Organic Colloquium

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"Investigating Selectivity in Complex Systems: from Total Synthesis to Glycan Labeling"

Abstract: The indole diterpenoids constitute a family of natural products that exhibit potent and selective Big Potassium (BK) ion channel inhibition. We have developed a unified synthetic strategy towards the indole diterpenoid class, culminating in the total synthesis of several representative congeners, including paspaline A and emindole PB. Density functional theory calculations are utilized to interrogate a simplifying key bond formation in a predictive capacity to aid in the selection of the most favorable precursor substrate. This work highlights how retrosynthetic design can be augmented with quantum chemical calculations to reveal energetically feasible synthetic disconnections, minimizing time- consuming and expensive empirical evaluation. Furthermore, these studies provide modular entry to privileged indole diterpenoid class of natural products, enabling their application as tool compounds for interrogating BK channel dynamics, as well as therapeutic leads for channelopathies linked to BK channel dysregulation.

Glycans are ubiquitous and play important biological roles, yet chemical methods for probing their structure and function within cells remain limited. Strategies for studying other biomacromolecules, such as proteins, often exploit chemoselective reactions for covalent modification, capture, or imaging. Unlike amino acids that constitute proteins, glycan building blocks lack distinguishing reactivity because they are composed primarily of polyol isomers. Moreover, encoding glycan variants through genetic manipulation is complex. To address these limitations, we have developed a new, generalizable strategy for monomer-selective glycan modification that exploits the reactivity of cellular glycosyltransferases by designing reagents with bioorthogonal handles that function as substrate surrogates. Further, we demonstrate the utility of these labeling reagents by using them to study the biosynthesis, localization, and dynamics of cell wall glycans in mycobacteria.

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