Construction of fused polycyclic ethers by strategies involving ring-closing metathesis

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Large fused polycyclic ether natural products of marine origin are some of the most complex and formidable synthetic targets found in Nature, and they continue to fascinate and inspire those engaged in target-directed synthesis and the development of new synthetic methods. Novel strategies for the rapid and stereoselective assembly of fused polyethers have been devised in which ring-closing metathesis reactions are used to accomplish cyclic ether construction. Two-directional and iterative ring construction approaches involving ring-closing metathesis are being employed to assemble polyether sequences found in marine natural products such as the ciguatoxins and gambieric acids.

Introduction

Laddered polyether natural products of marine origin, such as CTX-3C and gambieric acid A, are amongst the largest and most complex targets to have confronted practitioners of natural product synthesis.[1] Since the isolation and characterisation of brevetoxins A and B, the first members of the fused polycyclic ether family of natural products, in the early 1980s, a variety of structurally related and more complex laddered polyethers have been isolated from marine dinoflagellates and organisms that feed on these algae.[1] The fused polyether family of marine natural products now includes hemibrevetoxin B,[2] brevetoxins A and B,[3,4] the ciguatoxins,[5] gambieric acids A–D,[6] gymnocins A and B,[7] the yessotoxins,[8] adriatoxin,[9] the prymnesins,[10] gambierol,[11] brevenal,[12] and maitotoxin,[13] the largest and most toxic non-biopolymeric natural product to have been isolated.

At the time of their isolation, the brevetoxins were immediately recognised as highly alluring synthetic targets because of their unprecedented structures, high degree of structural complexity and potent neurotoxicity. However, throughout the 1980s a relatively small number of research groups attempted to synthesise these large marine polyethers. The reticence of synthetic chemists to engage in the construction of the targets at that time is attributable to their size and the general dearth of methods that were available for the stereocontrolled synthesis of medium-sized cyclic ethers.

Much of the early pioneering work on new synthetic methodology for the assembly of laddered polyethers was performed by Nicolaou and co-workers; their ambitious research program culminated in the synthesis of hemibrevetoxin B and the larger and more complex brevetoxins (A and B) in the mid-1990s.[14] Since the early 1990s, there has been an explosion of interest in the synthesis of laddered polyether natural products by other research groups and there is now a burgeoning literature concerning new methods for the synthesis of *trans* fused polycyclic ethers and their application to the synthesis of marine polyether natural products. In the past five years, several impressive total syntheses of fused polyether natural products of marine origin have appeared in the literature: the syntheses of gambierol by the groups of Rainier, Yamamoto and Sasaki,[15] CTX-3C by Inoue and Hirama (Fig. 1),[16] gymnocin A by Sasaki and co-workers,[17] and brevetoxin B by the groups of Nakata and Yamamoto[18] are testimony to tremendous advances that have taken place in this area of target directed synthesis.[19]

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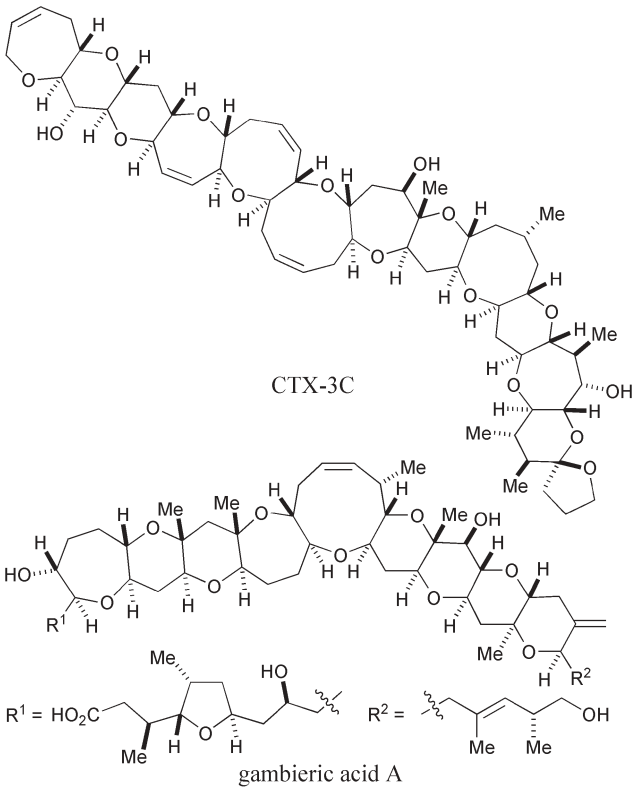
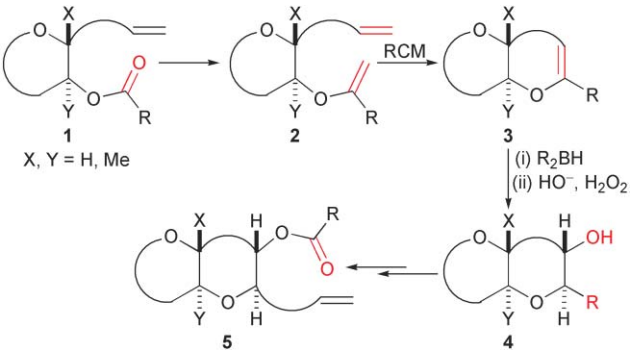


Fig. 1 Examples of laddered polyether natural products of marine origin.

The unique and enticing structures of the fused polyether marine natural products and the daunting synthetic challenges they present had fascinated me from the beginning of my scientific career. In 1994 my research group embarked on a new research programme with the goal of synthesising members of this class of natural product in a highly efficient manner. At that time, no member of the polyether family of natural products had been constructed by total synthesis. In fact, there was no single, general method for the assembly of cyclic ethers of all sizes found in the natural products and, in addition, medium-ring ether construction presented very significant challenges. Consequently, the primary objective of our new research programme was the identification of novel general strategies for the efficient synthesis of fused polycyclic ethers which would be robust and would rely on rapid iterative ring construction using a limited 'tool kit' of high-yielding synthetic transformations.

Cyclic ether synthesis by ring-closing metathesis of enol ethers

The first approach that we devised for the rapid iterative preparation of fused cyclic ethers involved sequential ring-closing metathesis (RCM) of an acyclic enol ether followed by hydroboration of the resulting cyclic enol ether (Scheme 1). The sequence would commence with the enol ether **2** prepared from the ester **1** (*vide infra*). Cyclisation by RCM and subsequent regioselective and stereoselective hydroboration of the cyclic enol ether **3** would deliver the alcohol **4**. Esterification and generation of an alkene in the side chain



Scheme 1

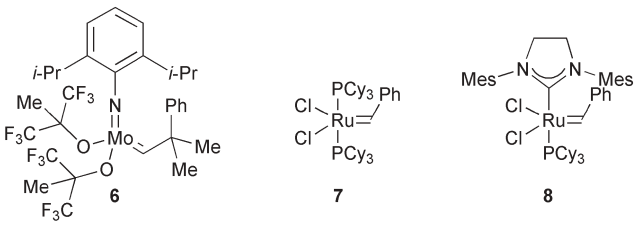
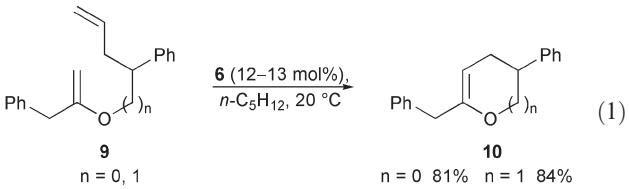


Fig. 2 Catalysts for ring-closing metathesis.

would then produce the compound **5**, bearing the same functional group motif found in the ester **1**, and complete one iteration of the ring construction sequence (Scheme 1).

There were no precedents for the successful RCM of enol ethers at the time we began to explore the synthetic sequence summarised above, but the stereoselective hydroboration of related cyclic enol ethers had been reported.[20] We expected to effect RCM using the molybdenum complex **6** or the ruthenium complex **7** (Fig. 2),[21,22] but recognised that reaction of an enol ether with either of these complexes would lead to a Fischer carbene type complex which might have reactivity characteristics differing from those of the original alkylidene complexes or intermediates generated by their reaction with unfunctionalised alkenes.

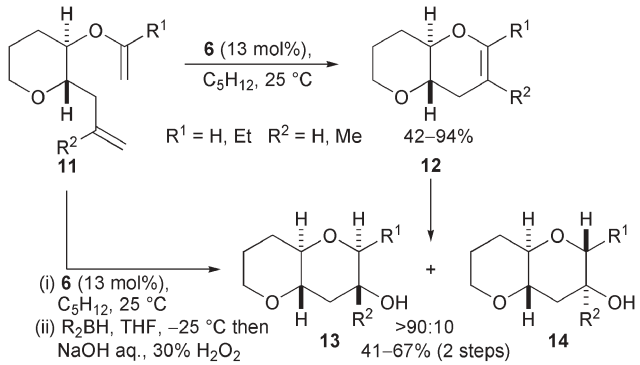
Shortly after the research project was initiated, Grubbs and co-workers demonstrated that is was possible to prepare the simple dihydrofurans and dihydropyrans **10** in good yield by RCM of the simple acyclic enol ethers **9** (eqn (1)).[23] Although this work provided an important precedent, relatively simple substrates were used and kinetically favourable rings were produced. It was not clear whether RCM of enol ethers could be used to prepare the more challenging medium-ring ethers (ring sizes 7–9) which are ubiquitous in laddered polyether natural products.



(1)

Grubbs and co-workers

Preliminary studies concerning enol ether RCM were performed using model systems in order to demonstrate that the reaction could be used to prepare fused systems possessing



Scheme 2

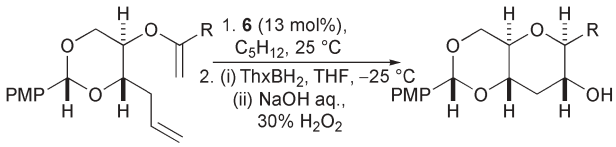
six- or seven-membered rings (Scheme 2). It was also necessary to establish whether subsequent hydroboration reactions would deliver cyclic ethers of the type found in the marine polyether natural products, in a highly stereoselective manner.

The requisite enol ether RCM precursors **11** were prepared in reasonable yield by methylenation of the corresponding esters using the Takai protocol (Scheme 2).[24] Treatment of the cyclisation precursors **11** with complex **6** (13 mol%) afforded the bicyclic enol ethers **12** in variable yields depending on the nature of the substituents R^1 and R^2 – variations in isolated yields were due to the instability of the cyclic enol ethers to chromatographic purification.[25] Efficient conversion of the enol ethers **12** into the required alcohols **13** was accomplished by regioselective hydroboration; high levels of diastereocontrol were achieved when thexyl borane was employed as the hydroborating agent at −25 °C. It was also possible to hydroborate the crude cyclic enol ethers **12** after short-path filtration to remove catalyst debris, so that extensive purification and handling of the acid-sensitive cyclic enol ethers was avoided. The yields of the bicyclic ethers prepared in this way ranged from good to excellent and the fact that the products were obtained in a highly diastereoselective fashion favouring the required isomer **13** instead of the diastereoisomer **14** was particularly significant.[25]

The RCM reactions of the enol ethers **11** using the ruthenium complex **7** (Fig. 2) were also explored. The ruthenium complex **7** is easier to prepare and handle than the molybdenum complex **6**, and is frequently used to construct heterocycles and carbocycles by RCM. Unfortunately, the complex **7** proved to be completely ineffective for the cyclisation of the *substituted* enol ethers **11** ($R^1 \neq H$) used in this study. Recently, the 'second generation' ruthenium complex **8** has been employed for the RCM of enol ethers, but at this early stage in our research program this pre-catalyst was not available.

The preparation of tetrasubstituted bicyclic enol ethers **12** (R^1, $R^2 \neq H$, Scheme 2) by RCM was also explored, but the precursors **11** (R^1, $R^2 \neq H$) failed to undergo ring closure upon exposure to either the complex **6** or **7**. Although tetrasubstituted cycloalkenes have been prepared by RCM, the relatively low reactivity of enol ethers combined with unfavourable steric interactions during the formation of tetrasubstituted systems appears to preclude intramolecular cyclisation of these substrates.

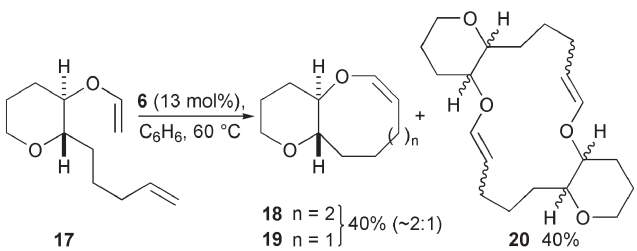
It was possible to use RCM reactions to prepare more highly functionalised cyclic ethers which could be used as building blocks for preparation of larger polyether arrays (eqn (2)). The substrates **15a** and **15b** (prepared from mannitol in non-racemic form) underwent sequential RCM and hydroboration to deliver fully functionalised tetrahydropyran building blocks **16a** and **16b** in good yield.[26] The alcohol **16b** possesses differential protection allowing selective functionalisation of the side chain and the secondary hydroxyl group followed by elaboration of either of the masked hydroxyl groups that are tethered in the cyclic acetal.



15 **a** R = Et 71% **b** R = $(CH_2)_3$OTBS 54% **16**

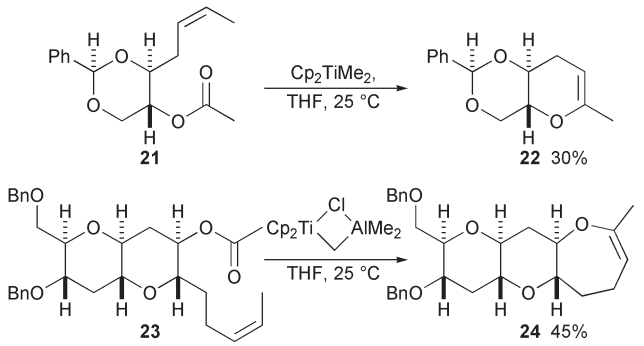
(2)

The construction of the most challenging medium-ring (eight- and nine-membered) cyclic enol ethers by RCM proved to be extremely problematic. It was possible to construct the eight-membered cyclic enol ether **18** by RCM of the substrate **17**, but the reaction was complicated by competing cyclodimerisation and isomerisation (eqn (3)).[25] Treatment of the vinyl ether **17** with the molybdenum complex **6** (13 mol%) under high dilution conditions afforded an inseparable mixture of the required cyclic ether **18** and the lower homologue **19** in a combined yield of 40% (~2 : 1 ratio), along with an equivalent amount of the cyclo-dimer **20**. The cyclic enol ether **19** was produced by sequential isomerisation and metathesis, which was unprecedented at the time. Subsequently, other reports of alkene isomerisation during RCM have appeared in the literature and it is now clear that isomerisation can be a significant competing process in cases where ring closure is relatively slow.[27] Analogous isomerisation products were not obtained from the RCM reactions of other enol ether substrates or during ring closure of allylic ether substrates to give eight- and nine-membered cyclic ethers (*vide infra*). The formation of the cyclodimer **20** at high dilution also indicates that ring closure is slow. Interestingly, re-submission of the cyclodimer **20** to the RCM reaction conditions did not lead to formation of further amounts of the enol ethers **18** and **19**, which suggests that the macrocyclic compound **20** is a "dead-end" product resulting from irreversible RCM.[25]



(3)

While our studies were in progress and just prior to disclosure of our preliminary results concerning RCM of enol ethers, Nicolaou *et al*. reported that olefinic esters could be converted directly into six- and seven-membered enol ethers by tandem methylenation and metathesis using an excess of the

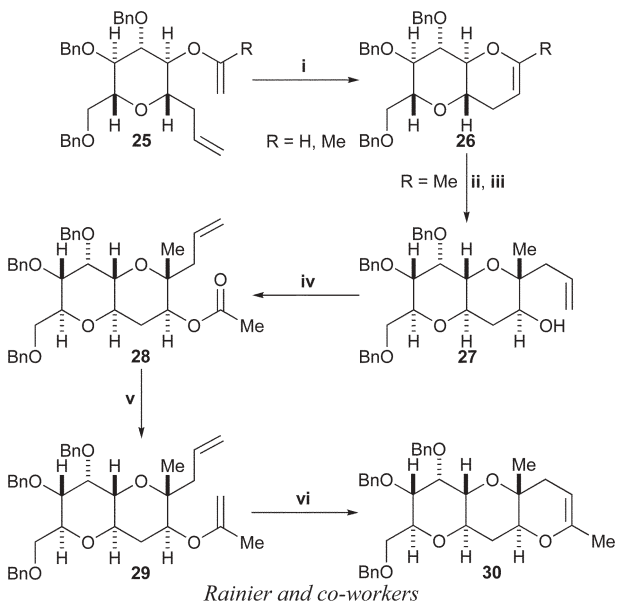


Nicolaou and co-workers

Scheme 3

Tebbe reagent (Scheme 3).[28] This approach has the advantage that ring closure can be effected directly from the ester, but the yields are modest in nearly all cases and sterically unencumbered acetates (*e.g.* compounds **21** and **23**) were employed as cyclisation precursors. Nevertheless, this work clearly demonstrates the potential of RCM for the construction of fused polycyclic arrays (*e.g.* enol ethers **22** and **24**) of the type found in the laddered polyether marine natural products.

The construction of polycyclic ethers by RCM of enol ethers has also been explored by Rainier *et al*.[29] In contemporaneous studies, they demonstrated that it was possible to convert the enol ethers **25** into the bicyclic enol ethers **26** by RCM mediated by the molybdenum catalyst **6** (Scheme 4). Instead of functionalising the cyclic enol ether products by hydroboration, Rainier *et al*. converted the enol ether **26** (R = Me) into an epoxide, *via* a bromohydrin, and then opened the epoxide at the anomeric position using allylmagnesium bromide to give the alcohol **27** as the major product (6 : 1 ratio of



Rainier and co-workers

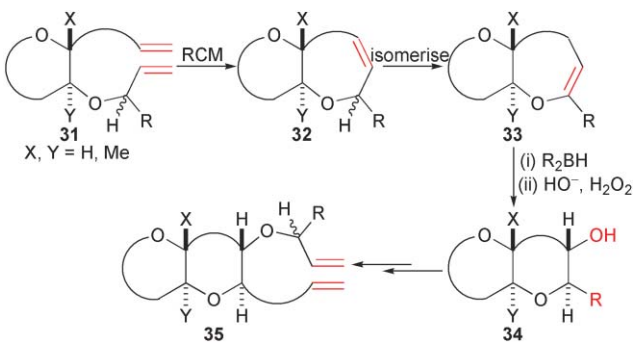
Scheme 4 *Reagents and conditions:* i, **6**, C_6H_{14}, 60 °C (R = H, 85%; R = Me, 76%); ii, NBS, DMF aq., −55 °C; iii, KH, 18-crown-6, PhMe, −65 °C then CH_2CHCH_2MgBr; iv, Ac_2O, DMAP, *i*-Pr_2NEt, CH_2Cl_2, 0 °C (37% over 3 steps); v, CH_2Br_2, Zn, $TiCl_4$, TMEDA, $PbCl_2$, THF, 60 °C (57%); vi, **6**, C_6H_{14}, 60 °C (80%).

diastereoisomers). Subsequent acetylation and methylenation of the resulting ester **28** then provided the enol ether **29** and a further RCM reaction delivered the cyclic enol ether **30**, demonstrating that it is possible to use the reaction sequence for the iterative construction of *trans*-fused polyethers containing tetrahydropyrans.[29] In more recent studies, Rainier *et al*. have shown that it is possible to use dimethyl dioxirane (DMDO) to directly epoxidise cyclic enol ethers in a stereoselective manner in cases where ring junction methyl groups or adjacent substituents are present to control the stereochemical outcome of the reactions.[29d] Subsequent opening of the epoxides at the anomeric position with a Grignard reagent or reducing agent then delivers fully functionalised cyclic ether units. This methodology has been exploited to good effect by Rainier *et al*. in a formal synthesis of hemibrevetoxin B and a total synthesis of gambierol.[29c,30,15e]

Construction of medium-ring cyclic ethers by ring-closing metathesis of allylic ethers

It was evident from our initial results that enol ethers are relatively unreactive substrates for RCM. In an effort to construct the synthetically challenging medium-ring cyclic ethers found in many fused polyether natural products, we turned our attention to an investigation of the more reactive allylic ethers as cyclisation precursors. Grubbs and Fu had already demonstrated that allylic ethers are excellent RCM substrates and have a similar reactivity profile to that of unfunctionalised alkenes.[31a] Crucially, Grubbs had also shown that RCM reactions of allylic ethers can be performed using the stable but less reactive ruthenium complex **7** instead of the molybdenum complex **6**.[31b]

A new sequence for the synthesis of medium-ring cyclic ethers was devised involving the RCM of allylic ethers rather than enol ethers (Scheme 5). In this sequence, ring closure of the substrate **31** would give the cyclic allylic ether **32** and subsequent metal-mediated isomerisation reaction would deliver the cyclic enol ether **33**. Hydroboration would then be performed as before to give the alcohol **34** and further elaboration would deliver the allylic ether **35** ready for subsequent annulation by RCM. The allylic stereogenic centre would be lost upon isomerisation to give the enol ether **33** and so in principle it would not be necessary to set the configuration at this centre prior to RCM. However, it was conceivable that the diastereomeric allylic ethers **32** would



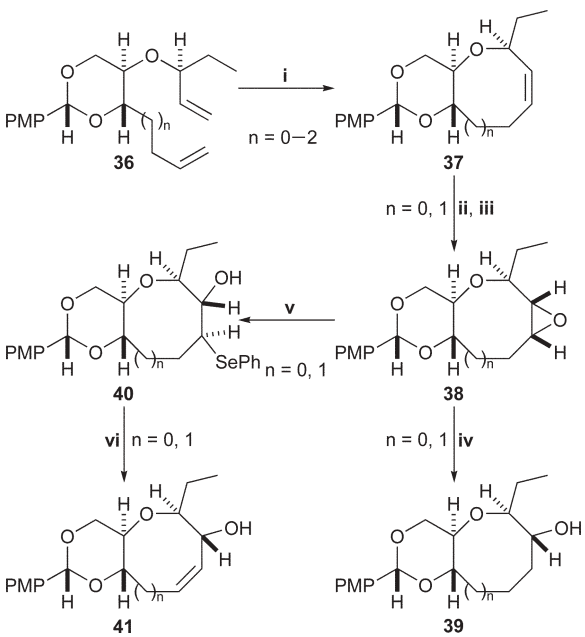
Scheme 5

undergo ring closure at different rates or that, in extreme cases, one diastereoisomer might not undergo RCM at all. In addition, there was the possibility that the diastereoisomeric cyclic allylic ethers **32** might behave differently during the isomerisation reaction.

The precursors **36** employed to study the allylic ether RCM reaction were readily prepared as single diastereoisomers in non-racemic form from (*R*)-2,3-*O*-isopropylidene glyceraldehyde (Scheme 6).[32] Initially, the configuration at the allylic stereogenic centre was deemed to be unimportant, but isomerisation after ring closure proved to be problematic and so it was necessary to control the configuration at the allylic stereogenic centre.

The RCM reactions of each of the allyl ethers mediated by the catalysts **6** and **7** were investigated (Scheme 6). Substrates having the relative stereochemical relationship between the allylic stereogenic centre and those adorning the cyclic acetal corresponding to that found in the natural products (*i.e.* the dienes **36**), underwent ring closure in excellent yield under moderately high dilution conditions.[32] However, the RCM reaction of the diastereoisomer of **36** (n = 2) having opposite configuration at the allylic stereogenic centre afforded the nine-membered cyclic ether product in very low yield. The differing behaviour of the substrate **36** (n = 2) and its allylic diastereoisomer is remarkable, and presumably reflects unfavourable steric interactions between the ethyl substituent and the cyclic acetal in the transition state required for cyclisation of this allylic ether substrate.

Isomerisation of the medium-ring allylic ethers **37** to give the corresponding enol ethers was not successful. Several reagents and protocols were investigated but these reactions resulted in slow isomerisation and the unstable enol ether products underwent substantial degradation at rates which were competitive with those of the isomerisation reactions. As a consequence it was necessary to devise methods by which the cyclic allylic ethers could be converted directly into fully functionalised medium-ring ether building blocks.

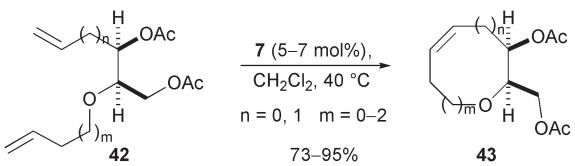


Scheme 6 *Reagents and conditions*: i, **6** or **7**, C_6H_6 or CH_2Cl_2, rt → 60 °C (n = 1, 86%; n = 2, 97%; n = 3, 86%); ii, NBS, DME, H_2O, rt; iii, *t*-BuOK, *t*-BuOH, C_6H_6, reflux (n = 1, 79% over 2 steps; n = 2, 72% over 2 steps, 8 : 1 ratio of isomers); iv, $LiEt_3BH$, THF, reflux (n = 0, 82%; n = 1, 91%); v, PhSeNa, EtOH, reflux; vi, 30% H_2O_2 aq., EtOH–THF, reflux (n = 0, 62% over 2 steps; n = 1, 61% over 2 steps).

Epoxidation of the cyclic allylic ethers was an attractive option that ultimately proved to be successful (Scheme 6).[32b] Epoxidation of the allylic ethers **37** with reagents such as *m*-CPBA or DMDO was highly stereoselective and delivered modest yields of epoxides, but the products were diastereoisomers of the required compounds. In contrast, indirect epoxidation of the allylic ethers by reaction with bromine under aqueous conditions and treatment of the resulting bromohydrins with base delivered the epoxides **38** in good yield and with high levels of stereocontrol favouring the required diastereoisomers.[32b] Remarkably, the intermediate bromonium ion was not intercepted by the ether oxygen during formation of the intermediate bromohydrin.

The epoxides **38** were converted into either saturated or unsaturated medium-ring ethers of the type commonly found in the laddered polyether toxins and related marine natural products (Scheme 6).[32b] Regioselective reduction of the epoxides **38** with Super-Hydride® afforded the alcohols **39** in excellent yield and without acetal cleavage. In the case of the epoxide **38** (n = 0), a small amount (7% yield) of the regioisomeric alcohol was also produced whereas ring opening of the epoxide **38** (n = 1) was entirely regioselective. The unsaturated cyclic ethers **41** were obtained in reasonable yield by regioselective opening of the epoxides **38** with sodium phenylselenide to give the selenides **40**, followed by oxidation and thermal elimination of the resulting selenoxides. Epoxide ring opening was regioselective and the sequence gave the allylic alcohol **41** (n = 0) predominantly and the homologue **41** (n = 1) exclusively.

Crimmins and Choy have employed a similar strategy to ours in order to prepare medium-sized cyclic ethers (eqn (4)).[33] In their work, the diacetates **42** possessing allylic or longer chain alkenyl ethers were employed as RCM substrates and the yields of cyclic ethers **43** ranged from good to excellent. The RCM substrates **42** differ from most of the substrates used in our work in one crucial respect: they do not possess a cyclic conformational constraint but instead rely on the conformational preferences of the open-chain system to predispose the precursor toward ring closure in high yield.



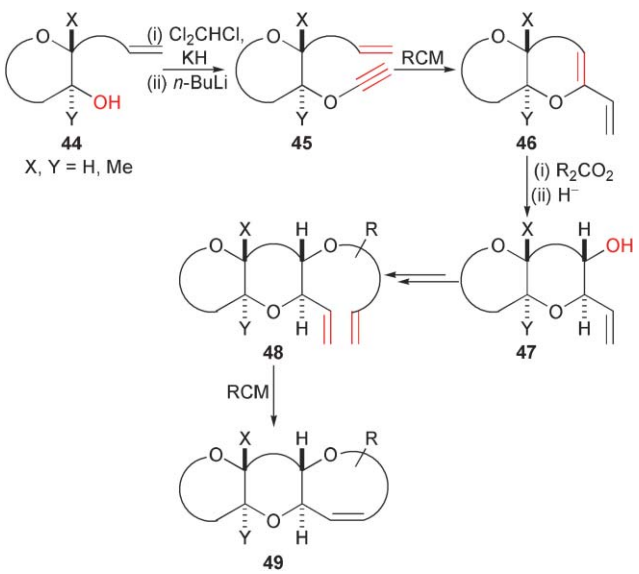
Crimmins and Choy

Crimmins and co-workers have firmly established the synthetic viability of their approach to cyclic ether construction by successfully using the methodology to synthesise the medium-ring ether marine natural products (+)-laurencin, (+)-prelaureatin, (+)-laurallene, (−)-isolaurallene and (+)-obtusenyne,[34] as well as fragments of the laddered polyether natural product brevetoxin A.[35]

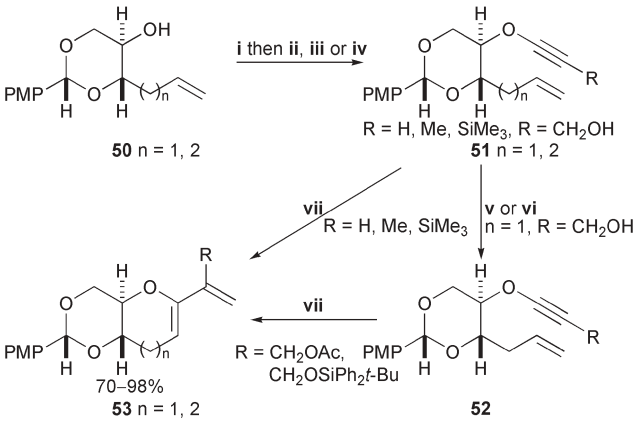
Synthesis of cyclic ethers by RCM of alkynyl ethers

The construction of cyclic ethers by RCM of alkynyl ethers has also been investigated as an approach to complement those routes involving the RCM of enol ethers and allylic ethers. At the time we embarked on this phase of our programme, several examples of the use of enyne RCM reactions to construct carbocycles and heterocycles had recently appeared in the literature.[36] It was clear from these early precedents that enyne RCM had the potential to increase the flexibility of our synthetic strategy. We expected that conversion of the alcohol **44** into the alkynyl ether **45** followed by enyne RCM would deliver the diene **46** as a versatile intermediate (Scheme 7). We anticipated that it would be possible to functionalise the diene **46** by selective epoxidation of the relatively electron-rich enol ether under mild conditions. Subsequent regioselective ring opening of the epoxy acetal would then deliver the alcohol **47**. Attachment of an unsaturated chain to the secondary hydroxyl group would then give the diene **48** and an additional cyclic ether could be constructed by RCM of the *O*-tethered alkene with the pendant vinyl group, to give the fused polycyclic system **49**. It was clear that incorporation of this reaction sequence into a general strategy for polyether construction would provide additional synthetic diversity and flexibility.

Preliminary studies were performed in order to establish whether alkynyl ethers[37] would undergo metathesis using the molybdenum complex **6** or the ruthenium complexes **7** and **8** (Scheme 8).[38a] It transpired that the molybdenum complex **6** is not a suitable pre-catalyst in the context of enyne RCM, and so we focussed on using the ruthenium complexes **7** and **8** to facilitate this transformation. We had already established that substituted enol ethers are much less reactive than standard alkenes in RCM reactions and are poor substrates for RCM using the ruthenium catalyst **7**, but it was not clear whether alkynyl ethers would display an analogous decrease in reactivity compared to conventional alkynes. It was also necessary to establish whether terminal alkynyl ethers would



Scheme 7



Scheme 8 *Reagents and conditions*: i, KH, THF, rt then Cl_2CCHCl, −50 °C → rt (82–90%); ii, *n*-BuLi, Et_2O, −78 → −10 °C then H_2O or MeI, DMPU (R = H, Me, 77–88%); iii, *n*-BuLi, Et_2O, −78 °C then Me_3SiCl, −78 → 0 °C (R = $SiMe_3$, 46–87%); iv, *n*-BuLi, Et_2O, −78 → −10 °C then CH_2O, −10 °C → rt (*n* = 1, R = CH_2OH, 66%); v, Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt (83%); vi, *t*-$BuPh_2SiCl$, imidazole, CH_2Cl_2, rt (94%); vii, **8**, CH_2CH_2, PhMe, 75 °C (70–98%).

be viable substrates because there was some literature data to suggest that terminal alkynes are poor substrates for RCM.

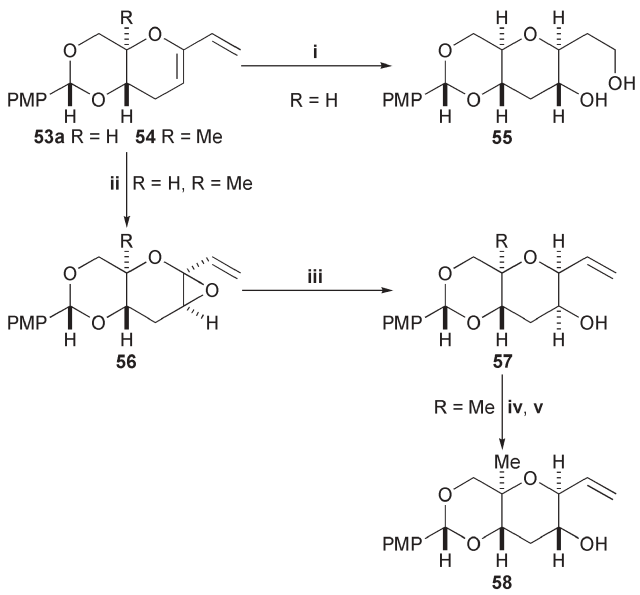
The functionalised alkynyl ethers **51** and **52** employed in the study were prepared using a modification of Greene's method for the synthesis of alkynyl ethers from hindered secondary alcohols (Scheme 8).[37] The original method involves deprotonation of the alcohol and reaction of the resulting alkoxide with trichloroethene followed by treatment of the resulting chlorinated enol ethers with *n*-butyllithium in a one-pot fashion. However, variable yields were obtained when this one-pot procedure was employed to convert the alcohols **50** directly into the alkynyl ethers **51** (R = H). Fortunately, reliable yields were obtained when the crystalline chlorinated enol ethers were isolated and then treated with *n*-butyllithium in a separate reaction. The combined yields over two steps were comparable to those obtained by Greene and co-workers when they used their one-pot procedure to prepare analogous alkynyl ethers. It was also possible to prepare the functionalised alkynyl ethers **51** (R ≠ H) directly from the chlorinated enol ethers by trapping the intermediate alkynyl anions with various electrophiles.[38]

The RCM reactions of the alkynyl ethers **51** and **52** promoted by the pre-catalysts **7** and **8** were explored in detail (Scheme 8).[38] Treatment of each substrate with the complex **7** in dichloromethane at reflux or the complex **8** in toluene at 80 °C, afforded the alkenyl-substituted cyclic enol ethers **53**. In several cases, the dienes **53** were crystalline solids and the structures were confirmed by X-ray crystallography.[38] In all but one case, the highest yields were obtained when more reactive complex **8** was employed as the pre-catalyst. When this ruthenium alkylidene complex was used, the six-membered cyclic ethers **53** (*n* = 1) were obtained in ~90% yield and seven-membered cyclic ethers **53** (*n* = 2) were formed in >70% yield. The complex **8** was a particularly effective pre-catalyst in cases where the alkynyl ether cyclisation precursor possesses a bulky substituent (*e.g.* $SiMe_3$) or a seven-membered cyclic ether is produced. The only case in which the complex **7**

proved to be superior to the complex **8** as pre-catalyst was for the cyclisation of the substrate **51** (n = 1, R = CH_2OH). When the reaction was performed using the ruthenium complex **8**, only a trace amount of the product **53** (n = 1, R = CH_2OH) was produced after several days, and most of the enyne starting material was recovered. In this case, the ruthenium centre appears to complex to the free hydroxyl group to such an extent that release of the catalyst from the metal alkylidene generated upon ring closure is prevented and an efficient catalytic cycle is not established.

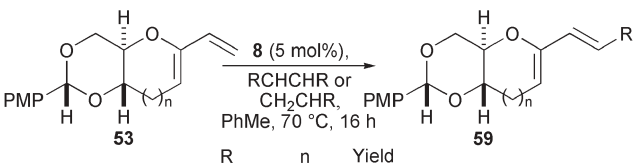
Two other important findings emerged from the results of the studies on the enyne metathesis reaction. Firstly, terminal alkynyl ethers, such as **51** (R = H) are good substrates for the ruthenium-catalysed enyne RCM reaction, and secondly the formation of seven-membered cyclic ethers **53** (n = 2) is significantly more difficult to achieve than ring closure to give the corresponding six-membered cyclic ethers **53** (n = 1).

Functionalisation of the dienes resulting from enyne RCM proved to be rather awkward. Hydroboration of the dienes **53** with borane or dialkylboranes led to complex mixtures of products that appeared to arise from rearrangement of the intermediate organoborane (Scheme 9). It was possible to convert the diene **53a** into the diol **55** by successive treatment with 9-BBN and borane–THF complex, but the yield was low and so this approach was deemed to be non-viable.[39] In contrast, sequential epoxidation of the dienes **53a** and **54** cleanly afforded the epoxides in a regioselective manner.[40] Subsequent selective ring opening at the anomeric position was accomplished by treatment of the epoxides **56** with Super-Hydride®. The products **57** had incorrect configuration at the hydroxyl-bearing stereogenic centre, but in the case of the alcohol **57** (R = Me) this was corrected by oxidation and subsequent stereoselective ketone reduction with sodium borohydride to give the required alcohol **58**.[40]



Scheme 9 *Reagents and conditions*: i, (i) 9-BBN, THF, rt then BH_3.THF, THF, 0 °C, (ii) NaOH aq., 30% H_2O_2 aq., rt (25%); ii, DMDO, CH_2Cl_2, 0 °C; iii, $LiEt_3BH$, THF, 0 °C (R = H, 61%; R = Me, 69%); iv, Dess–Martin reagent, CH_2Cl_2, rt; v, $NaBH_4$, CH_2Cl_2, MeOH (79%).

Another potentially attractive way of solving the problem of selective functionalisation of the dienes **53** (R = H) was to employ cross metathesis to install a complex side chain immediately after RCM of the alkynyl ethers **51** (R = H).[41] However, there were two obvious potential problems with this sequence of reactions: competitive dimerisation by homo-metathesis and re-opening of the ring in enyne metathesis products under the cross-metathesis conditions. The latter issue is critical because generation of an alkylidene from the dienes **53** could result in sequential opening of the ring and cross metathesis. Results from the groups of Grimaud and Lee[42] suggested that it would be possible to perform successful cross metathesis without competitive ring opening and so the reactions of the dienes **53** (R = H) with a variety of alkenes mediated by the ruthenium complex **8** were explored in detail (eqn (5)).[43] Cross metathesis of the diene **53** (n = 1, R = H) with allyl acetate to give the product **59** (n = 1, R = CH_2OAc) was successful, but a superior yield was obtained when the diacetate of (*E*)-2-butene-1,4-diol was used as the coupling partner. Coupling of the dienes **53** (n = 1) with allyltrimethyl-silane and the electron-deficient alkenes methyl vinyl ketone and methyl acrylate were also successful and delivered the products **59** in excellent yield.[44] However, the cross-metathesis reactions of the dienes **53** (n = 1) with acrolein, allyl bromide and allyl chloride were unsuccessful even though the diene was consumed during the reaction. The failure of these reactions is surprising because the cross metathesis of allylic halides with other alkenes is precedented. Cross metathesis reactions of the seven-membered ether **53** (n = 2) with allyl acetate, the diacetate of (*E*)-2-butene-1,4-diol, and methyl acrylate were also successful affording the products **59** (n = 2) in excellent yield.



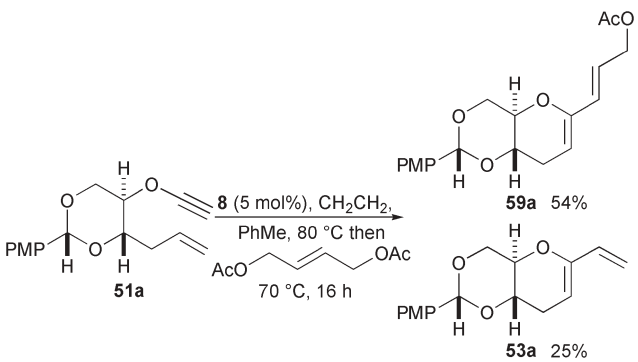
R	n	Yield
CH_2OAc	1	92%
CH_2SiMe_3	1	85%
CO_2Et	1	82%
COMe	1	60%
CH_2OAc	2	83%
CO_2Et	2	88%

(5)

The cross-metathesis reactions of the substrates bearing a pendant 1,1-disubstituted alkene were investigated, but only starting material was recovered in each case. Similarly, attempted cross metathesis of the vinylic substrates **53** with simple 1,1-disubstituted alkenes failed to deliver the expected trisubstituted alkene cross-metathesis products; substantial amounts of starting material were recovered from these reactions.

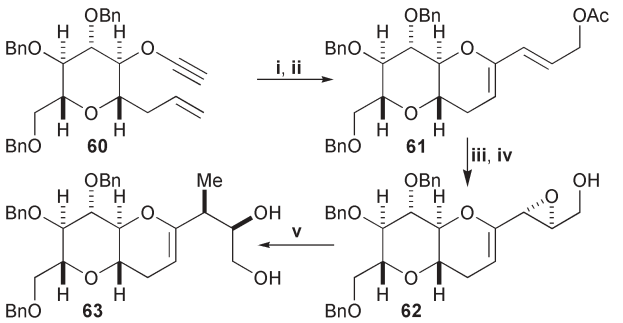
An attractive extension to the cross-metathesis approach to diene functionalisation is the possibility of performing ring-closing enyne metathesis and diene cross metathesis in a single operation. Performing the reactions in a one-pot manner presents some practical difficulties because RCM is usually

carried out under an atmosphere of ethene using moderate dilution, whereas cross metathesis is undertaken at higher concentrations with evaporative loss of a volatile alkene. Clearly, it is not possible to completely satisfy both sets of optimum reaction conditions simultaneously in a true one-pot process, but nevertheless a detailed exploration of the reaction was undertaken (eqn (6)).[43] After considerable experimentation, it transpired that the one-pot reaction could be performed by effecting enyne RCM at 80 °C in toluene (0.2 M) under an atmosphere of ethene, and then adding the diacetate of (*E*)-2-butene-1,4-diol and performing cross metathesis at 70 °C whilst purging the system with argon. Under these reaction conditions, the cross-metathesis product **59a** was obtained in 54% yield along with the RCM product **53a** in 25% yield (eqn (6)).[43] The concentration at which the reaction is performed is crucial to the success of the one-pot reaction. When the reaction was performed at higher concentrations of greater than 0.2 M, the proportion of the RCM product **53a** relative to the acetate **59b** was reduced, but the overall yield of the latter was poor. At lower concentrations (<0.01 M) there was little cross metathesis and the intermediate diene **53a** was obtained as the major product. It was also crucial for enyne RCM to be complete prior to addition of the cross-metathesis partner; mixing the alkynyl ether **51a** and the diacetate of (*E*)-2-butene-1,4-diol prior to addition of the ruthenium complex **8** led to a complex mixture of products.



(6)

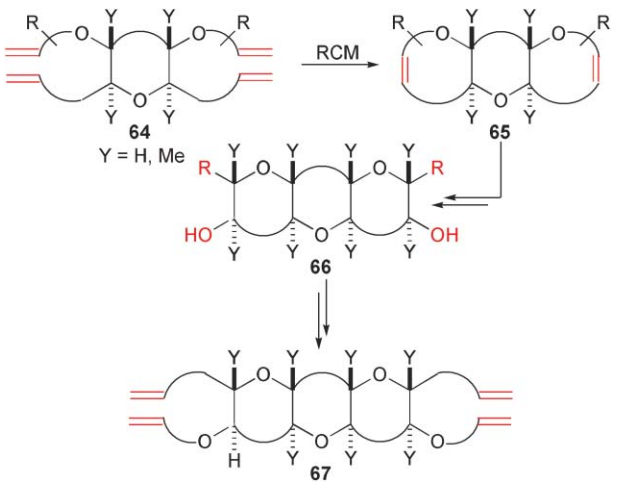
The successful replacement of the vinyl group of the enyne RCM products **53** (R = H) with elaborate side chains in a single operation is an important development. In addition to allowing rapid chain extension, cross metathesis allows selective functionalisation of the side chain to be performed without affecting the enol ether. The enol ether can then be functionalised at a later stage *i.e.* after side-chain manipulation. For example, enyne RCM of the alkynyl ether **60** followed by cross metathesis of the resulting diene with the (*E*)-2-butene-1,4-diol diacetate afforded the diene **61** in good yield (Scheme 10).[43] Acetate cleavage followed by Sharpless asymmetric epoxidation of the resulting allylic alcohol led to stereoselective and regioselective side-chain oxidation and delivered the epoxide **62**. A branching methyl substituent was then introduced by regioselective epoxide opening. The resulting diol **63** possesses a variety of functionality that can be elaborated independently.



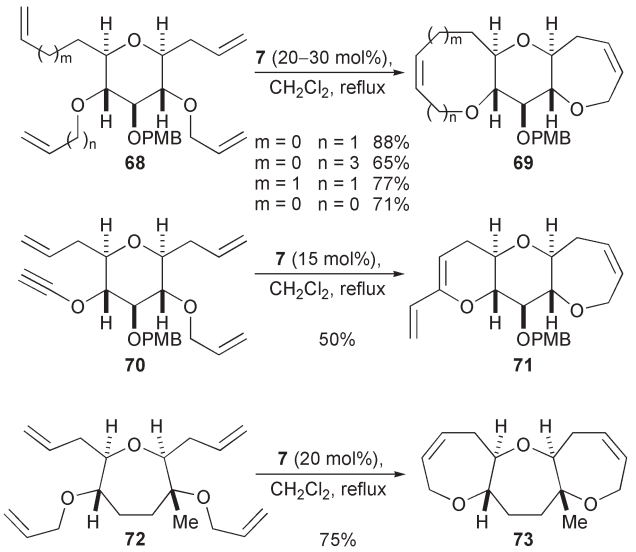
Scheme 10 *Reagents and conditions*: i, **8** (5 mol%), CH_2CH_2, PhMe, 80 °C (82%); ii, **8** (5 mol%), $AcOCH_2CHCHCH_2OAc$ (3 equiv.), PhMe, 80 °C (75%); iii, K_2CO_3, MeOH, rt (91%); iv, $Ti(O\textit{i}\text{-}Pr)_4$ (10 mol%), (+)−DET (15 mol%), *t*-BuOOH, CH_2Cl_2, −20 °C; v, MeLi, CuCN, Et_2O, −60 → 0 °C (55% over 2 steps).

Two-directional synthesis of fused polycyclic ethers

The pseudo-symmetrical nature and stereoregularity of laddered polyether natural products and the fact that high yields are obtained from the RCM reactions means that two-directional ring construction strategies involving metathesis are conceivable. In principle, two-directional chain extension would allow rapid construction of polycyclic systems that could then be joined to give the full laddered ether arrays by fragment coupling. As illustrated in a general form below (Scheme 11), double RCM of the monocyclic substrate **64** bearing four unsaturated side chains would deliver the tricyclic system **65**. Conversion of the diene **65** into the diol **66** followed by side-chain (R) elaboration and installation of the requisite unsaturated 'arms' by etherification would deliver the intermediate **67**. A second iteration of the two-directional synthetic sequence could then be performed to give a pentacyclic system corresponding to approximately half of one of the polyether natural products. It is important to note, that there are several significant challenges and potential problems inherent in this approach *e.g.* chain differentiation, issues of protecting group introduction and removal, and the requirement for high yielding reactions at every stage. It is particularly important to avoid multiple protecting group manipulations otherwise



Scheme 11

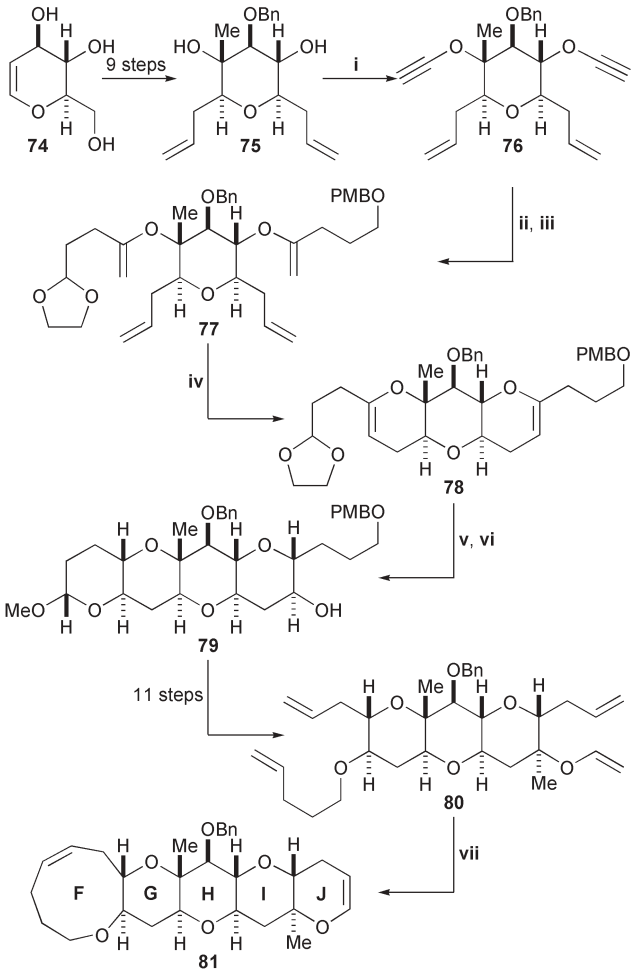


Scheme 12

the efficiency of the two-directional approach is greatly diminished.

The feasibility of two-directional synthesis using RCM was explored using model substrates **68**, **70** and **72** (Scheme 12).[44] The *trans*-fused tricyclic ethers **69**, **71** and **73** containing various ring sizes (six- to nine-membered) were prepared in reasonable to excellent yield by two-directional double RCM of substrates containing combinations of enol ether, allylic ether and alkynyl ether groups as reaction partners for the side-chain alkenes.[44] Competing ring closure across the existing cyclic ether to give bridged bicyclic or tricyclic systems was not observed during any of the reactions.

The success of our studies with the model systems prompted us to apply the two-directional strategy to the synthesis of the pentacyclic F–J fragment found in the gambieric acids (Scheme 13).[45] The synthesis commenced from D-glucal (**74**) which was converted into the fully functionalised H-ring fragment **75** in just nine steps. The first two-directional reaction involved conversion of the diol **75** into the bis(alkynyl ether) **76** by adaptation of Greene's procedure for alkynyl ether synthesis.[37] Subsequent selective sequential carbocupration[46] permitted installation of two different side chains in a highly regioselective manner and delivered the bis-enol ether **77** in excellent yield.[45] Double RCM of the substrate **77** then proceeded in high yield to give the tricyclic bis(enol ether) **78**, and hydroboration[20a] followed by mild oxidative work-up under buffered conditions afforded the required diol along with traces of diastereomeric products. Acid-catalysed cyclisation permitted selective protection of the hydroxyl group of ring G and the resulting acetal **79** was then 'armed' ready for a second double two-directional RCM reaction. Treatment of the compound **80** with the Grubbs second-generation pre-catalyst **8** delivered the complete gambieric acid F–J fragment **81**, demonstrating the viability of an iterative two-directional strategy involving RCM for the construction of complex fused polyether fragments of the type found in the laddered marine natural products.[45] The strategy is now being employed to construct a system bearing the F-ring methyl substituent and



Scheme 13 *Reagents and conditions*: i, KH, Cl_2CCHCl, THF, 0 °C then *n*-BuLi, Et_2O, −78 → −40 °C (88%); ii, $PMBO(CH_2)_3MgBr$, CuBr, LiBr, THF, −95 → −78 °C (85%); iii, $(OCH_2CH_2O)CH(CH_2)_2MgBr$, CuCN, LiCl, THF, −78 °C (84%); iv, **8** (10 mol%), PhMe, 70 °C (89%); v, thexyl borane, THF, 0 °C → rt then $NaBO_3{\cdot}4H_2O$, pH 7 buffer (62%); vi, TsOH, MeOH, rt (71%); vii, **8** (10 mol%), PhMe, 80 °C (60%).

the requisite functionality required for attachment of the A–D fragment prior to closure of the E ring and completion of the synthesis.[47]

Summary and future work

Ring-closing metathesis (RCM) offers a general and highly efficient approach to the construction of fused polycyclic ethers. Several other groups have recently employed or are employing RCM reactions for the synthesis of marine natural products of the laddered ether type. In addition to the synthetic endeavours of the Rainier and Crimmins groups already mentioned,[15e,29c,35] Hirama and co-workers made extensive use of RCM reactions in their total synthesis of CTX-3C.[16] Yamamoto and co-workers have also used RCM to assemble the final ring during their synthesis of gambierol and have used the reaction during their total synthesis of brevetoxin B.[15c,d,18b] In addition, other researchers have used RCM reactions to prepare small sub-units and polycyclic

fragments of marine polyether natural products such as yessotoxin and the gymnocins.[48]

The results presented above show that synthetic strategies for the construction of fused polyether natural products involving RCM offer flexible, efficient and rapid access to fragments of the type found in fused laddered ether marine natural products such as the ciguatoxins and gambieric acids. However, further significant improvements in synthetic efficiency should be possible provided that methods permitting more rapid access to RCM precursors are forthcoming. Two-directional strategies for polyether construction in which several synthetic operations are performed in parallel greatly minimise the total number of steps required to assemble large fused polyether fragments and are potentially very powerful. Further optimisation of two-directional reactions and implementation of strategies involving several of these reactions are currently under investigation, as are methods for the efficient coupling of polyether fragments to give large arrays containing more than 10 rings. The objective of developing a universal strategy for the efficient synthesis of fused polyethers containing any combination of ring sizes based on a small but highly efficient synthetic 'tool kit' remains as our ultimate goal.

Acknowledgements

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