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Formation of medium-ring heterocyclic compounds by two-directional ring-closing metathesis reaction

Titas Biswas
Department of Chemistry, Gurudas College, Kolkata 700054, West Bengal, India

Author's E-mail: titas.biswas@gmail.com

Abstract

A synthetic method based on the tandem application of two-directional ring-closing metathesis reaction as key-steps has been established for the synthesis of medium ring heterocyclic compounds.

Keywords: Medium ring heterocyclic compounds, two-directional ring-closing metathesis.

Introduction

The word "metathesis" refers to the exchange of covalent bonds between two molecules that occurs between two molecules. When alkylidine moieties are redistributed between two alkenes in the presence of a catalytic quantity of a metal carbene, it is referred to as alkylidine redistribution. It occurs in olefin chemistry. Olefin metathesis has been employed in four different kinds of reactions, which are as follows: (a) Ring-opening metathesis polymerization (ROMP) is a polymerization reaction in which a beginning cyclic olefin polymerizes as a result of opening the ring of the ring (Nomura and Schrock, 1996), (b) The process by which an acyclic diene is turned into a cyclic olefin is known as ring-closing metathesis (RCM), (c) Cross Metathesis (CM) is a reaction where two different olefins react to form a new olefin as the product (Blechert and Connon, 2003) and a volatile olefin (usual ethylene) as the by-product, (d) Ring-opening metathesis (ROM) is a reaction where two cyclic olefins react to form a new acyclic olefin (Mehta and Nandakumar, 2002).

Earlier, I described (Biswas, 2020) the utility of ring-closing enyne metathesis for the preparation of heterocyclic compounds. The description in this review involves utilization of two-directional ring-closing metathesis as a route for the preparation of medium-ring heterocycles of interest. A brief review of the previous work (Chattopadhyay et al., 2007) along with my work (Chattopadhyay et al., 2006) on two-directional ring-closing metathesis (TDRCM) is made separately below.

The first report on TDRCM of a tetraene in a one pot manner leading to bicycle formation was reported by Fu et al., (1993) and it involved the preparation of the bis-pyrrolenine **8** from its precursor **7** (Scheme1).

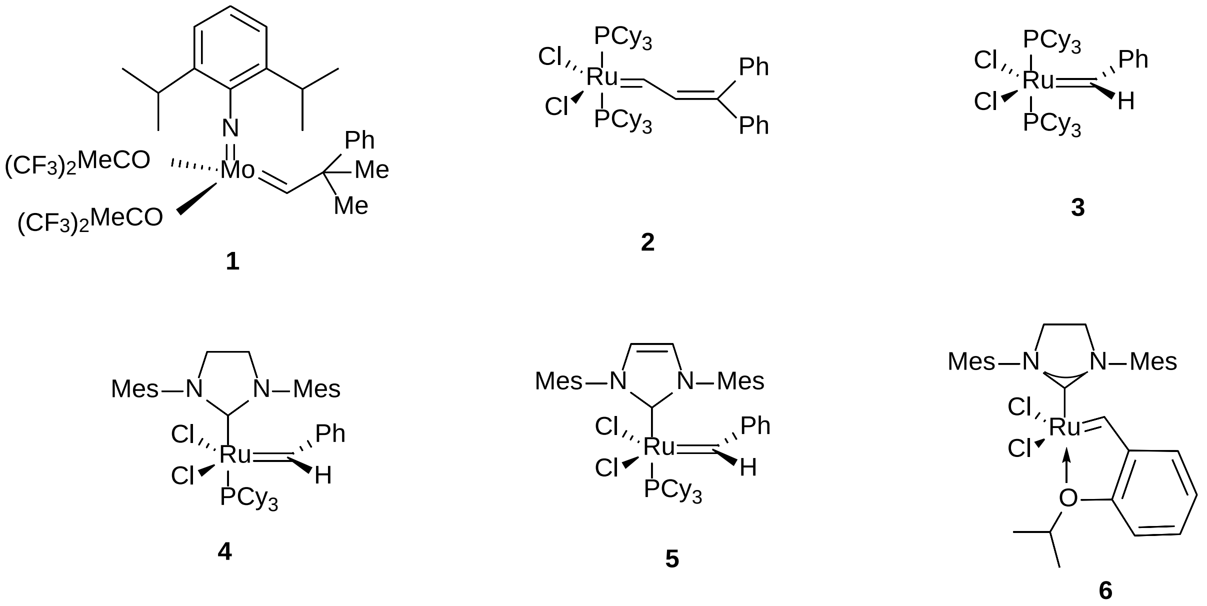
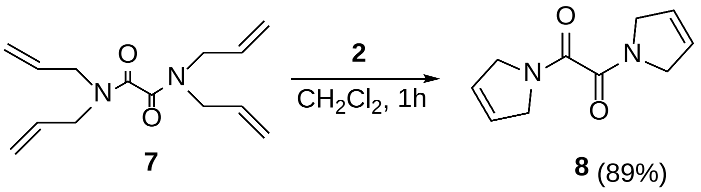


Fig. 1. Schrock's molybdenum catalyst 1 and Grubbs' first- and second-generation catalysts 2-6 were used in this experiment.



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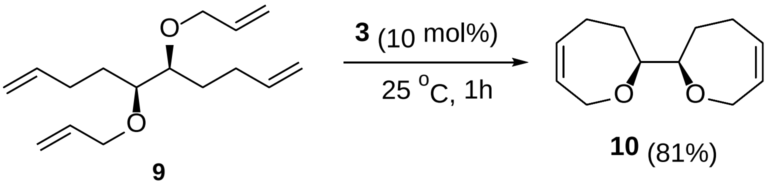
8 (89%)

Scheme 1. Synthesis of bis-pyrrolenine by TDRCM of a tetraene.

The notion of repeated RCM reaction of a properly prepared polyene has been successfully used in a one-pot method to supply fused-, bridged-, and spiro-cyclic systems of interest, including medium-ring heterocycles (Wallace, 2003; Bassindale et al., 1999). For example, the TDRCM of the bis (O-allyl) ether 9 with the Grubbs' catalyst 3 formed the bis-oxepine derivative 10 in reasonable yield, as shown by Crimmins and Choy (1999) (Scheme 2).



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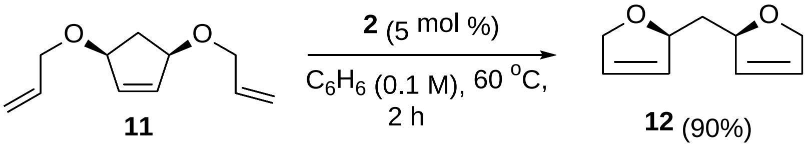
10 (81%)

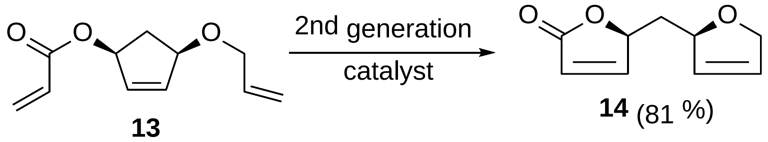
Scheme 2. Preparation of bis-oxepin by TDRCM of bis(O—allyl) ether.

During the following years, more synthetic applications of multiple RCM-reaction have been reported, and some general aspects of this useful reaction have been reported in the literature. Zuercher et al., (1996) reported the combination offering-opening metathesis with TDRCM to form bicyclic olefin from a cyclic olefin e.g., formation of **12** from **11** (Scheme 3).



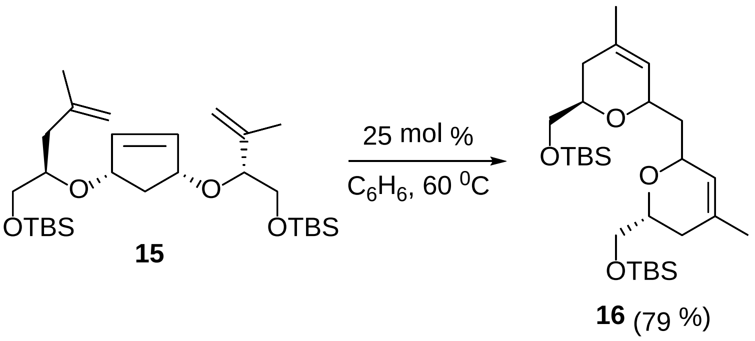
Scheme 3. A cyclic olefin is used in the synthesis of a bicyclic olefin.

It was also able to carry out the tandem ring-opening and ring-closing metathesis reaction of electron-deficient olefins (e.g., 13) using Grubbs' second-generation catalyst 5 (Choi and Grubbs, 2001) (Scheme 4).



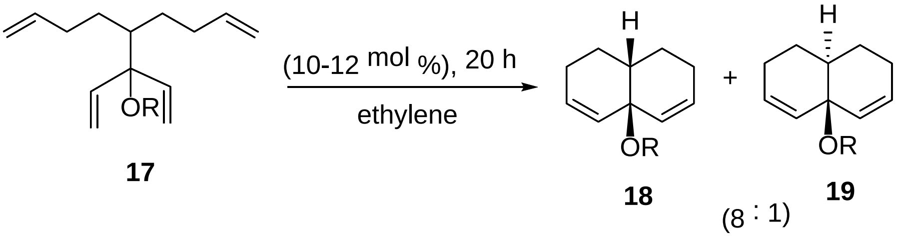
Scheme 4. Synthesis of α,β-unsaturated lactone.

Burke et al., (1998) prepared the C(22)-C(34) fragment (**16**) of Halichondrin B *via* tandem ring-opening utilizing double ring-closing metathesis of bis ether **15** (Scheme 5).



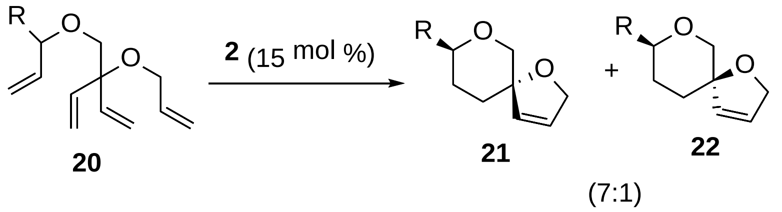
Scheme 5. Metathesis of a cyclic olefin involving a tandem ring-opening double ring-closing reaction.

Lautensand Haughes (1999) studied diastereoselectivity in two-directional ring-closing metathesis reaction and made some interesting observations. They treated the tetraene **17** with Grubb's catalyst, which selectively led to the *cis*-decalin system **18** (Scheme 6).



Scheme 6. Synthesis of *cis*-decalin from a tetraene.

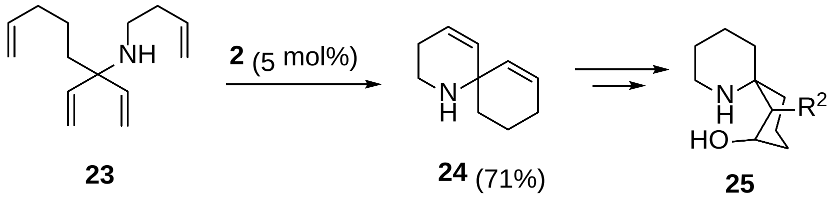
According to the preceding example, the creation of cis-decalin demonstrates that some of the reactions during the two-directional ring-closing metathesis process are not completely reversible. It has also been found (Schmidtand Westhus, 2000) that a similar diastereoselective spirocycle is formed from acyclic tetraenes e.g., in the conversion of **20** to **21** & **22** (Scheme 7).



Scheme 7. Formation of spirocycle from acyclic tetraene.

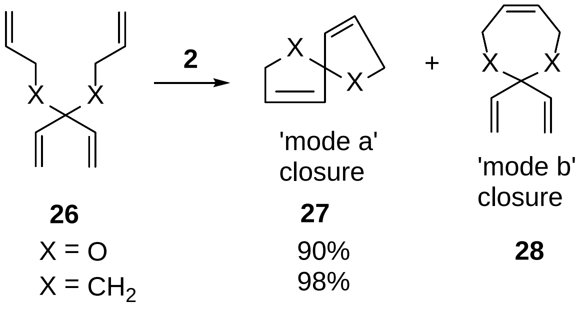
When looking for the cause of this diastereoselectivity, the authors used an NMR tube and discovered that the five-membered ring forms quicker than the six-membered ring. This is the first time that this has been discovered. A mechanistic rationale has also been proposed.

A synthetic strategy to functionalized spiropiperidines involving TDRCM has been reported (Edwards et al., 2002), and the intermediate **24** was synthesized from the tetraene **23** applying such methodology was converted to an analogue **25** of histrionico-toxin (Scheme 8).



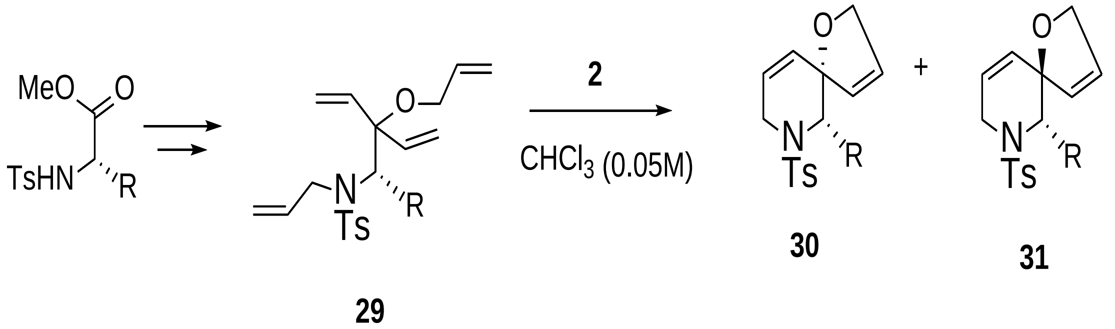
Scheme 8. Preparation of spiropiperidine involving TDRCM from a tetraene.

Bassindale et al., (1999) studied the multiple RCM of the tetraenes of the general structure **26** (Scheme 9) and reported that TDRCM of **26** provided 5-membered ring closure **27** over 7-membered ring closure **28**.



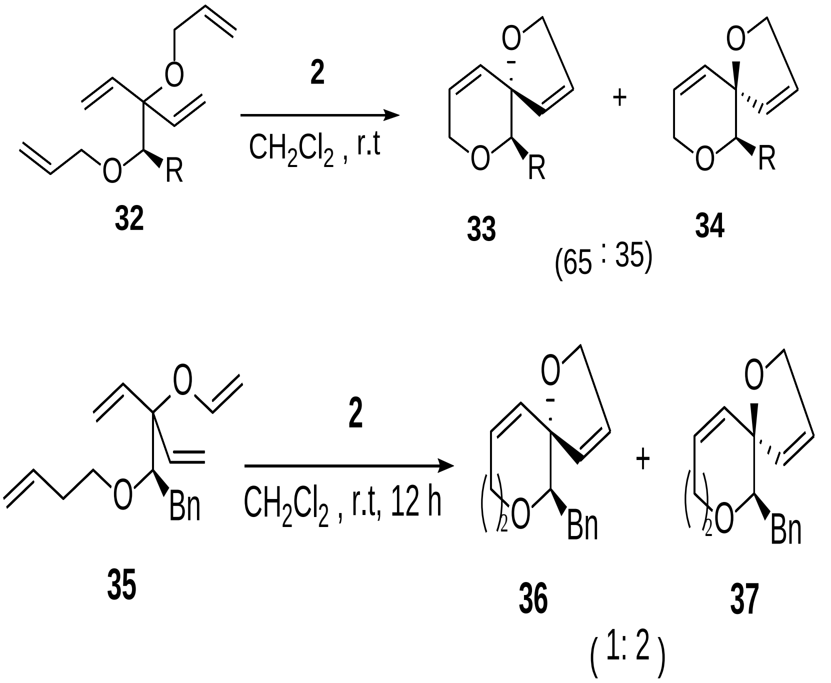
Scheme 9. TDRCM of tetraenes prefer 5-membered ring closure over 7-membered.

Wallace et al., (2000) reported on the use of the stereoselective double ring-closing metathesis process for the synthesis of spirocyclic molecules, which they described as follows: As a result, the amino acid generated tetraene 29 preferentially (by 92 percent) resulted in the formation of the spirocycle (Scheme10).



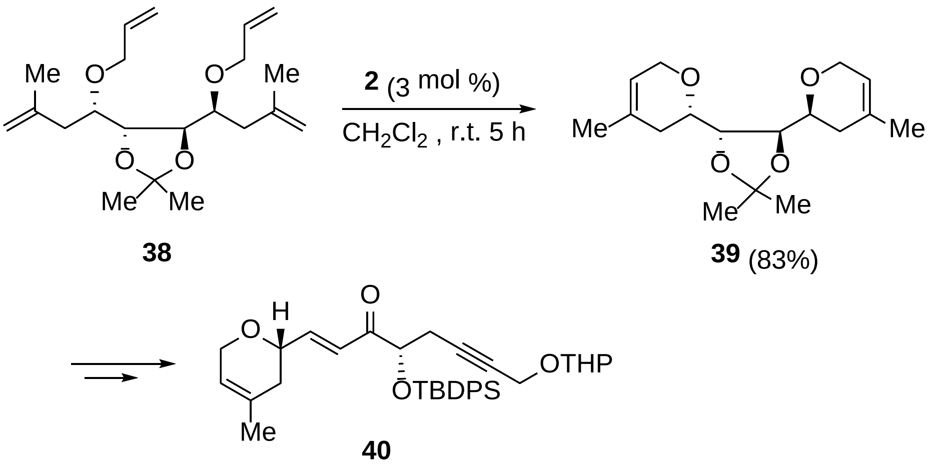
Scheme 10. Stereo-selective TDRCM of amino acid-derived tetraene.

Using this broad notion of stereoselective double ring-closing metathesis process to synthesise spirocyclic compounds, Wallace et al., (2001) extended it later on to the synthesis of spiro-furopyran derivatives, which they successfully prepared 33 and 34 (Scheme 11).



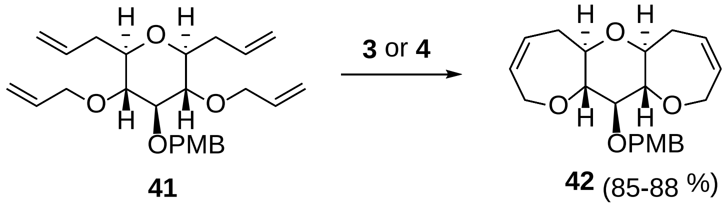
Scheme 11. Synthesis of spiro-furan derivatives by dia-stereoselective TDRCM.

Ahmed et al., (2001) reported convenient preparation of bis-pyran products by applying TDRCM methodology. Thus, the bis-pyran derivative **39** was prepared (Scheme 12) and utilized to prepare the C_{15}-C_{27} (**40**) fragment of the natural product laulimalide.



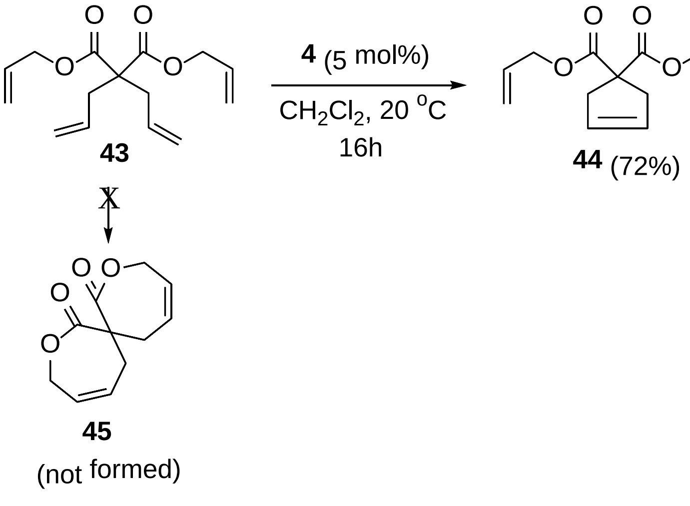
Scheme 12. Synthesis of bis-pyran derivative.

As part of a programme towards the total synthesis of brevetoxins, Clark and Hamelin, (2000) developed an elegant methodology for preparing polycyclic ethers by TDRCM. This work represented the methodology's first examples of medium ring ether formation. The general concept is illustrated by the conversion of the tetraene **41** to the bis-oxepin **42** (Scheme 13).



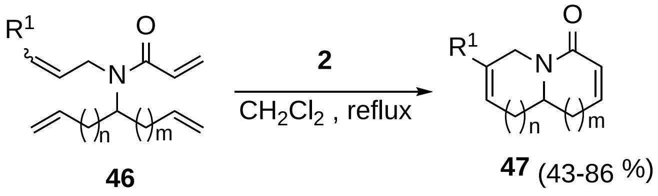
Scheme 13. Synthesis of bis-oxepin derivatives by the concept of TDRCM methodology.

Wybrow et al., (2002) treated the malonate derived tetraene **43** with the Grubb's catalyst **4** and observed the preferential formation of a five-membered ring over a seven-membered ring (Scheme 14).



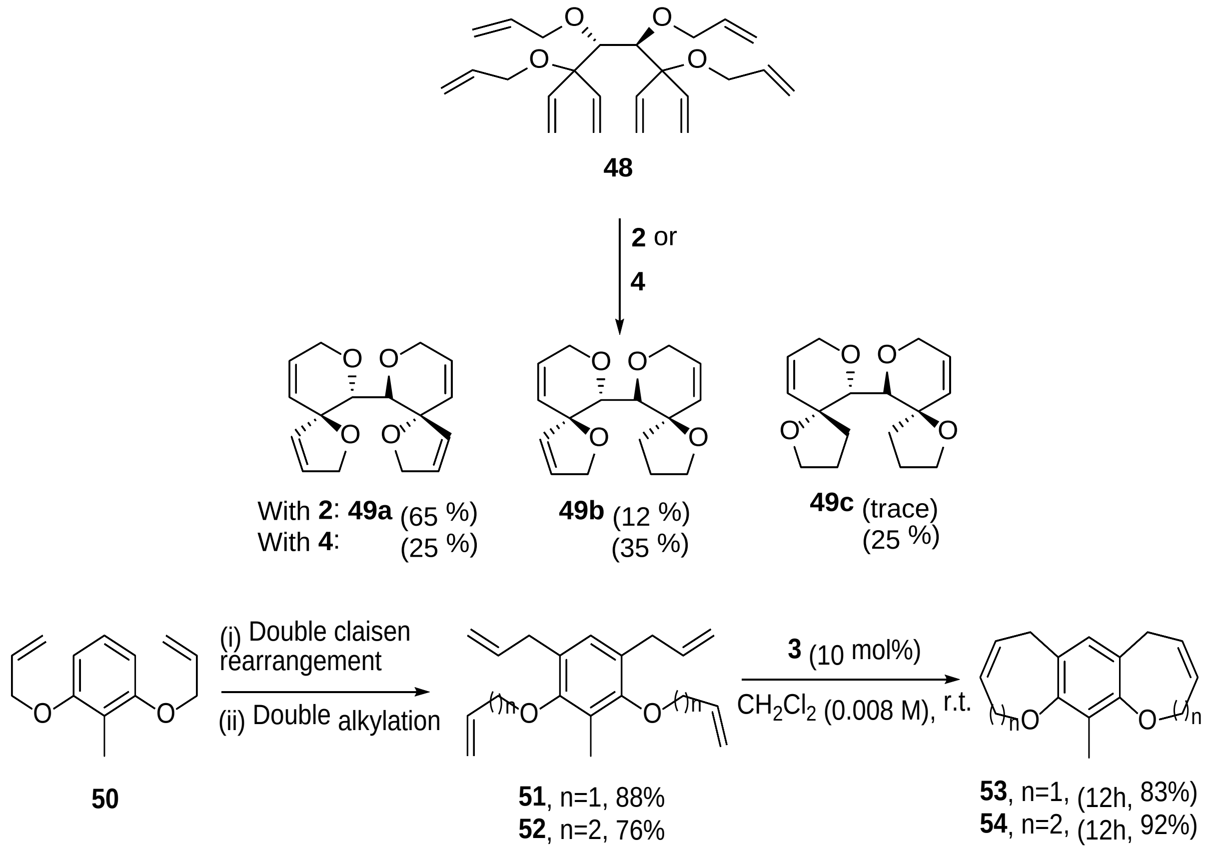
Scheme 14. The creation of a five-membered ring is preferred over the construction of a seven-membered ring.

The bicyclic izidine alkaloid skeleton has been prepared (Ma and Ni, 2002) by TDRCM of substrate **46** using the ruthenium catalyst **2** (Scheme 15).



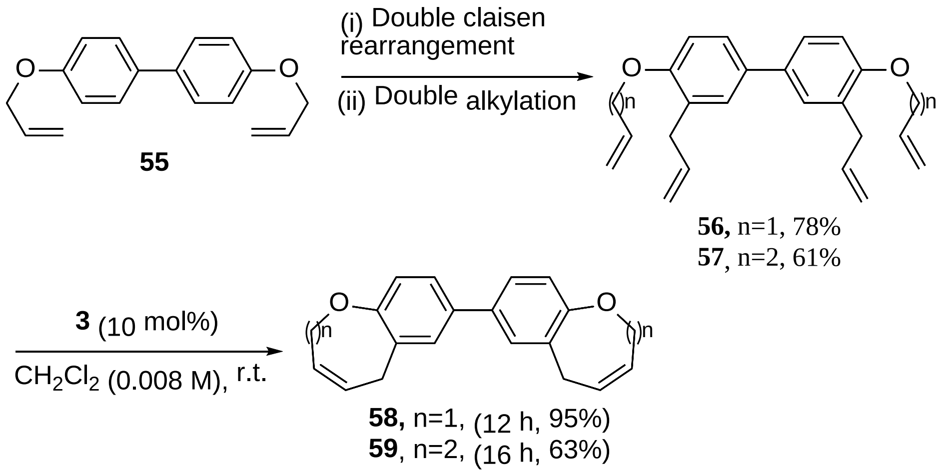
Scheme 15. Synthesis of izidine alkaloid skeleton.

Wallace (2003) reported the first example of a quadruple ring-closing metathesis reaction. Thus, the reaction of the C_2 symmetric octa-ene **48** afforded the bis-spirocyclic compounds **49** in high yield (Scheme 16).

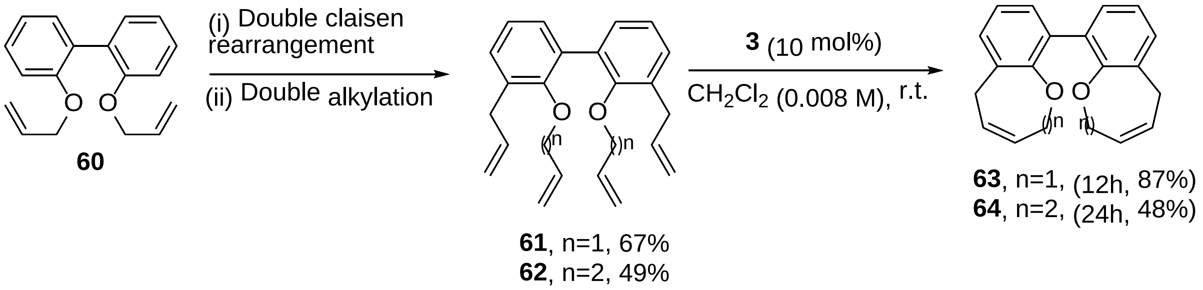


Scheme 16. Preparation of bis-spirocyclic compounds from octa-ene.

Chattopadhyay et al., (2006) developed a synthetic strategy based on the tandem application of doubleClaisen rearrangement and two-directional ring-closing metathesis reaction as key-steps for the synthesis oftri- (**53, 54**) (Scheme 17), tetra (**58, 59)** &(**63, 64**) (Scheme 18) and pentacyclic (**67**) (Scheme 19) benzofused bisoxepin and bisoxocin derivatives.

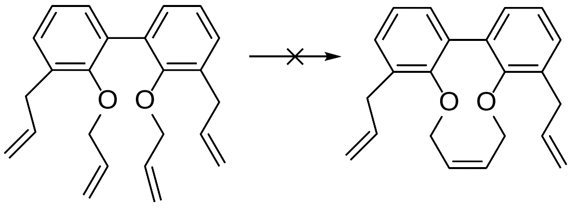


Scheme 17. Bicyclic benzofused bisoxepin and bisoxocin derivatives are formed during the reaction.



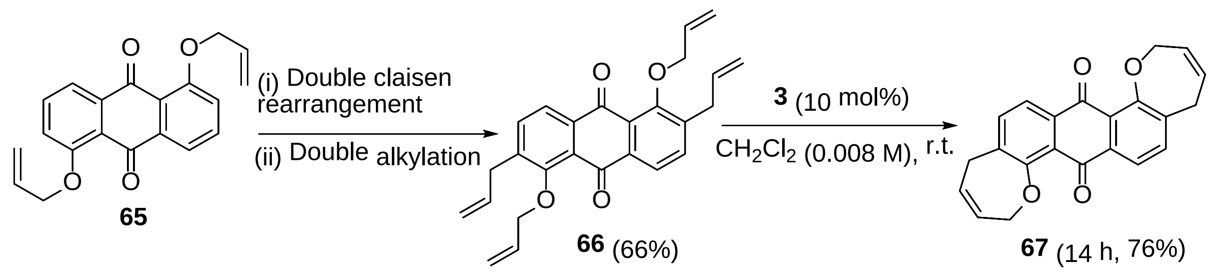
Scheme 18. Bisoxepin and bisoxocin derivatives derived from tetracyclic benzofused bisoxepin and bisoxocin.

In the case of compound 61, we were able to investigate if any selectivity might be detected during the TDRCM process since there is also the potential to produce a ten-membered heterocyclic ring involving the RCM of the two allyl ether units.



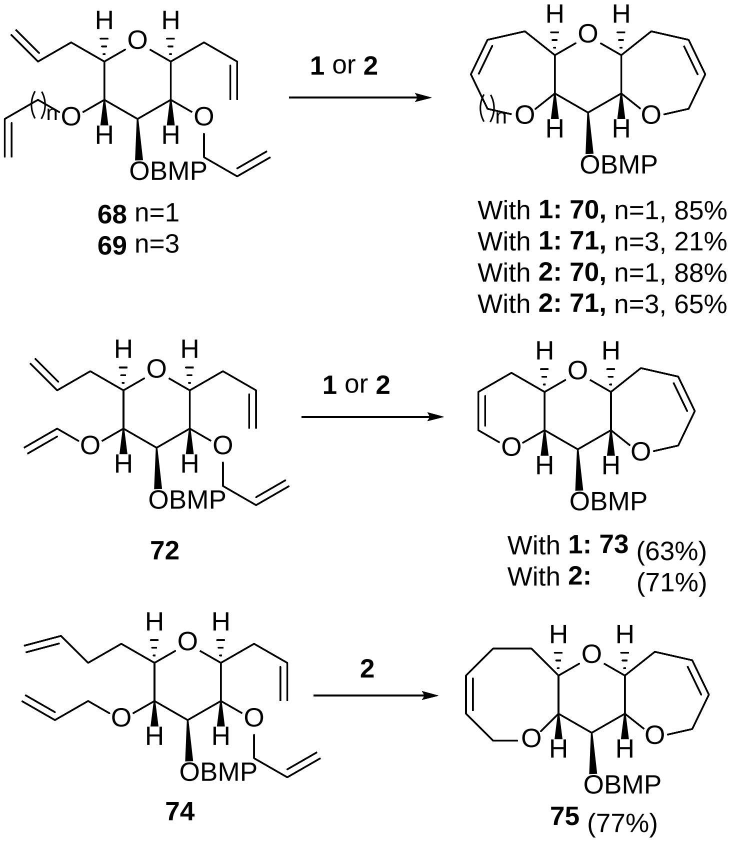
61

The attempted TDRCM of 61, on the other hand, produced just a colourless liquid with an 87 percent yield of the bis-oxepin derivative 63, which was satisfactory in our estimation.



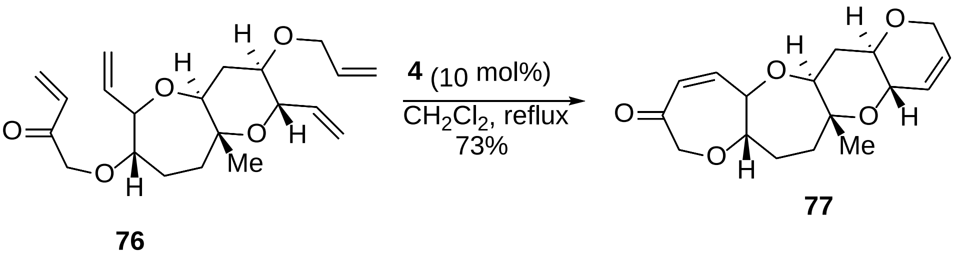
Scheme 19. The reaction results from the formation of pentacyclic benzofused bisoxepin and bisoxocin derivatives.

Clark et al., (2000) reported a synthetic strategy for synthesising polycyclic ethers involving a two-directional ring-closing metathesis reaction (Scheme 20). The two-directional ring-closing metathesis reactions of the precursors **68**, **69**, **72** and **74** were done using molybdenum catalyst **1** and the ruthenium catalyst **2** to compare their efficacy. Two-directional ring-closing metathesis reaction of the substrate **68** led to two seven-membered rings **70**. A seven-membered and nine-membered ring 71 were formed in low yields when 69 was treated with the molybdenum catalyst 1, while the ruthenium catalyst 2 produced the ring 71 in high yields when 69 was treated with the catalyst 2. TDRCM of the substrate 72 in the presence of either catalyst 1 or 2 resulted in forming a six-membered ring 73 in high yield and a seven-membered ring 73 in low yield. Treatment of substrate **74** with catalyst **2** provided the formation of an eight-membered and a seven-membered ring **75** in good yield.



Scheme 20. Formation of polycyclic ethers.

Inspired by previous work, Clark et al., (2007) later prepared the tetracyclic fused polyether core of the marine natural product hemibrevetoxin B using a two-directional ring-closing metathesis reaction. Two-directional ring-closing metathesis reaction of the tetraene **76** with the Grubbs' second generation ruthenium catalyst (**4**) provided the fused polyether **77** in good yield (Scheme 21).



Scheme 21. Formation of tetracyclic fused polyether.

Conclusion

The above considerations suggest that two-directional ring-closing metathesis processes have been successfully carried out in a one-pot setting, resulting in the production of diverse medium-ring heterocycles in a very efficient manner.

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