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PAPER

Synthesis of fused multicyclic compounds containing macrocycles by dienyne ring-closing metathesis and Diels–Alder reactions†

Hyeon Park and Tae-Lim Choi*

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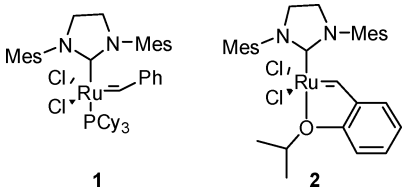
Fused bicyclic compounds comprising small and large rings were synthesised by dienyne ring-closing metathesis (RCM) using Grubbs' catalyst. By taking advantage of faster small ring cyclisation compared with macrocyclisation, single isomers were obtained rather than mixtures of two isomers with different ring sizes. Using this process, various fused bicyclic compounds comprising small rings (5–7- membered) and large rings (14–17- membered) were obtained. By increasing reaction temperature and catalyst loading, the product conversion was improved in a predicted manner. This method produced *E*-olefins on the macrocycles with high selectivity. Also, the selectivity issues of tandem RCM for the synthesis of fused bicyclic compounds comprising small and medium rings were investigated. Lastly, the prepared bicyclic compounds with small and large rings contained 1, 3-dienes that underwent a further modification reaction, such as Diels–Alder, to produce more complex compounds. These Diels–Alder reactions produced tri- and tetracyclic compounds containing a macrocycle with single diastereomers, suggesting that the methodology demonstrated here could be a powerful tool for rapid preparation of highly complex molecules.

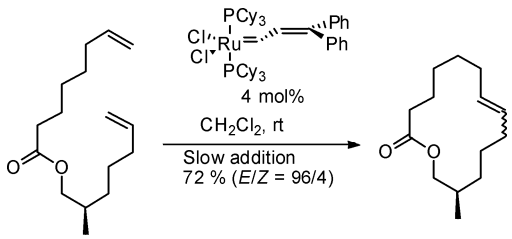
Introduction

The olefin metathesis (OM) reaction has become one of the most important reactions in organic synthesis because it provides an easy and mild method to catalytically generate new carbon–carbon double bonds.[1] This has led to the development of various reactions, such as cross metathesis, ring-opening metathesis, and ring-closing metathesis (RCM), which have been widely used among both the organic and polymer communities. Among these reactions, many organic chemists have been attracted to RCM because of its easy access to various ring structures.[2] Furthermore, the development of highly active catalysts with *N*-heterocyclic carbene (NHC) ligands[3] broadened the substrate scope allowing diverse functional groups into the ring with high productivity.



1 **2**

Macrocyclisation is an important synthetic methodology because many natural products contain macrocycles. Many reactions, such as Yamaguchi macrolactonisation,[4] radical-mediated macrocyclisation,[5] and Prins macrocyclisation,[6] have been used to synthesise various macrocycles. However, previous methods suffered from problems such as low productivity or the use of toxic reagents or excess chemical reagents. As an alternative method, the RCM reaction has emerged as an effective tool for macrocyclisation (Scheme 1).[7] This was well demonstrated in the recent work from E. Lee's lab, who utilised macro-RCM as the key reaction for the total synthesis of (+)-Exiguolide.[8]

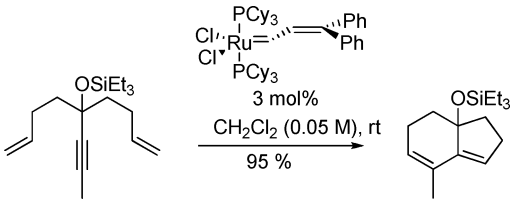


Scheme 1 Macrocyclic RCM reaction using a ruthenium catalyst.

Many fused cyclic compounds comprising rings of various sizes, from small to large,[9] were synthesised by tandem radical cyclisation. However, controlling reactive intermediates to give the desired product can be difficult, and generation of toxic residues remains a problem. Again, the RCM reaction has been recognised as an alternative method since Grubbs' first report on the synthesis of fused bicyclic compounds by a tandem dienyne RCM reaction (Scheme 2).[10] This tandem RCM reaction was proved to be a

Department of Chemistry, Seoul National University, Gwanak 599, Gwanak-ro, Gwanak-gu, Seoul, 151-742, Korea. E-mail: tlc@snu.ac.kr; Fax: +82 2-889-1568; Tel: +82 2-880-6658

† Electronic supplementary information (ESI) available: ^{1}H, ^{13}C NMR spectrum data, refractive index, and HRMS spectrum data of substrates are available. See DOI: 10.1039/c1ob05683b



Scheme 2 Dienyne RCM reaction for synthesis of bicyclic compounds.

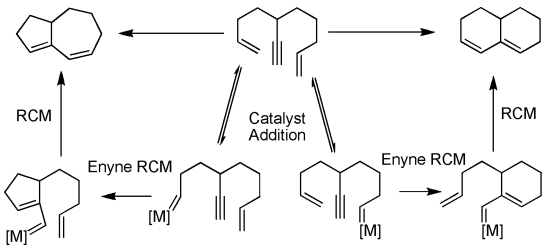
powerful tool because it was used to build the core skeletons in a number of total syntheses of natural products.[11]

Although many useful molecules have been synthesised by RCM, a further post-modification reaction on the RCM products can provide more molecular diversity. For example, after an enyne metathesis reaction, products with 1,3-dienes were synthesised, and with appropriate dienophiles, Diels–Alder reaction was frequently used as the post-modification reaction.[12] However, examples of Diels–Alder reactions on bicyclic compounds produced by dienyne RCM reactions are rare.[13]

Recently, we demonstrated a versatile tandem reaction combining macrocyclisation and dienyne RCM to give bicyclic compounds comprising small and large rings.[14] Herein, we report the details of our preliminary results of the tandem RCM reaction. The resulting fused bicycles containing macrocycles proved to be good dienes for the Diels–Alder reaction, producing fused multicyclic compounds containing macrocycles.

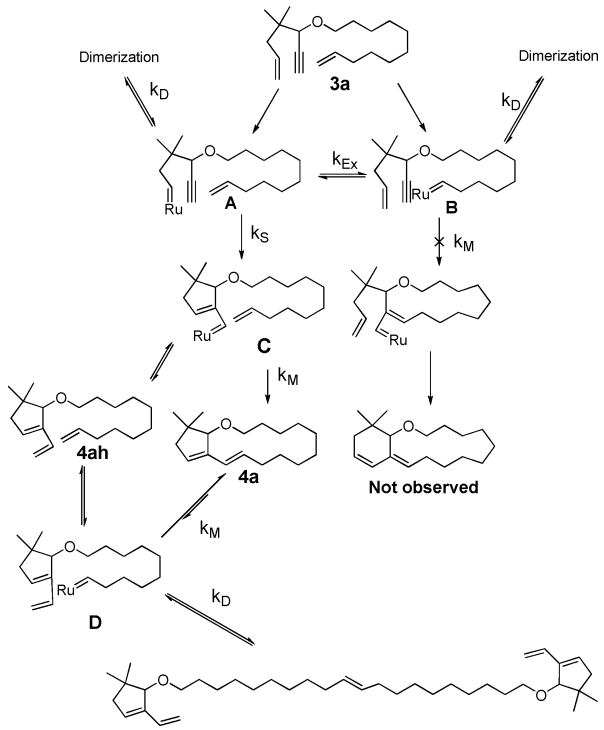
Results and discussion

To synthesise fused bicyclic compounds containing small and large rings by dienyne RCM, dienyne substrates containing short and long tethered alkenes are required. However, there is one potential problem in this asymmetric dienyne RCM reaction: dienyne substrates with different lengths of tethers give two products with different ring sizes[10] (Scheme 3). This is due to the catalyst reacting with both terminal alkenes with no preference. To prevent this problem, one terminal alkene was protected as a disubstituted internal alkene, allowing the catalyst to react with the less hindered terminal alkene first.[10,15] More recently, increasing the reaction concentration also enhanced the selectivity by increasing the exchange rate between the two possible carbenes (Scheme 4),[16] but this strategy is not suitable for macrocyclisation because low concentrations are required to avoid undesirable oligomerisation.



Scheme 3 General reaction pathway in dienyne RCM.

The key to overcome the selectivity issue in the synthesis of bicyclic compounds is controlling the rates of cyclisation. To synthesise fused bicyclic compounds comprising small and large rings, we reasoned that the selectivity issue might be eliminated by taking advantage of the different cyclisation rates

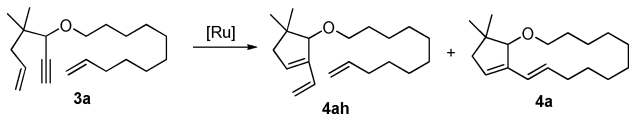


Scheme 4 Selective dienyne RCM containing macrocycles.

between the small ring (k_S) and the large ring (k_M). To test this hypothesis, substrate **3a** was treated with catalyst **1** under a diluted concentration, and indeed the reaction produced **4ah** and **4a** only (Scheme 4). A more detailed study by ^{1}H NMR revealed that **4ah** was the initial intermediate product, which then underwent the final macrocyclisation to give **4a**. This provided an important insight into the reaction pathway; as the catalyst reacted with either of the two terminal alkenes, metal carbene intermediate **A** or **B** formed. These metal carbenes underwent an enyne RCM reaction with the nearby alkyne or an exchange reaction between **A** and **B**. Lastly, dimerisation of **3a** might have occurred by a cross metathesis reaction. Here, only intermediate **A** provided productive RCM due to rapid cyclisation, k_S. On the other hand, **B** did not undergo any productive reaction due to much slower k_M and k_D. Instead, the exchange reaction proceeded to form **A** again, which then produced **4ah** immediately. After the initial enyne RCM reaction that formed small rings exclusively, intermediate **C** or **D** underwent the final macrocyclisation to form the desired fused bicyclic product. Overall, these processes (k_S, $k_{Ex} > k_M$, k_D) pushed the equilibrium to one pathway, leading to the selective formation of the final product **4a**.

Previously, Fogg and co-workers reported that during their studies of macrocyclisation of dienes, the dimer and the oligomers formed initially as kinetic products and then reacted further to yield the desired macrocycles.[17] However, from our NMR monitoring study, no dimer or oligomers were observed; there was direct conversion to **4ah** and **4a**. We believe the difference was due to instantaneous RCM, giving **4ah** which contained one terminal olefin and a less reactive conjugated olefin with a bulky substituent. This might have reduced the chance of dimerisation compared to substrates with two readily reactive terminal olefins.

Table 1 Dienyne RCM reaction optimisation[a]



Entry	Catalyst	Solvent	Temp.	Yield of **4a**	**4ah** : **4a**[b]
1	**1**	DCM	45 °C	N/A	1 : 2
2	**2**	DCM	45 °C	N/A	1 : 2
3	**1**	1, 2-DCE	55 °C	N/A	1 : 1.2
4	**1**	Toluene	55 °C	73%	1 : 12
5	**1**	Toluene	70 °C	82%	1 : 14

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst was added to a substrate in 4 mM degassed solvent. Solution was heated for 24 h under reflux conditions. [b] Ratio was determined by ^{1}H NMR analysis.

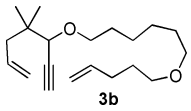
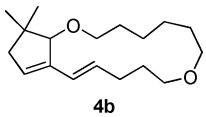
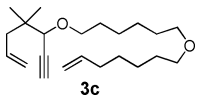
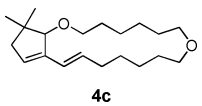
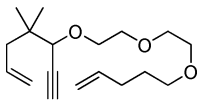
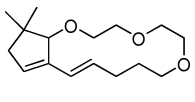
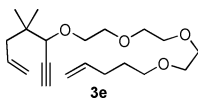
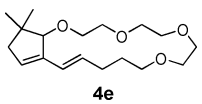
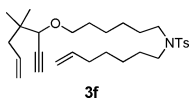
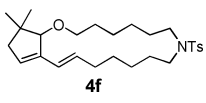
Also, the cyclopentyl moiety might have induced a biased structure favoring macro-RCM over dimerisation.

As shown in Scheme 4, the dienyne RCM reaction of **3a** can produce **4ah** or **4a**. When substrate **3a** reacted with 5 mol% of catalyst **1** in dichloromethane (DCM) at 45 °C, a 1 : 2 mixture of **4ah** and **4a** was observed (Table 1, entry 1). The reactivity toward macrocyclisation did not improve when catalyst **2** was used instead (Table 1, entry 2). To push the reaction to complete cyclisation, further optimisation was performed. To raise the reaction temperature to 55 °C, 1,2-dichloroethane (1,2-DCE) was used as the solvent, but it was less favorable for macrocyclisation, giving almost equal amounts of **4ah** and **4a** (1 : 1.2, Table 1, entry 3). However, switching the solvent to toluene greatly improved the conversion, forming the desired product in 73% yield (Table 1, entry 4). A further increase in temperature to 70 °C increased the catalyst activity, giving **4a** with 82% yield (Table 1, entry 5). Also, the reaction product showed only the *trans* isomer on the macrocyclic alkene. This selectivity is noteworthy because *E*/*Z* stereoselectivity in macrocyclic RCM reactions remains a serious issue.[18]

To expand the scope of the reaction, various compounds with different tether lengths were synthesised to prepare bicyclic [*n*.3.0] (*n* = 12–15) compounds. In particular, fused bicyclic compounds with 14- to 17-membered rings were prepared with 85–95% isolated yields at 55 °C from substrates containing multiple oxygen atoms on the long tether (Table 2, entries 1–4). The improved conversion was due to the pseudo *gem*-dialkyl effect, in which the carbon–oxygen–carbon bond angle becomes smaller than the carbon–carbon–carbon bond angle due to lone pair electrons on oxygen.[19] Therefore, the macro-RCM reaction containing more oxygen atoms (**3b**–**e**) gave better yields than that of **3a**.[20] Also, introducing nitrogen resulted in good productivity, although 70 °C was required for high conversion (Table 2, entry 5).

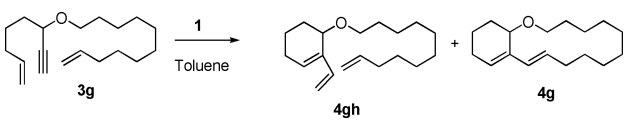
Synthesis of fused bicyclic compounds with 6-membered rings is important because cyclohexyl derivatives are abundant in natural products. Therefore, synthesis of 6-membered bicylic compounds was also optimised. Substrate **3g** showed low conversion to **4g** under the same conditions as the 5-membered ring derivative. Increasing the catalyst loading to 10 mol% gave a 1 : 1.5 mixture of **4gh** and **4g** (Table 3, entry 1). Increasing the temperature to 70 °C showed an enhanced yield of **4g**, and further increase in the temperature to 90 °C gave 87% isolated yield (Table 3, entries 2–3). Since the initial cyclisation of 6-membered rings completed

Table 2 Dienyne RCM reaction of various substrates[a]

Entry	Substrate	Product	Temp. (Yield)
1	 **3b**	 **4b**	55 °C (95%)
2	 **3c**	 **4c**	55 °C (85%)
3	 **3d**	 **4d**	55 °C (91%)
4	 **3e**	 **4e**	55 °C (85%)
5	 **3f**	 **4f**	70 °C (87%)

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM toluene. Solution was heated for 24 h under reflux conditions.

Table 3 Synthesis of 6-membered ring containing fused bicycle[a]



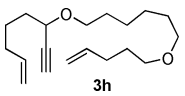
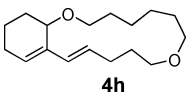
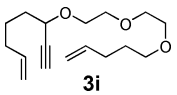
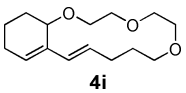
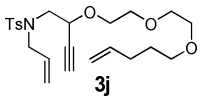
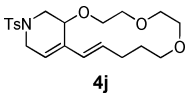
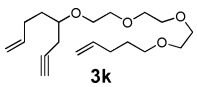
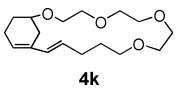
Entry	Catalyst	Temp.	Yield of **4g**	**4gh** : **4g**[b]
1	10 mol (%)	55 °C	N/A	1 : 1.5
2	10 mol (%)	70 °C	59%	1 : 8
3	10 mol (%)	90 °C	87%	1 : 28

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM toluene. Solution was heated for 24 h under reflux conditions. Additional 5 mol% catalyst was added and the solution was heated for another 24 h. [b] Ratio was determined by ^{1}H NMR analysis.

almost immediately after addition of the catalyst, we concluded that the macrocyclisation was slower than that of the cyclopentene containing substrates.

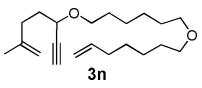
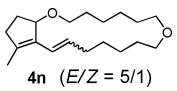
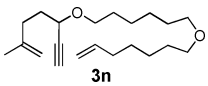
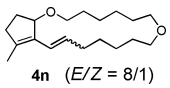
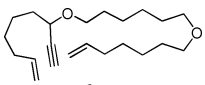
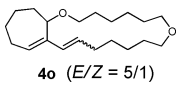
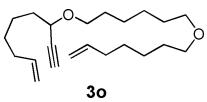
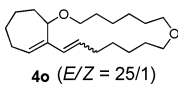
Similar to 5-membered ring containing fused bicycles, introducing oxygen atoms in the long tether resulted in better productivity in tandem RCM reaction. Addition of one oxygen atom resulted in 75% yield of **4h**, even with 5 mol% catalyst (Table 4, entry 1). Adding more oxygen atoms improved the conversion so that the desired product was synthesised under milder conditions at lower temperature (Table 4, entry 2). Nitrogen was also introduced in the small ring (Table 4, entry 3), although the reaction required higher temperature and higher loading of the catalyst to achieve 71% yield. A bridgehead fused bicyclic compound was also synthesised by dienyne RCM (Table 4, entry 4). Although the final product

Table 4 Synthesis of various 6-membered ring containing fused bicycles[a]

Entry	Substrate	Product	Conditions (Yield)
1	 **3h**	 **4h**	5 mol% **1**, 100 °C (75%)
2	 **3i**	 **4i**	5 mol% **1**, 55 °C (71%)
3[b]	 **3j**	 **4j**	8 mol% **1**, 90 °C (71%)
4[b]	 **3k**	 **4k**	10 mol% **1**, 70 °C (69%)

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM toluene. Solution was heated for 24 h under reflux conditions. [b] Additional 3–5 mol% catalyst was added and the solution was heated for another 24 h.

Table 6 Synthesis of fused bicycles with a mixture of stereoisomers[a]

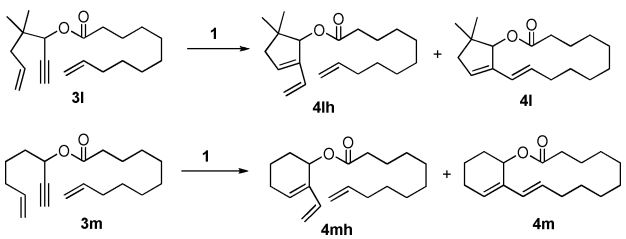
Entry	Substrate	Product	Conditions (Yield)
1	 **3n**	 **4n** (*E*/*Z* = 5/1)	5 mol%, 55 °C, 4 mM (63%)
2	 **3n**	 **4n** (*E*/*Z* = 8/1)	5 mol%, 90 °C, 4 mM (87%)
3[b]	 **3o**	 **4o** (*E*/*Z* = 5/1)	10 mol%, 70 °C, 2 mM (27%)
4[b]	 **3o**	 **4o** (*E*/*Z* = 25/1)	15 mol%, 100 °C, 2 mM (63%)

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM toluene. Solution was heated for 24 h under reflux condition. *E*/*Z* ratio was determined by ^{1}H NMR analysis. [b] Additional 5–10 mol% catalyst was added and the solution was heated for another 24–48 h.

contained an anti-Bredt olefin, which was not readily formed in small bridgehead molecules, reduction in strain due to the long flexible chain on the macrocycle allowed the formation of the desired product in 69% yield.

The synthesis of macrolactones was investigated because they comprise the core skeletons of many natural products. Interestingly, substrates with ester groups showed a different result for the dienyne RCM reaction. Unlike the previous reactions, which showed good conversion using toluene as the solvent, these ester substrates showed decreased reactivity in toluene (Table 5, entry 1). However, by changing the solvent to 1,2-DCE, conversion to the 14-membered macrolactone, **4l**, greatly increased to 73% yield (Table 5. entry 2). It seemed that the polar solvent 1,2-DCE induced faster macrocyclisation to **4l** containing an ester group. Synthesis of a 6-membered ring containing fused bicyclic

Table 5 Synthesis of fused bicycles containing an ester group[a]



Entry	Substrate	Conditions	Yield of **4**	**4xh** : **4x**[b]
1	**3l**	5 mol% **1**, toluene, 55 °C	19%	1 : 0.23
2	**3l**	5 mol% **1**, 1,2-DCE, 55 °C	73%	1 : 10
3	**3m**	5 mol% **1**, 1,2-DCE, 55 °C	N/A	1 : 1
4[c]	**3m**	10 mol% **1**, 1,2-DCE, 70 °C	83%	1 : 10

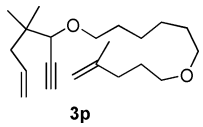
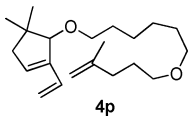
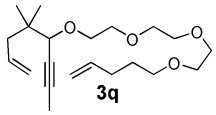
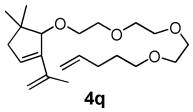
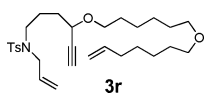
[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM solvent. Solution was heated for 24 h under reflux conditions. [b] Ratio was determined by ^{1}H NMR analysis. [c] Additional 5 mol% catalyst was added and the solution was heated for another 24 h.

compounds was successful, resulting in better conversion when 1,2-DCE was used as the solvent. Similar to previous cases, the substrate with the 6-membered ring required more forcing conditions, such as higher catalyst loading and higher temperature, for good conversion (Table 5, entries 3–4).

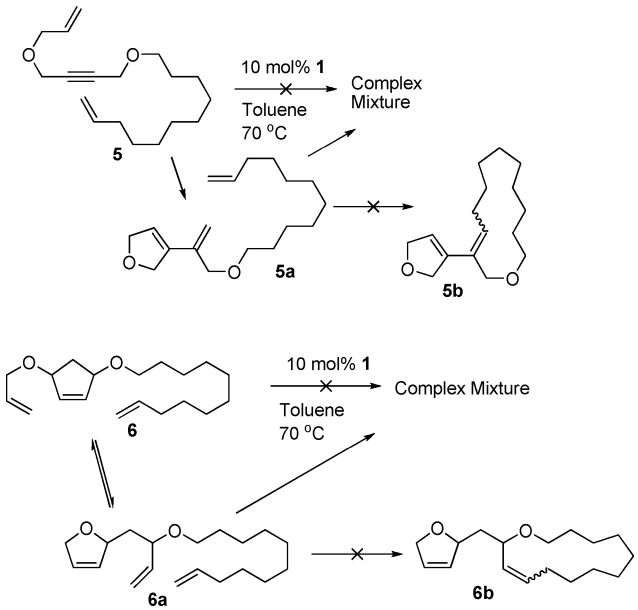
Although most macro-RCM reactions produced *E*-olefins on the macrocyclic alkenes, mixtures of *E*/*Z* isomers were observed in the following cases. The first case was the synthesis of a fused bicyclic compound containing a synthetically challenging tetrasubstituted alkene on the small ring (Table 6, entries 1–2). Initially, a moderate yield of **4n** was obtained with an *E*/*Z* ratio of 5/1. However, increasing temperature not only increased the isolated yield (63% to 87%), but also improved the stereoselectivity (*E*/*Z* = 5/1 to 8/1). The second example was the synthesis of a fused bicyclic compound containing a 7-membered ring which proved to be more challenging than bicycles comprising 5- and 6-membered rings because the initial RCM for the 7-membered ring formation was much slower. Therefore, to achieve good conversion to **4o**, a higher temperature (100 °C) and higher catalyst loading (15 mol%) with longer reaction times were required. At low conversion (Table 6, entry 3), an *E*/*Z* ratio of 5/1 was obtained for the macrocyclic alkene, but again, higher selectivity (*E*/*Z* = 25/1) was obtained at higher conversion (Table 6, entry 4). In both examples, *E*/*Z* selectivity increased with higher conversion due to enhanced catalyst activity. As the catalyst became more active at higher temperature, reversible *E*/*Z* isomerisation on the macrocyclic alkene occurred more frequently, leading to the formation of a more stable *E* isomer.[7d]

Although the substrate scope for fused bicyclic macrocyclisation was quite broad as seen in the previous tables, several substrates did not lead to desired products. Unlike the previous example, in which the fused bicyclic compound with an additional methyl substituted olefin on the small ring was successfully prepared (Table 6, entry 2), synthesising fused cyclic compounds containing an additional substitution on the alkene of the macrocycles to

Table 7 Unsuccessful examples of tandem RCM[a]

Entry	Substrate	Product	Conditions (Yield)
1	 **3p**	 **4p**	5 mol% **1**, 55 °C (66%)
2	 **3q**	 **4q**	5 mol% **1**, 55 °C (74%)
3[b]	 **3r**	Complex mixture	10 mol% **1**, 100 °C

[a] General reaction conditions: Under Ar atmosphere, 5 mol% catalyst **1** was added to substrates in 4 mM toluene. Solution was heated for 24 h under reflux conditions. [b] Additional 5 mol% catalyst was added and the solution was heated for another 24 h



Scheme 5 Attempts to prepare non-fused bicyclic compounds.

make trisubstituted alkenes failed, giving only molecules with incomplete cyclisation (Table 7, entries 1–2). Because the additional substitution made it harder for the catalyst to perform the productive metathesis reaction, the macrocyclisation rate became even slower, leaving only small ring-closed products. Synthesis of an 8-membered ring containing fused cyclic compounds was even more challenging (Table 7, entry 3) due to intrinsically low reactivity of RCM toward the formation of 8-membered rings. Even with high catalyst loading at an elevated temperature, this reaction gave a complex mixture of molecules, and clean conversion to the initial 8-membered ring was not observed.

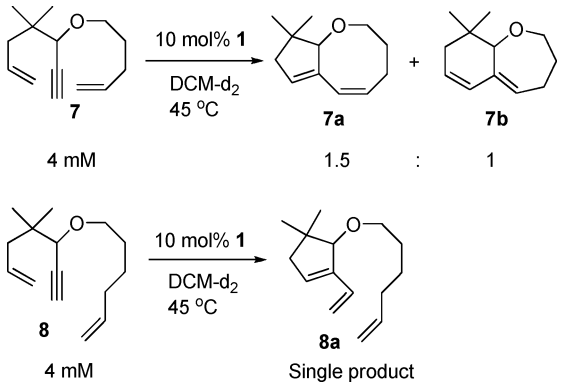
In previous examples, the terminal alkynes were used as the key synthon for tandem RCM reactions. In order to extend the scope of the reaction, a diene containing an internal alkyne, **5**, was prepared with the expectation of producing a non-fused bicyclic compound **5b** *via* small ring cyclisation with **5a** as an intermediate for tandem macro-RCM reaction (Scheme 5). However, all our attempts failed and only a complex mixture was obtained. As shown in previous examples (Table 7, entry 1–2), macrocyclisation of 1,1-disubstituted alkenes was challenging, so that the intermediate **5a** underwent side-reactions to generate a mixture of other products.

In order to avoid formation of the 1,1-disubstituted alkene as an intermediate during the tandem macrocyclisation, another substrate **6** which could lead to a non-fused bicyclic compound comprising small and large rings by tandem ring-opening ring-closing metathesis (RO-RCM) reaction was prepared.[21] Initially, we expected that substrate **6** would undergo RO-RCM reaction to generate an intermediate **6a** from small ring cyclisation followed by the slow macrocyclisation to produce **6b**. Again, disappointingly, only a complex mixture was observed upon adding the catalyst, suggesting that side-reactions were predominant. As shown in the previous successful tandem RCM, it seems that the intermediate with diene linked in the cyclic conformation might be the key for efficient tandem RCM reaction by facilitating macrocyclisation.

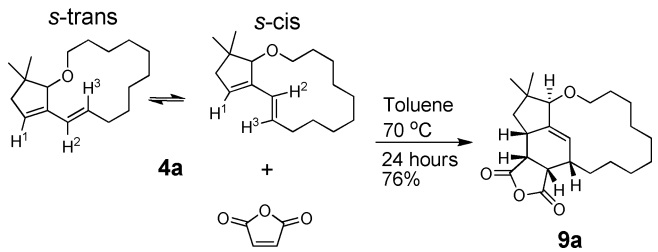
We have investigated the selective synthesis of fused bicyclic compounds by taking advantage of the rate difference between cyclisation of small and large rings. This exclusive selectivity was possible because k_S and k_{Ex} were far greater than k_M (Scheme 4). Thus, further experiments were designed to study selectivity for the synthesis of fused bicyclic compounds comprising small and medium rings by estimating the relative rates of k_S, k_{Ex} and the rate for cyclisation of the medium ring, k_{Med}. When substrate **7** reacted at 4 to 20 mM, two products with a 1.5 : 1 ratio of **7a** and **7b** from non-selective RCM were observed during crude NMR analysis. The 5- and 7-membered ring cyclisations occurred almost equally at low concentration, implying that the cyclisation rates of 5-, 6-, and 7-membered rings were faster than the k_{Ex} between two different terminal alkenes at low concentration. At higher concentration, k_{Ex} might dominate over 7-membered ring cyclisation rate, giving higher selectivity for **7a**,[16] but side reactions, such as dimerisation and oligomerisation, would occur. However, when substrate **8** reacted at low concentration, only **8a**, with a 5-membered ring, was observed during crude NMR analysis. Although complete tandem RCM did not occur, this suggested that the ring-closure rate of the 8-membered ring (k_{Med}) was much slower than k_{Ex}, resulting in complete selectivity, similar to the cases of tandem macrocyclisation.

So far, we have demonstrated that the fused bicyclic compounds comprising small and large rings were efficiently prepared by tandem dienyne RCM reactions. This method would be more useful if further manipulation of the RCM products were possible, giving more diversity. For a typical dienyne RCM reaction, 1,3-diene, a potential functional group for Diels–Alder reaction, is formed at the end of the reaction. However, prior to our preliminary communication, there have been no previous reports of Diels–Alder reactions on the dienes of fused bicycles formed by dienyne RCM reactions because the products were composed of two small or medium rings (Scheme 5). Thus, there was no chance of forming *s-cis* dienes but *s-trans* dienes only, which cannot participate in Diels–Alder reactions.[10a] On the other hand, we reasoned that dienes on the bicycles comprising small and large rings might adopt the *s-trans* conformation as well due to the presence of flexible chains on the macrocycles. The first evidence

for this came from a nuclear Overhauser effect (NOE) study on substrate **4a**, which showed that vinyl proton H^1 interacted with proton H^3 in addition to an adjacent proton H^2 (Scheme 7). Also, very crude computational analysis using molecular mechanics methods suggested that the energy difference between *s-cis* and *s-trans* conformations was quite small. This suggested that substrate **4a** might adopt both *s-trans* and *s-cis* conformations, implying that these dienes could undergo Diels–Alder reactions with dienophiles. Indeed, when treated with maleic anhydride at 70 °C, a cycloaddition product **9a** with a single diastereomer was obtained in 76% isolated yield.



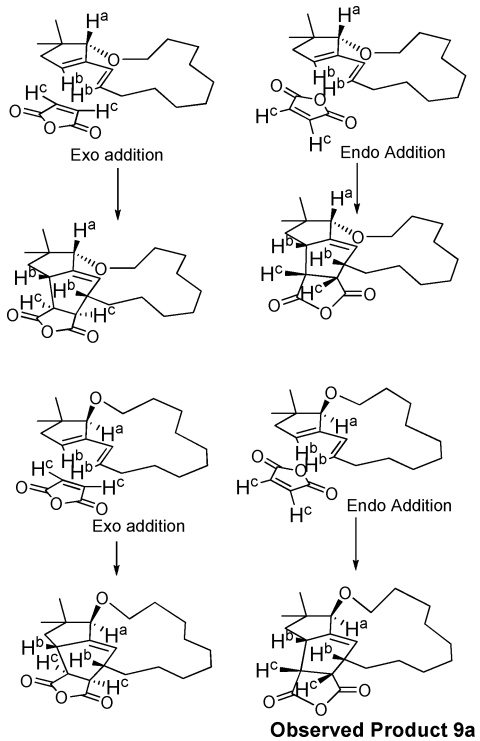
Scheme 6 Tandem RCM to synthesise fused cyclic compounds with small and medium rings.



Scheme 7 Diels–Alder reaction of a fused cyclic compound synthesised by the dienyne RCM reaction.

As shown in Scheme 8, the Diels–Alder reaction could give four different diastereomers depending on how the dienophile approached the fused bicyclic diene molecule. First, the dienophile could add to the diene from two different sides, but the dienophile would preferentially approach from the less sterically hindered side, H^a, and away from the more sterically hindered ether linkage. Second, the dienophile could approach the diene with *endo* orientation over *exo*. To determine the molecular structure of the adduct, a 1D NOE study was conducted and showed that H^a interacts with neither H^b or H^c, suggesting that they were *anti* to one another.[22] Also, the NOE study showed that H^b interacted with H^c, confirming that the product isolated was the predicted **9a** isomer due to *endo* selective addition of the dienophile from the less hindered side of the fused cyclic diene.

Reactions between maleic anhydride and various dienyne RCM products containing 5-, 6-, and 7-membered rings in toluene at 70 °C gave good yields of Diels–Alder products (74–76%) comprising tetracyclic compounds (Table 8, entries 1–3). In all cases, single diastereomers with the predicted stereochemistry



Scheme 8 Origin of stereochemistry for the Diels–Alder reaction.

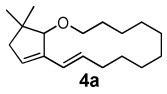
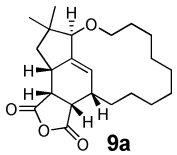
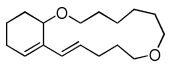
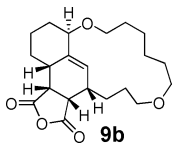
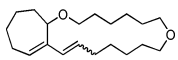
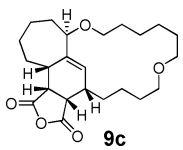
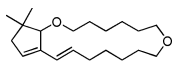
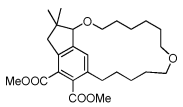
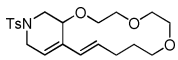
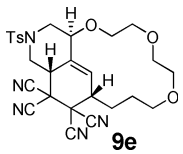
were obtained. To test dienophiles other than maleic anhydride, dimethyl acetylenedicarboxylate was reacted with **4a**. Even at higher temperatures, this Diels–Alder reaction was much slower than the previous cases with maleic anhydride as a dienophile. We expected to obtain the Diels–Alder product with a 1,4-cyclohexadiene moiety, but **9d** with an aromatic ring was the only isolated product. Presumably, the initial Diels–Alder product of 1,4-cyclohexadiene quickly underwent aromatisation under the reaction conditions, giving a tricyclic compound with the aromatic ring (Table 8, entry 4).[23] Since the Diels–Alder reactions were conducted at elevated temperatures, it was unclear whether equilibrium between *s-cis* and *s-trans* isomers of the dienes was possible at room temperature. Thus, a stronger dienophile, tetracyanoethylene, was added to **4l** at room temperature, and the product **9e** was isolated with excellent yield (Table 8, entry 5). This confirmed our initial assumption that the fused cyclic compounds containing macrocycles could adopt the *s-cis* diene conformation at room temperature due to the flexible chains on the macrocycles.

As the Diels–Alder reactions were performed with the same solvent and the same temperature, the dienyne RCM and Diels–Alder reactions could be conducted sequentially in a one-pot reaction. Substrate **3c** was treated with catalyst **1** at 70 °C, and after 24 h, addition of two equiv. of maleic anhydride produced the fused tetracyclic compound **10** with 37% isolated yield (Scheme 9). Although the yield was low, this result demonstrated that the complexity of the molecules could be rapidly built up by the combination of one-pot tandem dienyne RCM and Diels–Alder reactions, producing the tetracycle from an acyclic starting compound.

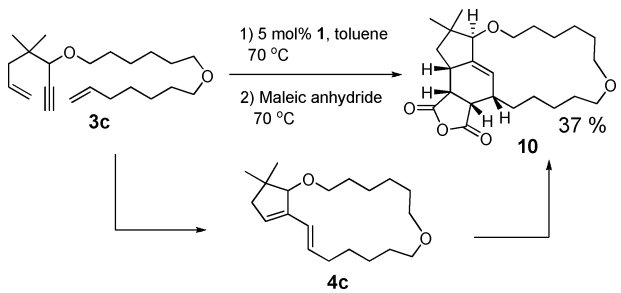
Conclusions

We presented a full report on the synthesis of fused cyclic ring compounds comprising small and large rings with high selectivity,

Table 8 Diels–Alder reaction on the dienyne RCM products[a]

Entry	Diene	Dienophile	Product	Yield
1	 4a		 9a	76%
2	 4k		 9b	74%
3	 4h		 9c	75%
4[b]	 4c		 9d	66%
5[c]	 4l		 9e	83%

[a] General information: Under Ar atmosphere, 2 equiv. dienophiles was added to dienes in 0.3 M toluene. Reaction flask was heated to 70 °C for 4 h. [b] Reaction flask was heated to 100 °C for 48 h. [c] Reaction proceeded at room temperature for 24 h.



Scheme 9 Sequential RCM–Diels–Alder reaction in one-pot reaction.

generality, and predictability by dienyne RCM reactions using ruthenium catalyst **1**. Because the cyclisation rate was significantly faster for the small rings compared with the macrocycles, the synthetic pathway was driven to produce single isomers. This methodology efficiently produced fused bicycles with small rings from 5- to 7-membered rings and macrocycles from 14- to 17-membered rings, demonstrating the versatility of the reactions. Generally, higher conversion to complete macrocyclisation was achieved with higher temperature or higher catalyst loading. Also, the RCM reaction products underwent Diels–Alder reactions with exclusive stereocontrol. The combination of tandem dienyne RCM and Diels–Alder reactions provided a powerful method to rapidly build complex molecules, especially those multicyclic compounds containing macrocycles.

Experimental section

Typical procedure for dienyne ring closing metathesis reaction (Table 1)

To a 2-neck round bottom flask, reaction substrate **3a** (28.8 mg, 0.1 mmol) was added. The reaction flask was filled with argon gas, followed by degassed solvent addition (25 ml, 4 mM). After 5 mol% catalyst (4.2 μmol) was added, the solution was heated to 70 °C for 24 h. Then, the solvent was removed by evaporation and the product was purified with silica gel column chromatography (ethyl acetate–hexane = 1 : 50). Inseparable mixtures of the final product **4a** and **4ah** with incomplete macrocyclisation were obtained in a 14 : 1 ratio. The reported yield was calculated by subtracting the portion of the half-closed product. R_f 0.24 (ethyl acetate–hexane = 1 : 50)

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 6.120 (1H, dd, J = 0.5, 16.0 Hz), 5.770 (1H, m), 5.674 (1H, t, J = 2.5 Hz), 3.993 (1H, d, J = 1.0 Hz), 3.725–3.314 (2H, m), 2.340–2.038 (2H, d, J = 17.5 Hz), 2.240–2.038 (2H, m), 1.610–1.510 (2H, m), 1.498–1.331 (12H, b), 1.267(2H, s), 1.144 (3H, s), 1.058 (3H, s)

^{13}C NMR (500 MHz, $CDCl_3$, ppm): δ 141.72, 132.05, 130.32, 126.85, 91.22, 68.54, 46.96, 42.38, 32.14, 30.26, 29.60, 26.75, 25.93, 25.81, 25.71, 24.66, 24.21, 23.03

HRMS (EI+) calcd. for $C_{18}H_{30}O$, 262.2297, found, 262.2298

General procedure for Diels–Alder reaction (Scheme 6)

To a 2-neck round bottom flask, fused bicyclic compound **4a** (23.8 mg, 0.09 mmol) was added, followed by addition of maleic anhydride (17.9 mg, 0.18 mmol). Toluene (1 ml) was used as the solvent, and the solution was heated to 90 °C for 4 h. Then, the solvent was removed by evaporation and product **9a** was purified by silica gel column chromatography (ethyl acetate–hexane = 1 : 5) to give 76% yield. R_f 0.28 (ethyl acetate–hexane = 1 : 5)

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 5.967 (1H, s), 3.690 (1H, t, J = 4.5 Hz), 3.656 (1H, s), 3.545 (1H, dt, J = 6.5, 2.5 Hz), 3.389 (1H, t, J = 8.5 Hz), 3.302 (1H, dd, J = 6, 3.5 Hz), 2.688 (1H, d, J = 8 Hz), 2.285 (1H, m), 1.977 (2H, m), 1.820 (2H, m), 1.645 (2H, m), 1.500 (4H, m), 1.359 (8H, m), 1.048 (3H, s), 0.891 (3H, s)

^{13}C NMR (500 MHz, $CDCl_3$, ppm): δ 172.10, 148.89, 124.56, 87.72, 71.58, 47.74, 44.23, 43.09, 38.13, 37.17, 36.45, 29.43, 28.30, 27.35, 27.10, 26.75, 26.57, 26.50, 26.45, 26.42, 21.42

HRMS (EI+) calcd. for $C_{22}H_{33}O_4$, 361.2379, found, 361.2377.

Acknowledgements

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