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Towards the Enzymatic Synthesis of Carbohydrates

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Editorial

Three major repeating biomacromolecules, nucleic acid, protein, and carbohydrate carry out most of the information transfer in living systems. Nucleic acid carries genetic information in the form of DNA and RNA; PCR (Polymerase Chain Reaction), a revolutionary technique developed in 1983 by K. Mullis, has become an indispensable tool in biological and biomedical researches for nucleic acid synthesis. On the other hand, solid-phase peptide synthesis, pioneered by R. B. Merrifield, allows preparation of desired peptides and proteins *in vitro* in a synthetic manner. However, due to the non-template based biosynthetic pathway of carbohydrates, access structurally defined homogeneous carbohydrate oligomers remains challenging when automated synthesis of oligonucleotides and oligopeptides is common.

Inventing new glycosylation reactions has been a long-standing passion for organic and carbohydrate chemists because carbohydrates represent a class of biopolymers which come in a far greater diversity of structures: branching character, stereochemical issue, various types of glycosidic bonds, and posttranslational modifications. A better understanding of the structures of naturally occurring oligosaccharides provides important information on the composition, linkage, branching type of these oligomers [1]. Key building blocks could thus be designed with appropriate protection groups to ensure desired linkage, branch and anomeric selectivity/specificity. With the development of modern organic chemistry, most naturally occurring oligosaccharides and glycoconjugates are synthetically available. However, these chemical approaches are hindered by tedious and time consuming protection and deprotection steps, unsatisfactory stereoselectivities, and low overall yields, making it impractical to prepare long-chain oligosaccharides and polysaccharides.

Bioorganic chemistry, the topic of a special issue of *Organic Chemistry: Current Research*, addresses exactly this difficulty, with reactions catalyzed by carbohydrate processing enzymes found in nature. Dating back half a century, this field was initiated with the growing understanding of sugar biosynthetic pathways [2] and the corresponding key enzymes: glycosyltransferases, glycosidases and their mutants. Though different enzymes utilize distinct donor molecules (e.g. sugar nucleotide, nitrophenyl glycoside, glycosylfluoride) and follow different mechanisms, the concept of "one enzyme-one linkage" makes enzymatic approaches, especially glycosyltransferases, a much more efficient, more regio/stereoselective, and more feasible route to produce oligosaccharides in large scale.

With the wide use of glycosyltransferases, attention has shifted to the combination of glycosyltransferase with other enzymes to produce more complex carbohydrates or glycoconjugates with biologically important elements. During the past twenty years, a multi-enzyme one-pot reaction fashion with only one purification step has becoming very popular in carbohydrate synthesis since most of the key enzymes are proved to be active under similar reaction conditions [3-4]. In addition to enhanced efficiency, problems such as the availability of high cost sugar nucleotide donors and product inhibition of glycosyltransferases have also been solved by following the biosynthetic pathways: The one-pot reaction can be further conjugated to sugar donor recycling system which generates expensive sugar donors from cheap precursors, realizing large-scale low-cost enzymatic synthesis of complex carbohydrates.

Another subject to emerge over the past decade is that *in vitro* multi-enzyme carbohydrate synthesis is transferred onto solid beads or into whole cells. Wang provided examples ("superbeads") wherein multi-enzymes are immobilized on Ni-nitrilotriacetic acid beads [5]. This technique enables reusing of the immobilized enzymes for several rounds and automated synthesis. To go one step further, many groups illustrated whole engineered bacterial cells expressing multi-enzymes for the large-scale synthesis of carbohydrates. This unique biotechnology avoids isolation and purification of the key enzymes. On this basis, Wang's "superbug" uses a single *Escherichia coli* strain containing all necessary genes for sugar donor regeneration and oligosaccharide synthesis on one single plasmid, demonstrating a powerful living synthetic factory [6].

The above examples testify the progress of carbohydrate synthesis with the development of organic synthesis, protein purification, and molecular genetics. Putative candidates for carbohydrate-active enzymes are adding to the current list with the advances of bioinformatics. Some exciting applications are emerging in this field, including synthesis and modification of carbohydrates *via* metabolic pathway engineering in organisms ranging from bacteria to zebrafish. These achievements, together with earlier examples offer a range of possibilities for the synthesis of biomaterials. In this regard, enzymatic synthesis of carbohydrates affords great opportunists for chemists or synthetic biochemists seeking to find new catalysts and molecular tools. We hope the journal "Organic Chemistry: Current Research" intrigues and inspires more chemists to achieve this goal.

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