The Enyne-Metathesis Reaction

The enyne metathesis is a bond reorganisation of an alkene and an alkyne to produce a 1,3-diene (Scheme 1). It has been used in both intramolecular and intermolecular applications, and is driven by the enthalpic stability of the 1,3-diene produced. Stereoselection is often low in intermolecular cases but can be controlled in intramolecular cases.

Mori and co-workers first pioneered the use of ruthenium carbene complexes in enyne-metathesis chemistry in 1994. Shortly afterwards, in 1996, the group published the synthesis of (−)-stemoamide; this was the first application of the enyne-metathesis reaction in a total synthesis (Scheme 2). The key step was the enyne ring-closing metathesis of precursor 1 using Grubbs’ second generation catalyst, which furnished the bicyclic product 2 in 87% yield and without any erosion of stereochemical integrity at the sensitive propargylic position. With this advanced intermediate in hand, only a few more steps were required to arrive at the targeted product.

The intramolecular enyne-metathesis reaction also offers a useful method for the synthesis of macrocyclic ring systems (Scheme 3). However, when applying the enyne ring-closing metathesis reaction to the synthesis of large rings, a number of selectivity issues arise relating to the orientation of ring closure. The ruthenium carbene intermediate 3 can undergo two possible modes of ring closure, termed endo and exo. These two pathways generate different metallacyclobutene intermediates 4 and 5, which subsequently yield the 1,2-disubstituted product 6 and 1,3-disubstituted product 7 respectively. The formation of common and medium sized rings by enyne ring-closing metathesis is typically constrained to follow an exo path, whereas macrocyclisations generally follow the endo mode of ring closure owing to the increased flexibility of the tether.

Enyne metathesis macrocyclisations are generally conducted under an atmosphere of ethylene; therefore, the metathesis reaction is believed to be directed away from the direct intramolecular enyne metathesis reaction which is inherently slow due to the effective concentration of the reacting termini. Instead, a two-step process has been proposed involving intermolecular enyne cross-metathesis with ethylene to generate 8, which subsequently undergoes a conventional intramolecular alkene ring-closing metathesis reaction. The less sterically hindered terminal double bond of the butadiene moiety would be expected to be engaged selectively in the macrocyclisation to give the formal endo enyne metathesis product.
In 2002, Shair and co-workers published the synthesis of the marine natural product (−)-longithorone A, which was inspired by the biogenetic hypothesis of the Schmitz group. The route employed a sequence of inter- and intramolecular Diels-Alder reactions to form much of the polycyclic architecture of the natural product (Scheme 4). This led them to conceive the macrocyclic compounds 209 and 210 as key synthetic intermediates. Recognising the characteristic 1,3-disubstituted butadiene system embedded within both compounds, the group planned to construct both intermediates through enyne ring-closing metathesis reactions. The cyclisation of both precursors with Grubbs’ first generation catalyst under an ethylene atmosphere proved successful with both excellent atropselectivity and E/Z selectivity. In the absence of an ethylene atmosphere macrocyclisation did not occur, therefore it is likely that both cyclisations proceed through the two-step process.