NON-ENZYMATIC ENANTIOSELECTIVE POLYENE CYCLIZATION

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INTRODUCTION:

The chemical transformation of a simple linear precursor into a complex and stereochemically rich polycyclic product represents one the most efficient ways to rapidly build molecular complexity. Nature uses this strategy extensively in the biosynthesis of natural products as exemplified by the cyclization of the single precursor squalene (**1**) into a broad range of hopanoids and steroids (Figure 1).[1]

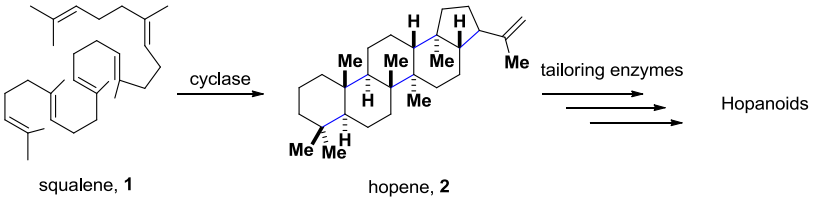

Figure 1: Enzyme mediated conversion of squalene to hopene

SQUALENE-HOPENE-CYCLASE MECHANISM:

The first studies to explore the mechanism of the polyene cyclization where undertaken by Stork[2a] and Eschernmoser[2b] in the 1950's and lead to the Stork-Eschenmoser biogenic isoprene rule. This hypothesis states that the addition of an olefin to a carbenium ion will occur via a stereospecific and concerted antiparallel addition leading to the *trans*-decalin product as seen in the steroids and hopanoids (**2**). Investigations of the enzymatic mechanism of squalene-hopene cyclase (SHC) indicate that the enzyme plays three vitals roles: (1) conformational restriction of **1** to favor a single cationic cyclization pathway, (2) activating a single pro-chiral face of the 2,3-olefin and (3) stabilization of the developing carbocations thereby accelerating the cyclization reaction.[3] Developing an artificial cyclase capable of performing all three of these functions represents a formidable challenge in asymmetric catalysis, but would provide for an efficient method to synthesize complex molecular frameworks.

ENANTIOSELECTIVE POLYENE CYCLIZATION CATALYSTS:

The first successful example of a biomimetic enantio-selective cyclization was reported by Yamamoto[4a] using Lewis acid activated Bronsted acid (LBA) catalysis (Figure 2) in which complexing a Lewis acid to a chiral Bronsted acid creates a highly acidic proton in a chiral environment.[4b] This strategy was used

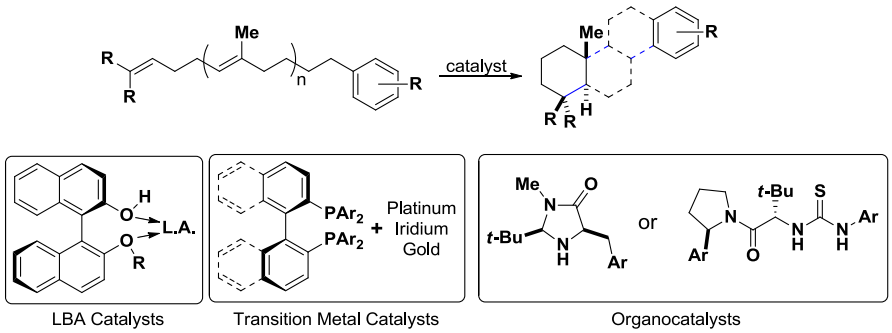

Figure 2: Strategies for enantioselective polyene cyclization reactions

successfully to prepare tricyclic products using a BINOL derivative complexed to $SnCl_4$[4c] or $SbCl_5$.[5]

The first enantioselective transition metal catalyzed polyene cyclization (Figure 2) was reported by Gagne[6] and used platinum complexed with a chiral phosphine ligand to activate a terminal olefin towards polyene cyclization. Following this report, the Toste[7] group used an alkyne complexed with gold as the active electrophile to initiate the polyene cyclization and in conjunction with a chiral BINAP derived ligand rendered the process asymmetric. Lastly, the Carriera group showed[8] that an allylic alcohol could be used to initiate cationic cyclization through formation of an Ir-allyl complex, which combined with a chiral BINAP derived ligand, led to high levels of enantioselectivity.

In 2007 Ishihara[9] reported the first example of an organocatalyzed enantioselective polyene cyclization using a chiral iodonium species to initiate cyclization. Organo-SOMO catalysis was later shown by MacMillan[10] to activate a terminal aldehyde leading to a radical cascade cyclization with a high degree of enantioselectivity. Simultaneously, Jacobsen reported[11] the use of thiourea catalysis to activate an N-acyliminium ion towards nucleophilic attack and polyene cyclization. This example was the first report to invoke both enantioselective formation of the first ring and an extended aryl surface to both stabilize the developing carbocationic intermediates and control the diastereoselectivity of the cyclization process analogous to the enzyme mediated process.

SUMMARY:

Enzymatic cyclases are effective catalysts capable of controlling both the initial olefin activation and the enantio- and diastereomeric course of the cyclization through conformational restriction. Synthetic attempts at polyene cyclization have provided methods by which to perform enantioselective activation, but they have not been able to use catalyst control to direct the course of cyclization. This represents an unsolved problem in asymmetric catalysis to which a solution would provide for an effective method by which to rapidly synthesize complex natural products with exquisite stereocontrol.

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