Total Synthesis & Drug Pursuits: The Good, the Bad, & the Ugly

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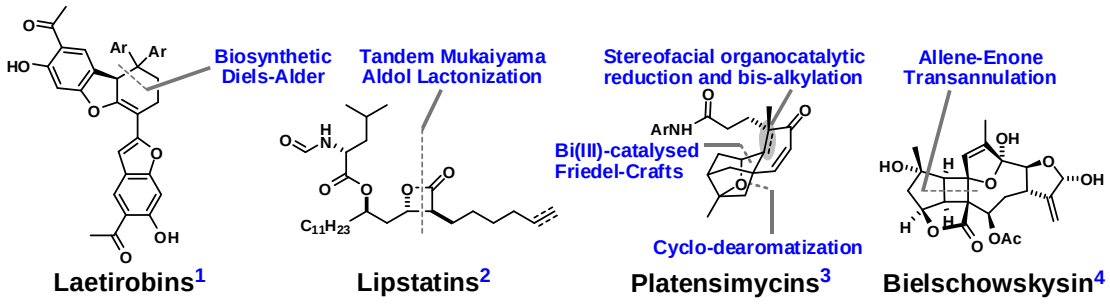
Natural products often unite structure and function in unforeseen ways. Such facets have long driven total synthesis and drug discovery campaigns. The challenge for the chemist is to orchestrate a sequence of synthetic methods into a workable, clever strategy. For the biologist, it is to reveal and cleverly harness drug targets in new, therapeutic ways. In our group, we aim to tackle such challenges by advancing methods and strategies in organic and medicinal chemistry.

Synthetically speaking, the complex multifunctionalized environments of natural products typically limit the effectiveness of a chosen method to achieve a desired reaction. Carbanions, organometalics and countercations, for example, will often experience competing interactions outside their designed or known roles. In a total synthesis or a chemical biology setting, each chosen method may be scrutinized on the basis of several interrelated criteria. These may include: chemo-, regio-, stereoselectivity; substrate-to-substrate, reagent stoichiometry; practicality, efficiency, scalability; solvent, reagent, time economy; atom, redox, protecting-group, step economy; substrate scope, versatility, diversity; steric, electronic, functional-group tolerance; biosynthetic, biomimetic, bio-orthogonal nature; budget, energy, ecology costs.

Such ideals need to be sensibly balanced within a multistep synthesis; whether a key building block is being constructed or a key coupling step is being optimized (or even devised). Herein, we present key methods and strategies that were advanced *en route* to uncovering the chemistry and biology of the (1) laetirobins[1], (2) lipstatins[2], (3) platensimycins[3], and (4) bielschowskysin[4].



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