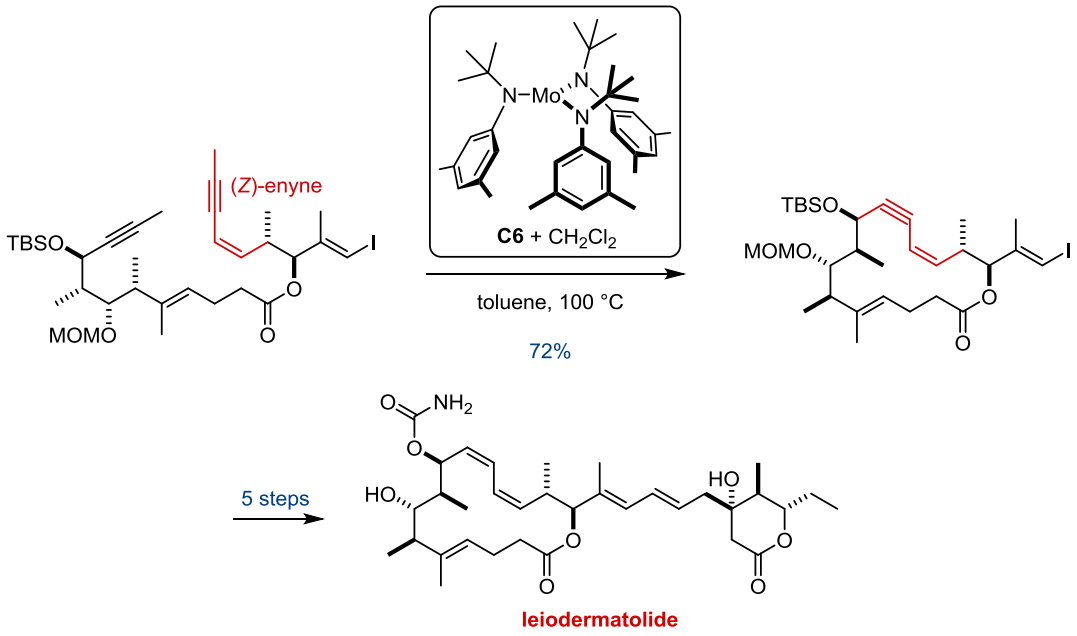
Abstract

Conjugated olefins are common motifs in natural products of marine origin, which continue to serve the pharmaceutical industry as lead structures for the development of novel drugs. Polyunsaturated sites within a macrocyclic framework pose a considerable challenge to synthetic organic chemists, since their selective assembly is not possible via the well-established olefin metathesis reaction.

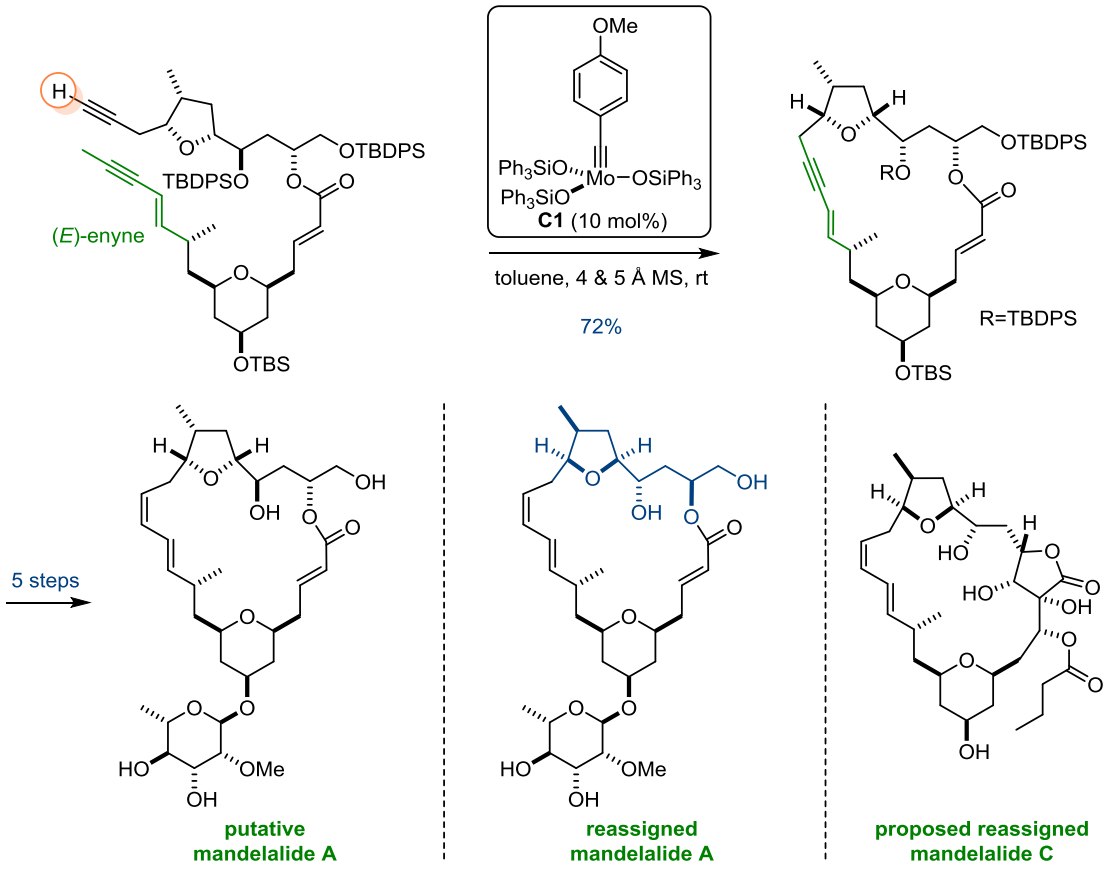
Ring-closing alkyne metathesis (RCAM) offers an indispensable alternative, as it tolerates a variety of polar functional groups and the catalysts display unmet selectivity for alkynes over olefins. To further elaborate the scope of this transformation, RCAM was combined with *syn*-selective semi-hydrogenation to achieve the synthesis of the cyclodienes found in leiodermatolide and mandelalide A.

Leiodermatolide, a natural product derived from a deep-sea sponge, was chosen as a target as it displayed high antimitotic acitivity against a variety of differenct cancer cell lines without interfering with purified tubulin, thus indicating a novel mode of action. Moreover, the structure could not be fully secured by the isolation team and led us to consider two possible diastereomers.



In the event, the natural product could be successfully synthesized and its structure assigned based on subtle differences in the NMR spectra of two diastereomeric compounds. A second generation synthesis was in turn developed that addressed the remaining bottlenecks of the initial approach and features a catalytic asymmetric propargylation of a highly enolizable β-keto lactone. Substantial amounts of material and a set of analogues were thus synthesized to allow for a deeper biological investigation. Until now, the acquired data points to centrosome declustering as the potential mode of action.

An even more challenging enyne-yne metathesis was pursued within the total synthesis of mandelalide A, a natural product isolated from a marine ascidian along with three related macrolides. Mandelalide A was chosen as the primary target for a synthetic endeavor as the most active member of the family.



After fragment synthesis and assembly, the RCAM reaction now engaged an enyne with a terminal alkyne, a structural motif that had been long beyond reach due to significant polymerization side-reactions. This was enabled by the use of the recently developed molybdenum alkylidynes bearing silanolate ligands. The resulting cycloenyne was subsequently semireduced and further transformed into the target molecule. However, the natural product had been misassigned by the isolation team, but was reassigned by inverting the whole northern fragment. Unfortunately, the promising biological activity could not be confirmed. Nevertheless, the project was extended to approach the closely related natural product mandelalide C.