PREFACE

Natural products continue to play an important role in the treatment of human disease. Among the most daunting limitations to the use of such species is the need for synthetic approaches to the significant quantities of material needed for biochemical study, preclinical and clinical evaluation and, ultimately, supply. Although synthetic chemistry has made tremendous advances in enantiopure synthesis, material limitations still loom large in the development of natural product therapeutics.

Enzymes are by now well established as chiral catalysts for the construction of small chiral synthons, and the use of various esterases, lipases, oxidoreductases, and other enzymes is well known both for the resolution of racemates and for the desymmetrization of optically inactive meso compounds. But the construction of complex natural products often requires dozens of transformations beginning from such simple starting materials. Complex materials are constructed *in vivo* through multiple sequential enzymatic transformations, producing products of startling complexity with apparent ease. The development of novel *in vivo* biosynthetic pathways might ease the material limitations for drug development: the construction and use of such pathways forms the focus of this volume of *Advances in Enzymology*.

A surprising number of biosynthetic pathways are modular, creating a diversity of products by subtle rearrangement of genes. This modular approach to natural product biosynthesis provides a potentially powerful approach to the construction of large numbers of related complex natural products and to the preparation on scale of single compounds. Two chapters in this volume, by Claudia Schmidt-Dannert and coworkers and by Mattheos Koffas and coworkers, review various aspects of such approaches. Glycosylation is increasingly recognized as a powerful modulator of the biological activities of complex natural products, both with regards to biological lifetimes and affinity and avidity at the target receptor. Chemical glycosylation is notoriously refractive, and *in vivo* approaches to glycosylation are especially attractive: the use of native and engineered

glycosyl transferases for the preparation of glycosylated natural products is described here by Williams and Thorson. Finally, Pimkin and Markham describe the structure, activity and inhibition of the nicotinamide-dependent inosine-5′-monophosphate dehydrogenase.

ERIC J. TOONE