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Transannular reactions in asymmetric total synthesis

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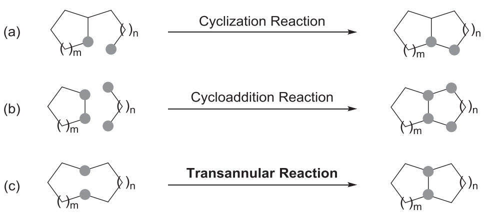
1. Introduction

The development of new strategies for the synthesis of complex molecules is one of the most active areas found in organic chemistry. Designing a good synthetic plan will allow chemists to lead to the final product in a minimum number of steps, thus reducing the number of bond forming processes, functional group transformations, protections, and deprotections. One of the major goals made by chemists when designing a synthesis plan for a target molecule is to find an idea, which can solve more than one synthetic difficulty at a time. Indeed, in very ingenious schemes, the plan is very simple and could solve more than one projected difficulty in less than one or two operations. In addition, for achieving a good overall yield high control for each step should be obtained. This means that the synthetic plan should allow very high stereochemical control together with high chemo- and regioselection for each chemical reaction.

Considering that most of the synthetic targets with potential interests like natural products or bioactive compounds are polycyclic structures, having efficient methods available for the stereoselective preparation of carbo- or heterocycles is of particular relevance when designing the corresponding synthetic plan. In this sense, several approaches exist for accessing to polycyclic architectures (Scheme 1). These can be classified according to three general types of reactions: (a) intramolecular reactions, in which a functionalized side chain reacts intramolecularly with another functionality present at a preexisting ring, (b) cycloaddition reactions (such as the Diels–Alder reaction or 1,3-dipolar cycloadditions), in which one of the partners participating in the process has already a cyclic structure, and (c) transannular reactions, a ring contraction reaction in which the two reacting functionalized centers are tethered together as part of a macrocycle.



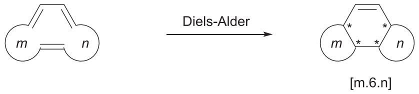
Scheme 1. Synthetic approaches to polycyclic frameworks.

While the two first approaches described in Scheme 1 have received a great deal of attention by the synthetic community, the use of transannular reactions as a general tool in the synthesis of polycyclic scaffolds remains significantly underdeveloped for many years. This is due to the requirement of a macrocyclic starting material, whose preparation entails in many cases a difficult synthetic problem by itself. However, advances in synthetic methodology for the preparation of medium and large rings led to many research groups to engage in the development of transannular reaction and in particular directing their efforts toward the application of this approach to the synthesis of complex targets. Nowadays, transannular reactions have emerged as a robust tool to approach polycyclic frameworks in a highly reliable way and have appeared as a highly useful alternative to the classical cycloaddition or cyclization reactions used to face the synthesis of such polycyclic structures.

With respect to stereochemical control, the conformational constraints associated to the approach of the reactive sites to each other in a transannular process make this reaction to be an ideal candidate for the asymmetric synthesis of chiral complex molecules containing multiple stereogenic centers. Despite this, whereas transannular processes have been employed for building up several relatively complex synthetic targets, almost all of them involve diastereoselective reactions and hence, a chiral enantioenriched starting material is required. Only very recently several examples regarding catalytic enantioselective transannular reactions have appeared in the literature. This review is directed to cover those examples in which a transannular reaction has been employed for the synthesis of natural products, pharmaceuticals, and other interesting compounds in an enantioenriched way.[1]

2. Transannular Diels–Alder reaction (TADA reaction)

The Diels–Alder reaction is regarded as one of the most efficient reactions for the construction of polycyclic frameworks in terms of atom economy, scope, and versatility.[2] The transannular version of this reaction[3] constitutes one of the most sophisticated applications of this cycloaddition, where macrocycles of different ring sizes are contracted to yield a tricyclic structure. In fact, the great majority of examples of transannular reactions described in the literature involve a Diels–Alder reaction as the transformation selected to induce the process. In particular, when applied to an $(m+n+2)$-membered cyclotriene substrate, a $[m.6.n]$ tricyclic framework is formed in which up to four contiguous stereocenters have been generated (Scheme 2).



Scheme 2. The general scheme for a transannular Diels–Alder reaction.

The conformational restrictions associated to the TADA process, together with the *endo*- or *exo*-selectivity and the diastereospecificity of Diels–Alder reactions imply that the stereochemical outcome of the transannular reaction can be easily predicted on the basis of the geometry of all the unsaturated moieties incorporated at the macrocycle.[4] In addition, and which is even more important for the practical applicability of this reaction toward the stereoselective total synthesis of complex chiral molecules, facial selectivity can also be easily controlled by the installation of stereogenic centers within the structure of the macrocyclic precursor.

2.1. TADA reactions in 13-membered macrocycles

13-Membered macrocyclic trienes are excellent candidates for transannular Diels–Alder reactions because these substrates lead to an unstrained [6.6.5] tricyclic framework. Moreover, the overall transannular process involves a release in strain when moving from the macrocyclic triene to the tricyclic product, which also contributes to the feasibility of the reaction, even though this might also depend on the geometry of the C=C double bonds involved in the process. A good example of this reactivity is shown in the enantioselective synthesis of (−)-*oblongolide*, a norsesquiterpene γ-lactone isolated from the fungus *Phomopsis oblonga* (Scheme 3)[5] in which a lactone **1** undergoes clean and fully diastereoselective transannular Diels–Alder reaction providing directly the target compound in excellent yield. The presence of a small methyl group at the stereocenter present in the starting material shows up to be enough to control the facial selectivity during cycloaddition, which is explained in terms of the preference for this substituent to locate in a pseudoequatorial position, which translates into a well-defined rigid conformation of the macrocycle during the transannular process. The formation of the tricyclic [6.6.5] system with a *trans–cis* ring junction results from both the *endo*-approach between the diene and the enoate moieties and the all-trans geometry of the triene system. Importantly, this all-*trans*