THE TRANSANNULAR DIELS-ALDER REACTION

Reported by Aaron Petronico February 20, 2014

INTRODUCTION

Since its discovery, the Diels-Alder reaction has been an efficient method for rapidly generating molecular complexity with perfect atom economy. However, one of the inherent disadvantages of the Diels-Alder reaction is the high entropy of activation, which can result in sluggish reactions or require harsh conditions. The high entropy barrier can be lowered by performing the Diels-Alder reaction intramolecularly, which has been very successful.[1] Alternatively, the intramolecular Diels-Alder reaction can be performed when the diene and dienophile are part of the same macrocycle, further lowering the entropy of activation and generating a tricyclic product.[2] The incorporation and reaction of Diels-Alder partners in a macrocycle is termed the transannular Diels-Alder reaction (TADA). This seminar will demonstrate how the TADA was discovered, developed into a useful synthetic tool, and applied to solve complex problems in synthesis.

DEVELOPMENT OF THE TRANSANNULAR DIELS-ALDER REACTION

Early Advances in the Transannular Diels-Alder Reaction

Tricyclic carbon skeletons are prevalent in natural products and the TADA could allow for efficient construction of these targets if the precursors were readily accessible and the outcomes of the reaction were predictable (Figure 1). Malonate alkylation,[3] macrolactonization,[4] and Stille cyclization[5] methods have all been employed to access different macrocylic TADA precursors. To test the predictability of TADA reactions, the Deslongchamps group synthesized 14-membered macrocycles of the eight possible diene and dienophile combinations leading to [6.6.6] tricyclic compounds. The results of these TADA reactions demonstrated that by examining the possible conformations of transition structures for the TADA, steric influence can be used to predict the stereochemical outcome of the reaction.[6]

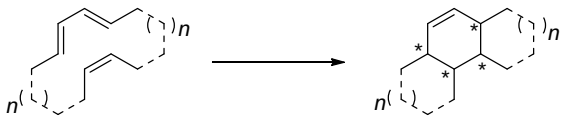

Figure 1: The Transannular Diels-Alder Reaction

Applications to Total Synthesis

An early application of the TADA is found in the synthesis of the antibiotic Dynemicin A and related compounds (Figure 2).[7,8] Key aspects of this synthesis include the formation of the

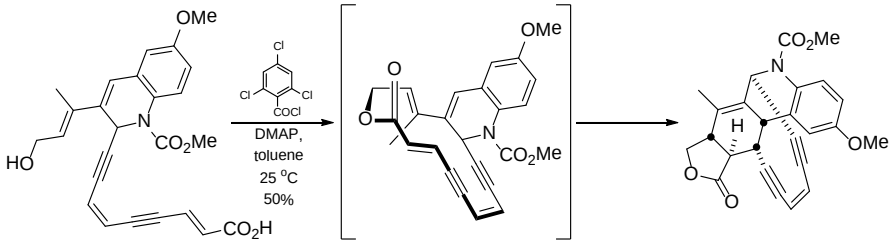

Figure 2: Use of TADA in the Synthesis of Dynemicin A

TADA precursor via macrolactonization followed by immediate [4+2] cycloaddition with high selectivity for the desired product due to the rigid nature of the ene-diyene macrolactone.

An innovative use of the TADA was its application toward the synthesis of anti-cancer target FR182877. The first published route of FR182877 implemented two Pd π-allyl substitution reactions in the formation of the macrocyclic precursor followed by a TADA and hetero-TADA reaction to form five of the skeletal rings and seven stereocenters.[9] An improvement on the original route implemented a similar TADA strategy toward FR182877, but instead used a Suzuki coupling and malonate alkylation to form their macrocycle and different Diels-Alder conditions, ultimately leading to higher overall yields.[10] (Figure 3)

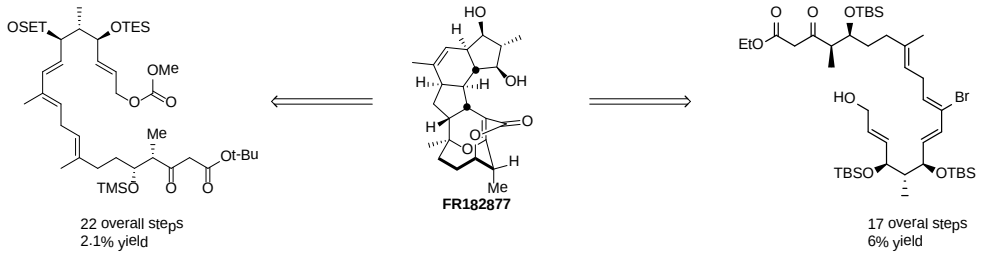

Figure 3: Routes toward FR182877

Controlling the TADA Reaction

As with all cycloadditions, control of diastereoselectivity in the TADA is crucial. Whereas the structure of the macrocycle often provides high diastereoselectivity, enhanced selectivity or inverted stereochemistry often desired. It was demonstrated that prudent use of steric directing groups can influence diastereoselectivity and this method was applied in the synthesis of the natural stereoisomer of (-)-spinosyn A.[11] A further element of control in the TADA reaction is to achieve enantioselectivity which is particularly difficult in transannular reactions. It was shown that a chiral oxazaborolidine Lewis acid induce can induce both high diastereoselectivity and enantioselectivity. Additionally the oxazaborolidine catalyst was shown to effect catalyst controlled diastereoselectivity.[12]

The TADA reaction generates molecular complexity in an atom economic fashion. The TADA is amenable to both complex natural product synthesis and asymmetric catalysis and will continue to be a useful tool in generating complex molecules.

References

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