27O-ISMS43 **Synthesis and Mechanistic Studies of Biakamides, Naturally-occurring Anti-austerity Agents Targeting Mitochondria**

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The microenvironment in tumor is suffered from limited supply of oxygen and nutrients. Some cancer cells such as pancreatic cancer are known to adapt these severe conditions and grow, and to acquire resistance to cancer chemotherapy and irradiation. Therefore, selective growth inhibitors against cancer cells under nutrient-starved conditions have the potential to be anticancer drugs with novel mode of action, and to be chemical tools for elucidating the adaptation mechanism to the conditions. Recently, we isolated novel polyketides named biakamides A-D as anti-austerity agents against human pancreatic cancer PANC-1 cells.[1] We then executed total synthesis, structure-activity relationship (SAR) study, and mechanistic analysis of biakamides.

Total Syntheses of biakamides were accomplished starting from an optically active 1,5-pentanediol derivative, and SAR study using various synthetic analogs led us to know the participation of some characteristic moieties of biakamides to their anti-austerity activity. Then, we designed and synthesized a photoaffinity probe derived from biakamides, to analyze their intracellular localization. Fluorescence imaging study revealed that the probe was selectively accumulated in mitochondria in PANC-1 cells.

1) Kotoku, N.; Ishida, R.; Matsumoto, H.; Arai, M.; Toda, K.; Setiawan, A.; Muraoka, O.; Kobayashsi, M. *J. Org. Chem.* **2017**, *82*, 1705-1718.