) All guadinomines showed no antimicrobial activity against yeasts, fungi and gram-positive and gram-negative bacteria at 10 μg/6 mm disk by the paper disk method.

#### 4. Biosynthesis<sup>4)</sup>

The biosynthetic gene cluster for guadinomine was identified and the biosynthetic pathway was proposed. Guadinomines are synthesized from a unique guanidinoacetate starter unit by a chimeric multimodular polyketide synthase, a nonribosomal peptide synthetase, carbamoyltransferase and tailoring enzymes.

#### 5. Total synthesis<sup>5,6)</sup>

Below is scheme of the total synthesis of guadinomine C<sub>2</sub> achieved by Ōmura's group (See Appendix-I).



## 6. References

1. [1016] M. Iwatsuki *et al.*, *J. Antibiot.* **61**, 222-229 (2008)
2. [1017] M. Iwatsuki *et al.*, *J. Antibiot.* **61**, 230-236 (2008)
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4. [1132] T. C. Holmes *et al.*, *J. Am. Chem. Soc.* **134**, 17797-17806 (2012)
5. [1006] T. Hirose *et al.*, *Chem. Eur. J.* **14**, 8220-8238 (2008)
6. [1109] T. Hirose *et al.*, *J. Syn. Org. Chem., Jpn.* **69**, 775-788 (2011)