## Bioinformatic-guided Natural Product Discovery via Reactivity Based Screening

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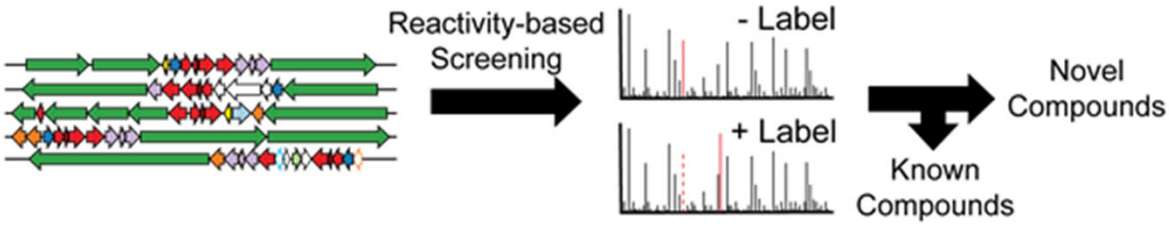
Natural products have been the source of a large portion of clinically used antimicrobial, antifungal and anticancer compounds. Actinobacteria, which have produced many of these drug leads, have been shown by genome sequencing to harbor many more natural product biosynthetic clusters. We employ a combination of bioinformatics prioritization and reactivity-based screening (RBS) toward both the discovery of novel natural products but also towards understanding their biosynthesis. By using bioinformatics prioritization, bacterial strains with the potential to produce electron rich alkene moieties are selected. The active production of novel electron-rich alkene containing natural products is then detected via differential mass spectrometry by reaction with a tetrazine containing probe molecule. This workflow is being used to both discover and characterize the family of mycosamine-containing polyenes as well as β-aminoacid utilizing macrolactams.




## *En Masse* Analysis Yields Prioritized Blocks and Bonds for Natural Product Synthesis

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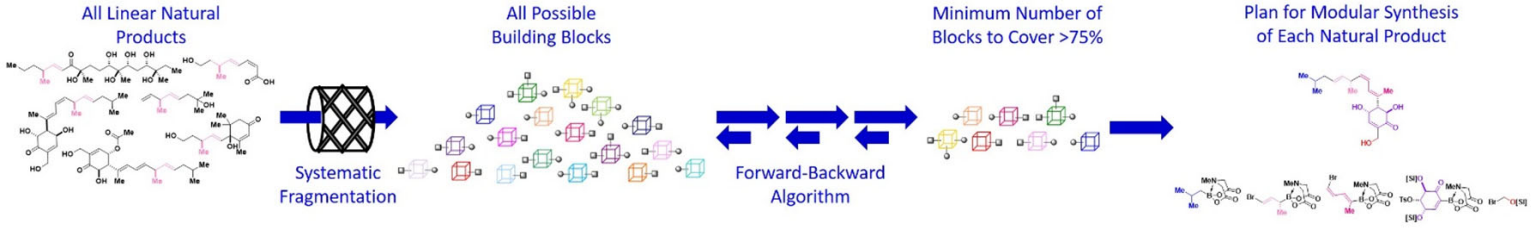
Currently the development of methods in organic synthesis is largely carried out on an *ad hoc* basis by determining the best retrosynthesis for each natural product in isolation. Conversely, we carried out a systematic deconstructive analysis of all linear natural products which reveals a prioritized list of building blocks and the required couplings to collectively access greater than 75% of the chemical space they occupy. For each coupling, analysis of the local chemical environment to a breadth of two heavy atoms reveals the necessary substrate scope to achieve a general coupling methodology. Preliminary analysis into primary $Csp^3$ boronates coupling to vinyl halides suggests that highly stereospecific couplings are accessible for *E* and *Z* olefins. Current efforts are aimed at extending the generality of this method to achieve the broad substrate scope required for generalized natural product synthesis.





18