Total Synthesis of Bioactive Natural Products - A Personal Perspective

David Y.-K. Chen, Ph.D.

Department of Chemistry, Seoul National University, Seoul, South Korea

Total synthesis of complex molecular architectures has long been recognized as the most powerful form of training for synthetic organic chemists. This historical discipline has a rich and glorious tradition in both teaching and research, and is an indispensible component in any chemistry department and scientific institutions. Scientifically, in addition to the synthetic challenges associated with the unprecedented molecular architectures, total synthesis serves as a platform for uncovering novel chemical reactivities and enables the understanding of chemo-, regio- and stereoselectivities in complex molecular systems. As such, this powerful vehicle for the invention of new synthetic strategies and methodologies, particularly concerning atom-atom bond forming/breaking reactions, catalysis, and asymmetric inductions, has a cemented position in synthetic organic chemistry.

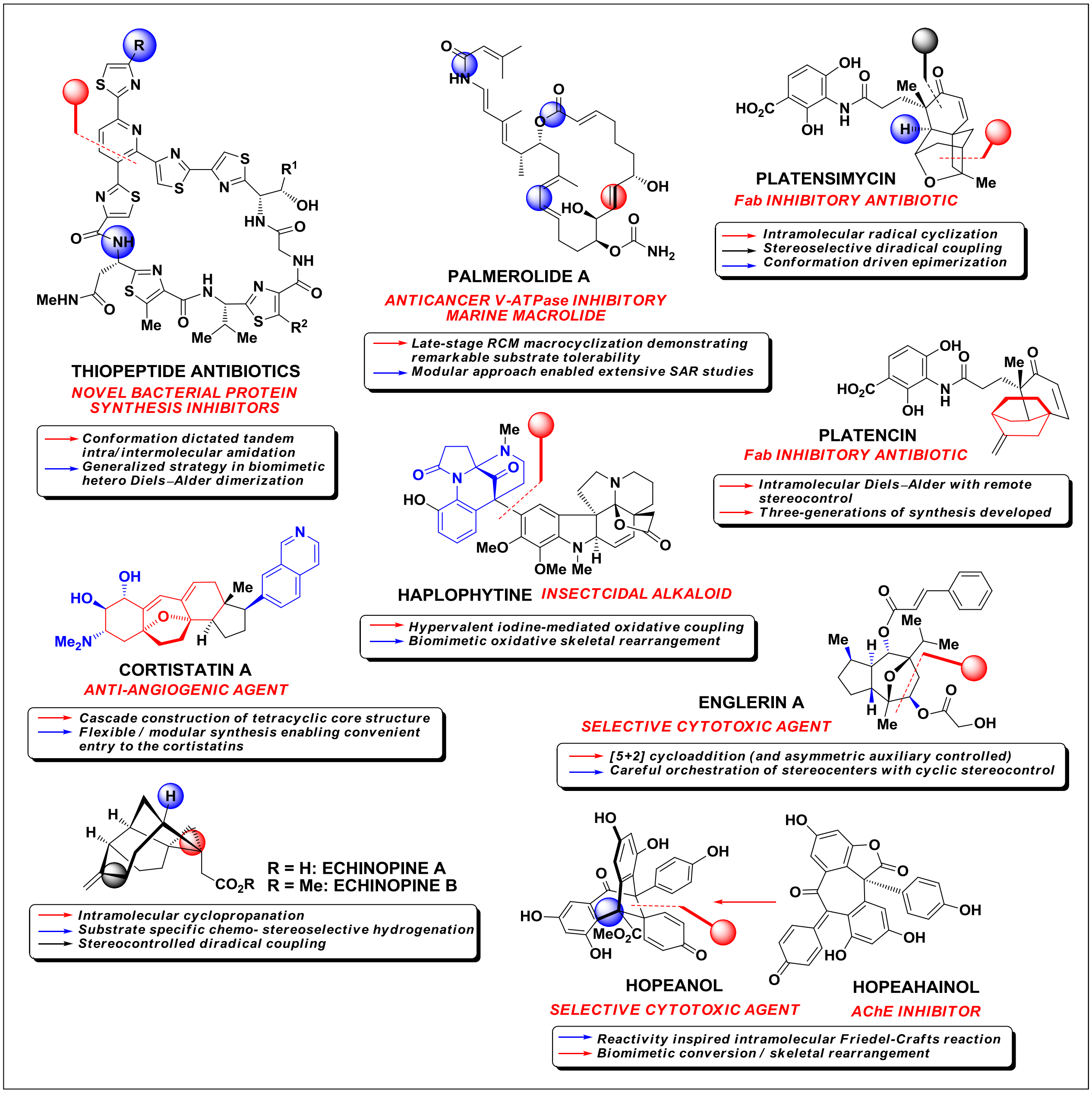

Figure 1: Completed Natural Products: Chemical Synthesis Laboratory @ Biopolis

In conjunction with the biological functions exhibited by these novel molecular entities, particularly in the context of bioactive natural products, application of synthetic organic chemistry to unfold the mechanism of biological action and the possibility of discovering novel chemotherapeutics are of great importance to the medical community. Indeed, a cursory literature survey revealed more than 70% of chemical entities currently in use or being developed in the biomedical community are either originated or inspired by natural products. Furthermore, in recent years there has been a resurgence of interests from the industrial sector concerning the application of natural products in the biomedical context. Clearly, strategic design and orchestrated execution of the synthetic plan are crucial to the success of any target-oriented total synthesis campaign. As such, beyond the scientific context, project planning and a goal-oriented mindset would be an essential component for the training of students and practitioner in this field. Indeed, such a mindset is not only beneficial but essential for the educational and professional development of the students. Therefore, the practice of total synthesis not only serves to advance chemical and biological sciences, but also nurtures the essential personal attributes for the next generation.

Chemical biology investigations of the bioactive natural products including both mechanistic and structure-activity-relationship studies have been carried out in-house or through collaborative activities: i) bacterial protein synthase and fatty acid synthase inhibitory antibiotics, the thiopeptides and platensimycin/platencin, respectively; ii) acetylcholine esterase inhibitory polyphenol, hopeahainol A; iii) V-ATPase inhibitory and selective cytotoxic agent against melanoma cancer cell line, palmerolide A; iv) anti-angiogenic and high affinity ligand for protein kinases ROCK and CDK8/11, cortistatin A; and v) selective cytotoxic agent against renal cancer cell line, englerin A.

1. **Total synthesis**: With the rich and diverse range of structurally novel and architecturally complex natural products in mind, total synthesis is the main thrust of the research activity. Strong emphasis has been placed on the strategic design of novel synthetic transformations, cascade reactions, and biogenetic inspired synthesis, employing modern synthetic technologies based on transition-metal and organo- catalysis. Convergent and yet flexible approaches have been demonstrated in order to maximize overall synthetic efficiency, and enabled the synthesis of rationally designed analogues for structural-activity-relationship studies. Synthetic strategies and technologies developed for the synthesis of the privileged natural product core structure have been investigated in a methodological manner. Novel reactivities uncovered during the total synthesis campaign are also being pursued in depth, and further expanded and applied in the context of target-oriented synthesis and synthetic methodology studies.

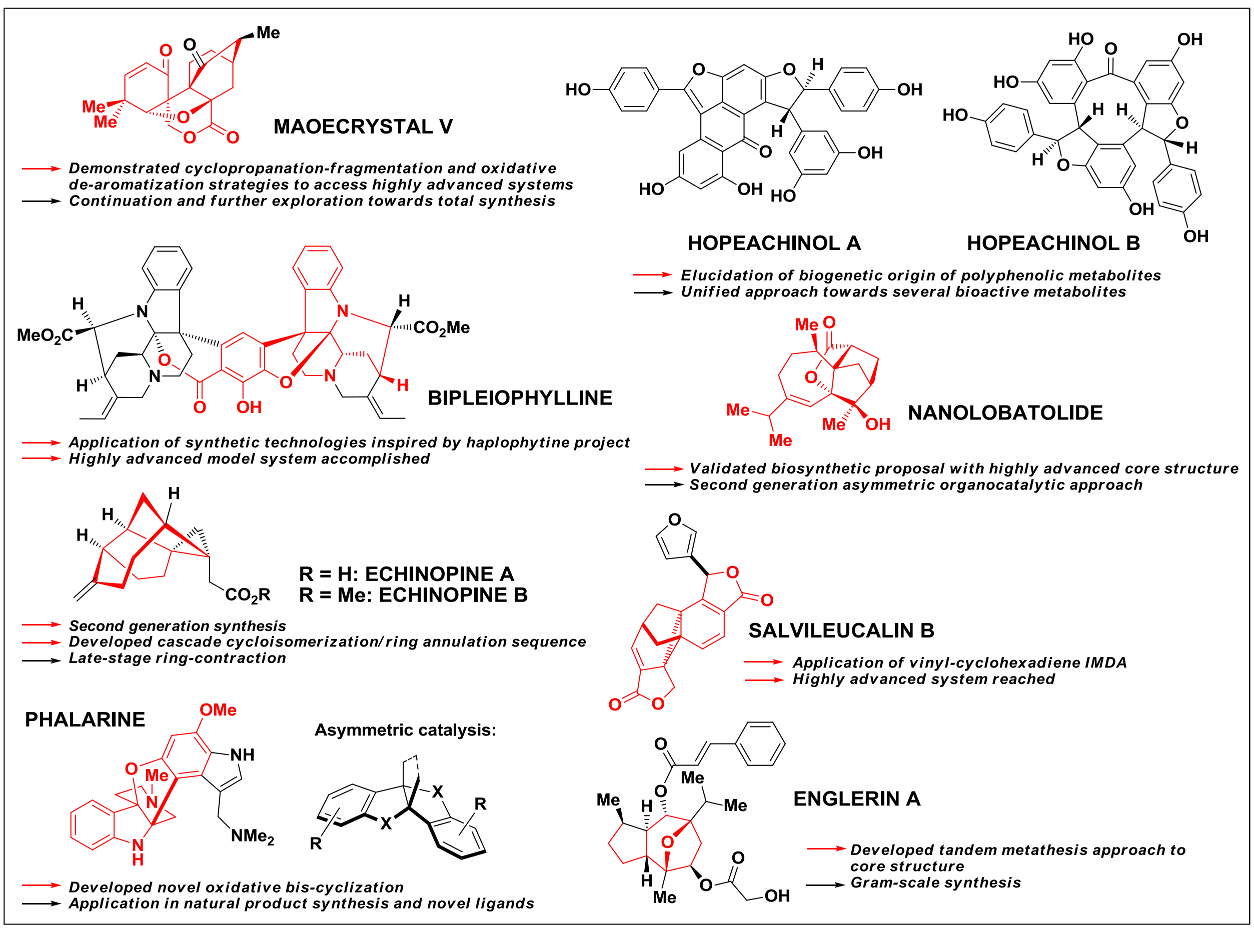

Figure 2: Selected current synthetic work

2. **Chemical biology**: The entry point of any successful chemical biology investigations begin with the identification of bioactive lead compound(s). As such, in the context of bioactive natural products, total synthesis and subsequent SAR profiling is an essential process. The identification of bioactive lead compound(s) are being pursued in parallel with target-identification studies for those compounds demonstrated promising biological profile but the mechanism of action remained unknown. Compound tagging and protein pull-down experiments are being pursued and validated with mass-spectrometry analysis, proteomic and gene expression profiling in a system-biology approach. Natural products often exhibit desirable phenotype outcome for the relevant disease area by exhibiting their biological actions through multiple mechanistic pathways. This offers a unique advantage over the traditional paradigm of "single-target" approach, which often proved inadequate to demonstrate the desired phenotypical outcome, despite exhibited potent activity in *in-vitro* assays. As such, natural product based drug discovery program not only present the opportunity for the discovery and development of novel therapeutics, but more importantly lead to a greater understanding of the underlying biochemical principals of the relevant disease area. Success of the chemical biology program critically depends on the multi-disciplinary, collaborative efforts across chemistry, biology and clinical research groups.

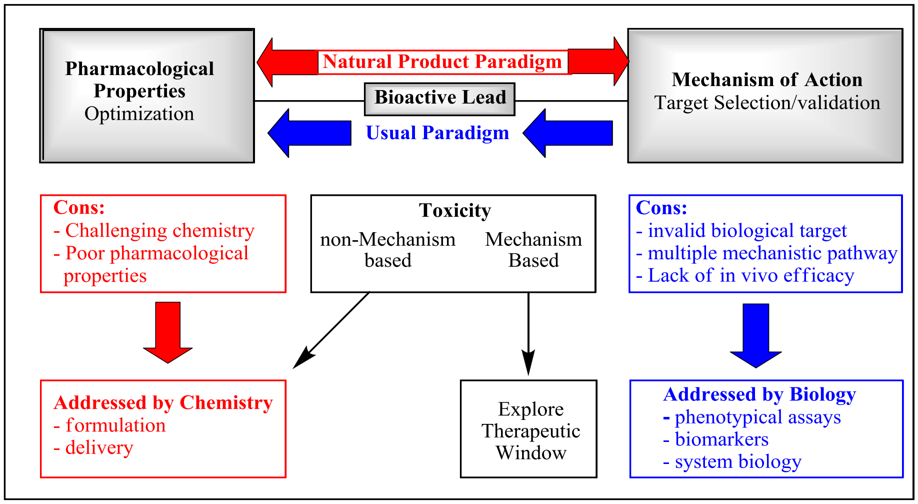

Figure 3: Natural Product based Chemical-Biology

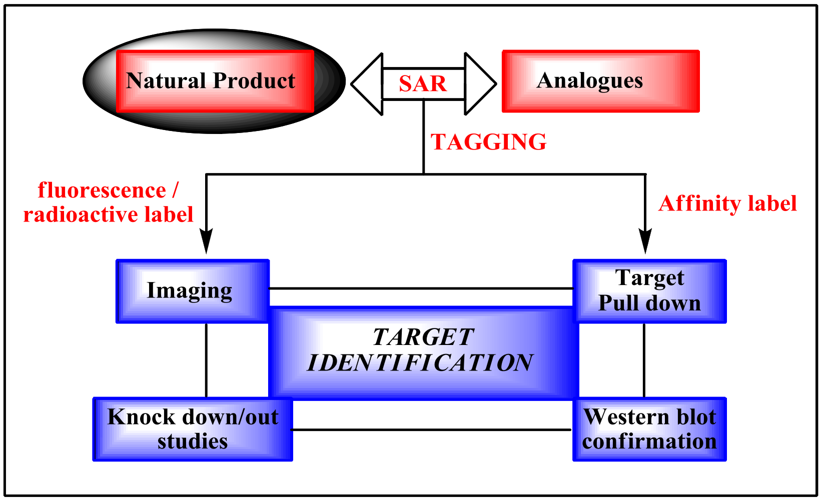

Figure 4: Target-Identification (Target-ID) Workflow

3. **New chemical spaces**: In a recent report, a detailed analysis of chemical entities at various stages of clinical development revealed a positive correlation between "complexity" and the clinical success of the compound. The measure of "complexity" was based on two parameters, fraction of sp^3 hybridized carbons (makes the compound more 3-dimensional), and the number of chiral centers. Indeed, such finding is perhaps not surprising in view of the diminishing level of success from traditional compound libraries containing largely "flat" aromatic moieties, to deliver lead compounds and clinical candidates. As such, an emerging area of research in both academia and industry has been focused on the design and synthesis of structurally complex molecular scaffolds. In view of the structurally complex molecular architectures originated from the bioactive natural products, and the synthetic strategies and technologies developed in the preparation of such structural motifs, library generation based on the privileged natural product scaffold present a valuable entry to "New Chemical Spaces". Indeed, this is an ongoing exercise where the design and synthesis of several core structures have been demonstrated. Such library is a valuable asset in any drug discovery settings, and biological screening of this library against a variety of biological targets will be actively pursued.

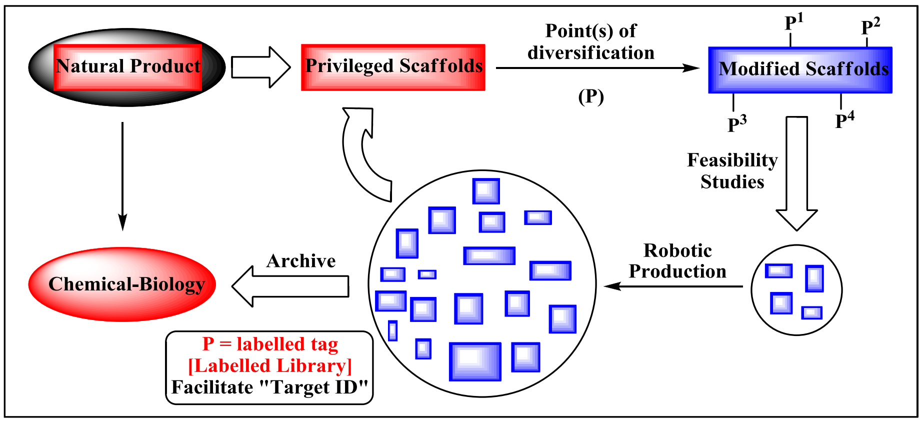

Figure 5: Explore New Chemical Spaces Workflow

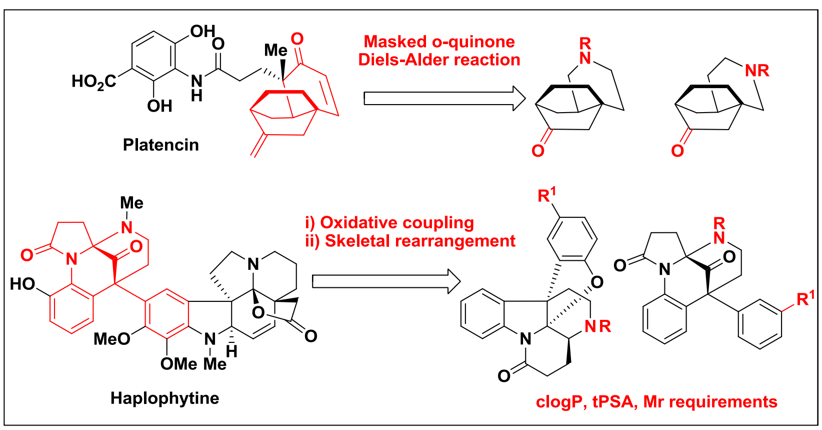

Figure 6: Explore New Chemical Spaces: Natural Product Based Approach

Conclusion:

Target-oriented total synthesis has been, and will continue to serve, as a powerful and indispensable vehicle in advancing chemistry and biology. Understanding chemical reactivities and selectivities through complex molecules provides a valuable entry to the invention of novel synthetic technologies and methodologies, and consequently elevating synthetic chemistry to new heights and dimensions. In parallel, translation of this wealth of synthetic knowledge has implicated wide-ranging applications in both physical and biological sciences. In particular, in the biomedical context, biologically active chemical entity originated and/or inspired by *Nature* has enabled the unraveling of numerous biochemical phenomenons behind the relevant disease areas, and represents a new paradigm in the discovery novel therapeutics. Indeed, it is with great anticipation that the historical and glorious tradition of chemical synthesis will continue to thrive and serves its value in both educational and scientific perspectives, thereby benefiting the humankind and society towards a better quality of life.