

First Total Synthesis and Determination of Absolute Configuration of Guadinomines, Potent Inhibitors of Type III Secretion System

○Tomoyasu Hirose, Toshiaki Sunazuka, Tsuchiya Satoshi, Tanaka Toshiaki, Kojima Yasuhiro and Satoshi Ōmura

(The Kitasato Institute, and Kitasato Institute for Life science, Kitasato University)

Enteropathogenic *Escherichia coli* (EPEC) belong to a family of related bacterial pathogens, including enterohemorrhagic *E. coli* (EHEC) O157:H7 and other human and animal diarrheagenic pathogens that form attaching and effacing lesions on host epithelial surfaces. Intimate attachment requires the type III-mediated secretion of bacterial proteins, several of which are translocated directly into the host cell. Therefore, it may be possible that the interruption of type III-mediated secretion relieves infectious diarrhea without elimination of microbial pathogens.

In the course of our search for inhibitors of the type III-mediated secretion system in microorganisms, Guadinomines A (**1**), B (**2**), C₁ (**3**), C₂ (**4**) and K01-0509 B (**5**) were discovered from the fermentation broth of *Streptomyces* sp. K01-0509 (**Fig. 1**). Due to the significant activity and the unique structure of Guadinomines, we undertook their total synthesis.

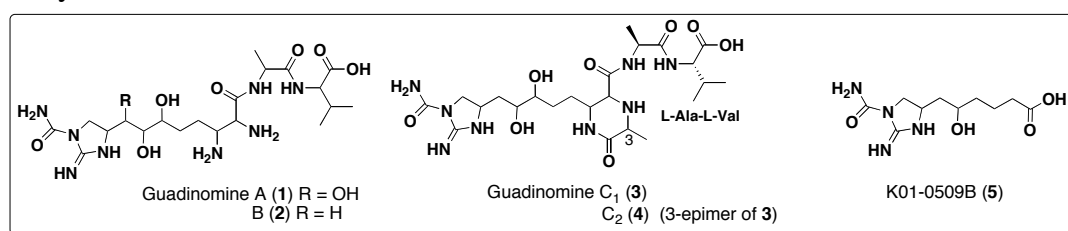


Fig. 1

We achieved the asymmetric total synthesis and determination of absolute configuration of Guadinomine B (**2**) and C₂ (**4**), involving asymmetric syntheses of K01-0509 B (**5**). The total synthesis of **4** features diastereoselective nucleophilic addition for enantioselective preparation of 1, 2-diol unit and the stereocontrolled construction of piperazinone moiety entailing Evans asymmetric aldol reaction, aziridine formation, regioselective azidolysis and S_N2 cyclization. Finally, we could complete to access Guadinomine C₂ (**4**) by asymmetric nitroaldol reaction, followed by iodine-mediated redox cyclization to form cyclicguanidine moiety. Synthetic **4** was identical to the natural **4** in all respects. Therefore, we could determine absolute configuration of natural Guadinomine C₂ (**4**).

The first total synthesis and determination of absolute configuration of Guadinomine B (**2**) will be also discussed.