【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Innovative catalysts for the synthesis of large- and medium-sized molecules bearing glycopeptides

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Research Area : Pharmaceutical Chemistry, Synthetic Organic Chemistry
Keyword : Synthetic Chemistry, Catalyst, Glycoside, Peptide, Large- and Medium-size Molecule

【Purpose and Background of the Research】

There has been a recent increase in the number of biomedicines being developed based on antibodies and nucleic acids. Most of the approved biological therapeutic agents are manufactured using biological methods because there are very few chemical tools available. However, there are several issues associated with the biological processes currently used, including (1) they cannot be used to prepare structurally pure compounds; (2) biological synthesis processes are expensive; and (3) the development of site-selective chemical modifications is challenging.

To develop efficient drug production processes, as well as therapeutic agents capable of contributing to life science research, there is an urgent need to establish facile, economical, and scalable synthetic methods for the preparation of chemically modified glycopeptides. However, most routine chemical reactions require the addition of excessive amounts of expensive and toxic dehydrating reagents, which leads to large amounts of chemical waste.

The aim of this project is to establish innovative synthetic methods using new catalysts for large- and medium-sized molecules via the site-selective modification of existing compounds composed of amino acids and monosaccharides.

【Research Methods】

The sustainable synthesis of glycopeptides requires the catalytic formation of peptide and glycosyl bonds without using dehydrating agents. Towards this goal, we have designed a series of new catalysts based on the mechanisms associated with the non-ribosomal peptide synthetase- and glycosidase-catalyzed preparation of peptide and oligosaccharides, respectively (Figure 1).

Catalyst **1a** consists of an arylboronic acid, which could activate the carboxylic acid moiety of an amino acid substrate, and a thiol group, which could act as a nucleophile for the subsequent formation of a thioester. We intend to investigate the catalytic efficiency of **1a** in (1) the aza-Michael addition for the synthesis of *N*-alkoxy-α-amino acids and (2) the formation of peptides without any dehydrating agents. It is envisaged that catalyst **1b** could be used to selectively activate the diol units found in monosaccharides using an arylboronic acid. By tuning the second functional group, we will be able to optimize this catalyst for (3) activation-free glycosylation processes and (4) the divergent synthesis of oligosaccharides.

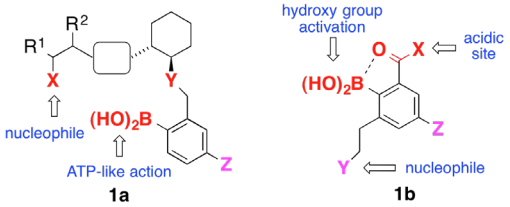

Figure 1 Enzyme-mimetic artificial catalysts

【Expected Research Achievements and Scientific Significance】

This research could result in the development of an environmentally benign manufacturing technology for the preparation of glycopeptides.

The development of new methods for the site-selective modification of glycopeptides will have a considerable impact on the life sciences.

【Publications Relevant to the Project】

- Hayama, N.; Azuma, T.; Kobayashi, Y.; Takemoto, Y. Chiral integrated catalysts composed of bifunctional thiourea and arylboronic acid: Asymmetric aza-Michael addition of α,β-unsaturated carboxylic acids, *Chem. Pharm. Bull.*, **2016**, *64*, 704-717.
- Azuma, T.; Murata, A.; Kobayashi, Y.; Inokuma, T.; Takemoto, Y., A dual arylboronic acid–aminothiourea catalytic system for the asymmetric intramolecular hetero-Michael reaction of α,β-unsaturated carboxylic acids, *Org. Lett.*, **2014**, *16*, 4256-4259.

【Term of Project】 FY2016-2020

【Budget Allocation】 123,300 Thousand Yen

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