Synthesis of a Universal Polyene Macrolide Building Block via a Novel Diastereotopic Group-Selective Lactonization

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The modular, flexible, and efficient synthesis of polyene macrolide antibiotics stands to enable the elucidation and understanding of the complex protein-like function of this clinically vital class of small molecules. Many of these compounds retain a common mycosamine-containing hemiacetal motif. We have synthesized a building block capable of introducing this ubiquitous structural element with high efficiency. This is enabled by the recognition of a symmetrical pattern of oxidation states within a key intermediate which allows for its construction via the novel diastereotopic group-selective lactonization of a pseudo C2-symmetric precursor accessible through bidirectional synthesis from readily available carbohydrate starting materials. In support of a previously untested literature hypothesis, this lactonization was found to be diastereoconvergent under both classical acid-catalyzed and ozonolytic lactonization conditions.