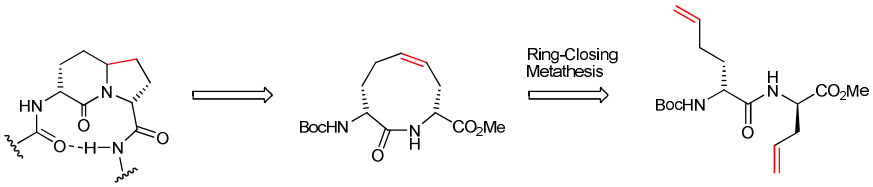
Research Interests

Dr John Mckendrick

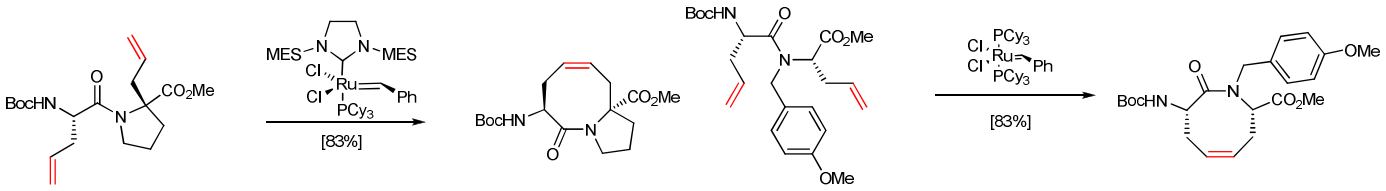
j.e.mckendrick@rdg.ac.uk Tel.: 0118 378 8246

Olefin Metathesis in Organic Synthesis

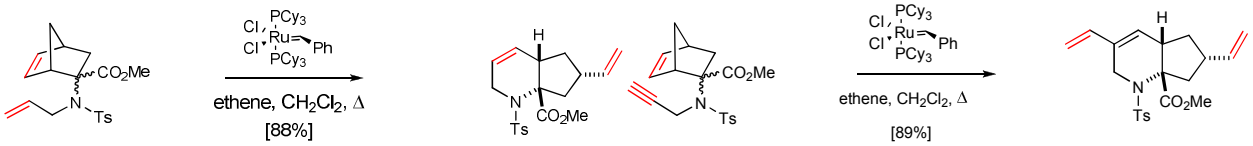
The importance of olefin metathesis in organic synthesis is now clearly established, the reaction has revolutionised the way synthetic chemists approach the synthesis of complex targets.[1] Our interest in the application of olefin metathesis in organic synthesis came from the simple disconnection below:



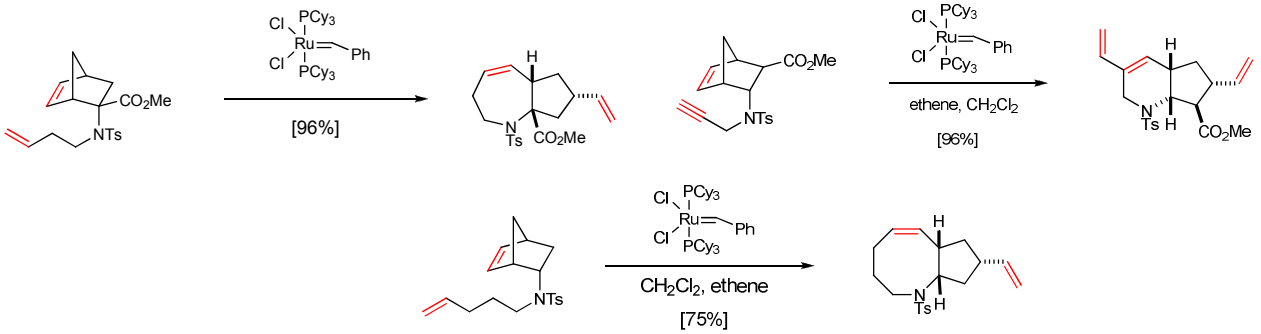
Exploring this disconnection has provided a number of challenges and new directions in our research. The first challenge arises from the fact that the reaction above fails for smaller rings due to the requirement for a *cis*-amide bond to enable RCM. Our solution, and that of Brimble and Reitz,[2] was to alkylate the amide nitrogen to give access to the required cis amide:



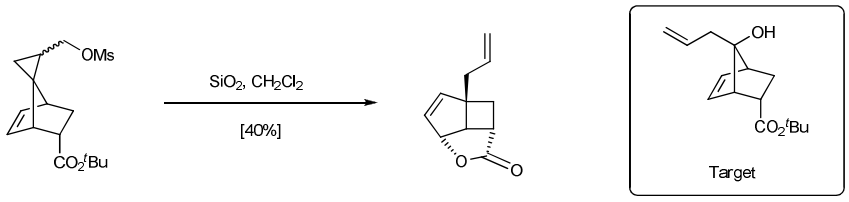
From RCM our research effort moved into the more challenging field of tandem metathesis; that is carrying out a ring opening metathesis reaction and subsequently a ring closing metathesis reaction to generate a new ring system:



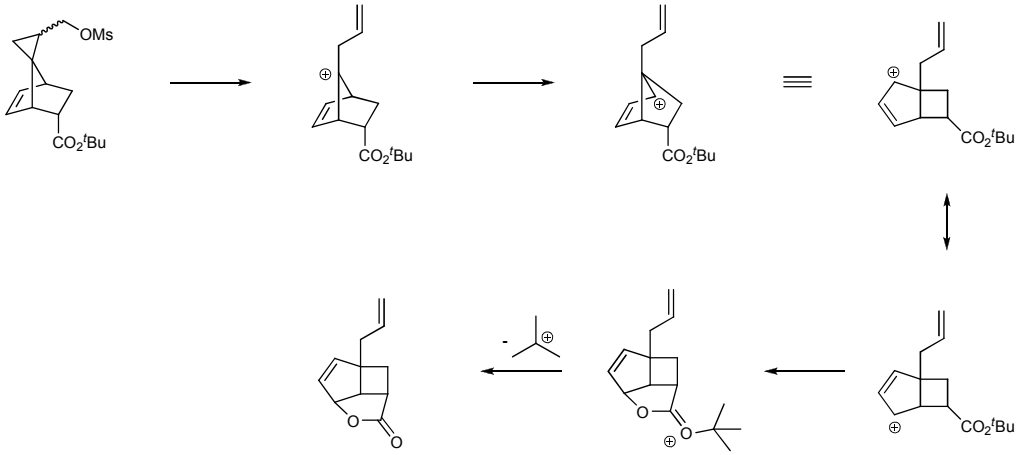
This methodology enables the synthesis of a number of highly constrained amines, α- and β-amino acids in excellent yields from easily accessed starting materials:[3,4,5]



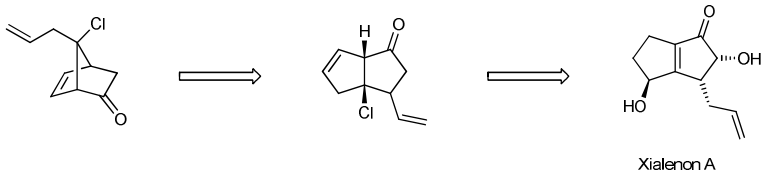
In an attempt to access a 7-allyl substituted norbornene derivative for natural product synthesis we encountered a series of structure dependent cationic rearrangements. Initially, preparation of a cyclopropylmethanol substituted norbornene should have enabled preparation of the 7-allyl substituted norbornene:



Analysis of this reaction and those of similar substrates revealed that the outcome of the reaction was highly dependent on the structure of the starting material. In the case above, a tri-cyclic lactone was found to be the major product. The mechanism for this rearrangement was proposed to involve a series of cationic intermediates:[6]



Current efforts are directed towards the application of this chemistry in the arena of natural products synthesis. In particular we are utilizing the lessons learnt from our olefin metathesis and rearrangement studies to develop a novel synthesis of xialenon A:



Xialenon A

References:

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Drug Delivery Systems for Drug Eluting Stents

A collaborative effort with Biointeractions Ltd

Coronary heart disease (CHD) is the leading cause of death in the developed world, with a death rate of greater than 450,000 per annum in the USA.[1] The disease usually begins with atherosclerosis (Figure 1), the build up of fatty deposits (plaque) on the inner lining of arteries, leading to a narrowing of the lumen (stenosis) and a consequential restriction in blood flow, which can result in angina, heart attack, stroke or vessel rupture.

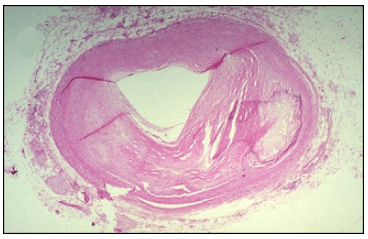

Figure 1: Atherosclerosis

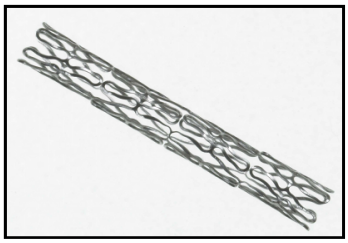

Figure 2: Coronary stent

Stents (Figure 2) have been employed, in conjunction with angioplasty, for the treatment of the disease since the early 1990's and have reduced problems such as recoil and negative remodelling.[2] However, the long term efficacy of bare metal stenting is limited by in-stent restenosis, which occurs in 15 to 30% of patients.[3] In-stent restenosis can be attributed primarily to neointimal hyperplasia. Investigations have culminated in the development of drug-eluting stents (DES), which utilise the stent struts as the drug delivery platform for the localised administration of an array of active agents.

Although current DES systems have proven successful in the treatment of in-stent restenosis, concerns still remain regarding the long-term efficacy of such systems. Inefficient drug delivery and late thrombotic complications, which are attributed to the poor biocompatibility of the polymer utilised as the delivery vehicle, have prompted a need for further development of such systems, as well as the drugs that are eluted.

Our research has been focused towards the development of a highly tuneable biocompatible delivery system (Figure 3) for the efficient release of drugs, such as paclitaxel (Figure 4) and rapamycin. Further, pendant functional groups present along the *co*-polymer backbone allow for chemical immobilisation of biologically active molecules, such as heparin. The successful immobilisation of therapeutic heparin onto our delivery system has been achieved *via* a thermally-induced *in situ* cross-linking of a suitable heparin derivative, which is aimed at providing the stent with long-term anti-thrombogenic properties.

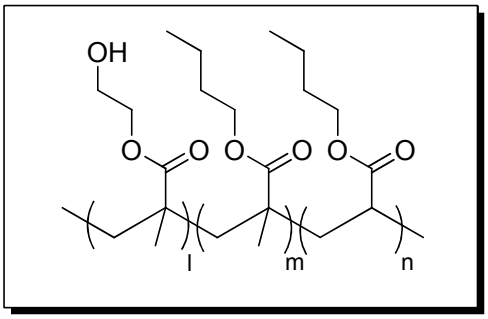

Figure 3. Poly(2-hydroxyethyl methacrylate-*co*-butyl methacrylate-*co*-butyl acrylate)

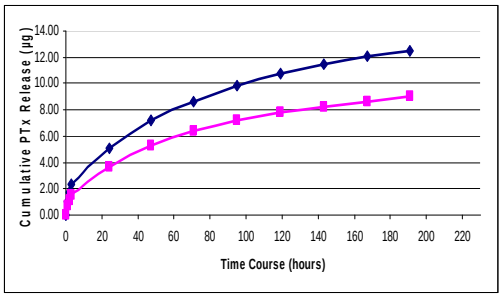

Figure 4. *In-vitro* paclitaxel release rates

Investigations have also been directed towards the synthesis of novel rapamycin analogues. Rapamycin carbonate esters (Figure 5) have been achieved *via* a highly regioselective enzyme mediated process. It is believed that this strategy will furnish potent anti-cancer/anti-restenotic agents, suitable for use in chemotherapy and DES applications.

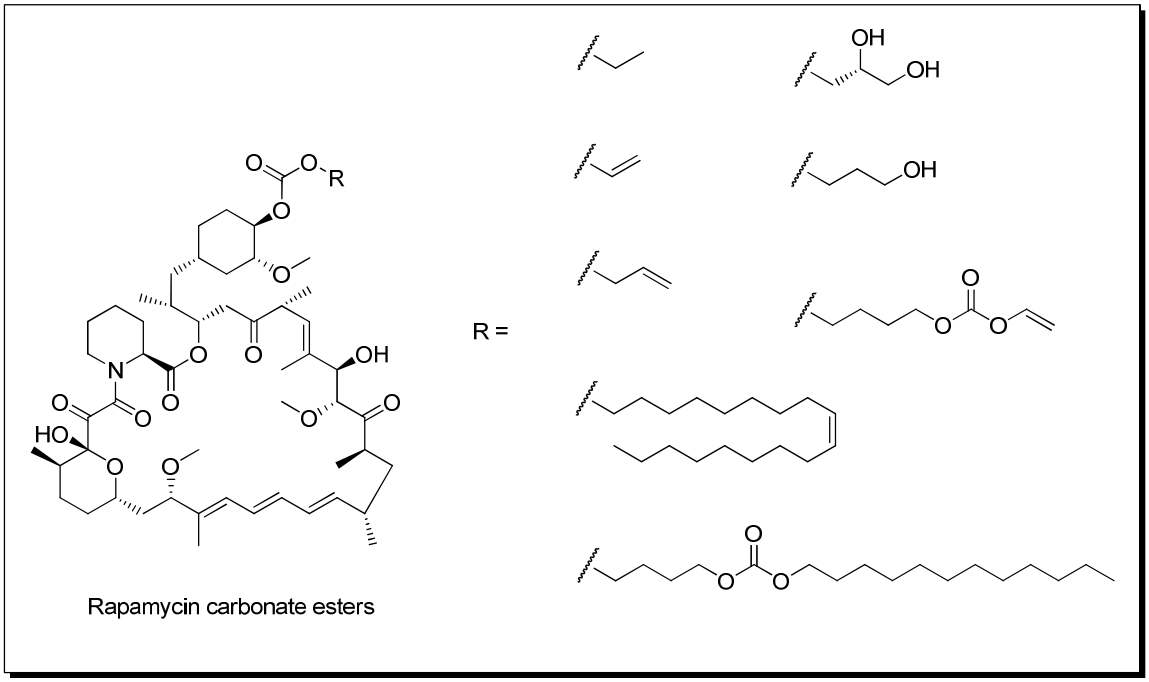

Figure 5. Carbonate esters of rapamycin

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