

Framework editing of bioactive compounds enabled by a catalytic process

Amir H. Hoveyda

A molecule's three-dimensional outline determines how well it recognizes and binds to a biological target, which is why precise framework editing is needed in drug discovery. However, modification of a bioactive molecule that is available in negligible quantities and/or is devoid of a readily diversifiable moiety can be difficult or nearly impossible. There are no programmable synthesis protocols specifically designed to generate surgically altered skeletal alterations. We will discuss the design of such a strategy for a set of bioactive bridged polycyclic alkaloids. At the heart of the approach is the conversion of readily available substrates ("build" stage) by a new catalytic multicomponent diastereo- and enantioselective process ("assemble" stage) to afford a densely functionalized and modifiable core platform. The multifunctional product is first used for a concise total synthesis of a naturally occurring alkaloid and then to access several skeletal variations through a combination of "modify" (one- or two-methylene addition and/or deletion), and "fold" (cyclization) operations. Shape analysis (calculated normalized principal moments of inertia, PMI) reveals that the majority of the eleven synthetic variants, some of which contain an additional and specific functional/stereochemical alteration, possess contours belonging to a less explored region of diversity space.