Synthesis Illuminates Amphotericin B Function, and Vice Versa

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Amphotericin B (AmB) is an important antimycotic that has the ability to form transmembrane ion channels. Despite extensive study for more than five decades, the structural and mechanistic underpinnings of its channel and antifungal activities have remained unclear. The degradative synthesis of a series of functional group-deficient probes has illuminated that the mycosamine appendage is required for promoting a direct binding interaction between AmB and ergosterol, ion channel formation, and antifungal activity. Also, iterative cross-coupling-enabled synthesis of another functional group-deficient probe has led to the discovery that AmB primarily kills yeast by simply binding ergosterol, and membrane permeabilization via channel formation is a second complementary mechanism that only marginally increases antifungal potency. The discovery that mycosamine-mediated sterol binding is critical for AmB function has, in turn, illuminated the need to develop synthetic approaches to create AmB probes lacking specific functional groups appended to the mycosamine unit. Towards this end, a site-selective functionalization strategy offers exceptional step-efficiency but comes with the challenge of selectively modifying just one of the ten hydroxyl groups appended to this complex natural product. Stimulated by this aim, we discovered that electronic tuning of acylating reagents provides a powerful new approach for maximizing the site selectivity of acylation reactions. Application of this method to the site-selective acylation of AmB has resulted in a degradative synthesis of C2′-deoxyAmB via deoxygenation.