Metathesis

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Allylmalonate as an Activator Subunit for the Initiation of Relay Ring-Closing Metathesis Reactions**

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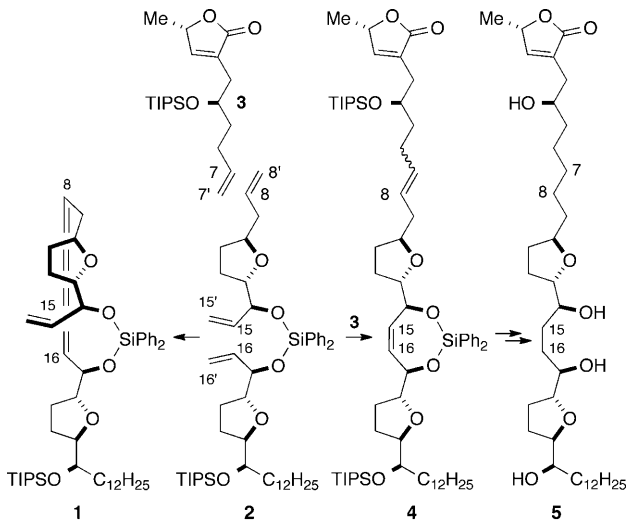
Our research group has previously described a total synthesis of (+)-gigantecin (**5**, Scheme 1) in which the importance of the sequencing of the competitive ring-closing metathesis (RCM) and cross-metathesis events was demonstrated.[1]

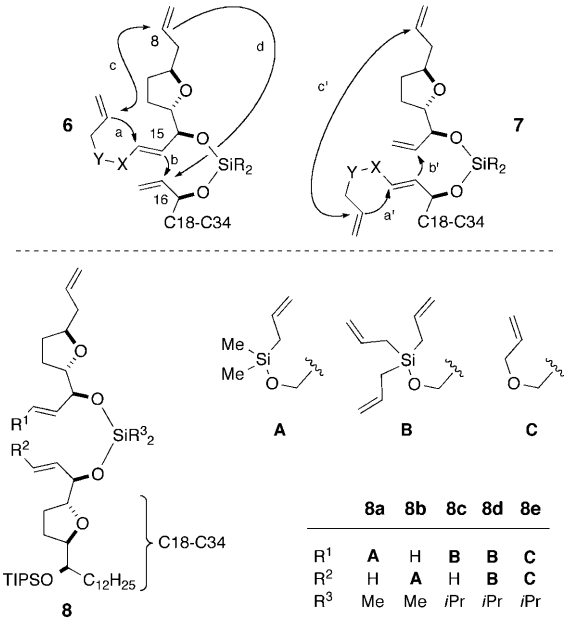


Scheme 1. Sequenced metatheses leading to (+)-gigantecin.[1] TIPS = triisopropylsilyl.

Significantly, when using the Hoveyda–Grubbs second-generation initiator (**HG2**),[2a] the RCM reaction of the key substrate **2** (Scheme 1) gave the 11-membered cyclic alkene **1** rather than the desired silacycloheptene derivative that would have arisen from closure of C15 with C16. In contrast, initial cross-metathesis of **2** with **3** to form the C7=C8 bond with subsequent RCM gave **4**, which was additionally manipulated in a straightforward fashion to give **5**.

Relay metathesis, of both the ring-closing (RRCM)[2b–e] and cross-metathesis[3] varieties, is a strategy for altering the outcome of competitive metathesis pathways in complex polyfunctional substrates. We felt we could use polyene intermediates such as **2** and **4** to explore the RRCM process. Herein we report observations that extend both the utility and our understanding of RRCM.

We wondered whether RRCM could be used to solve the regioselectivity problems outlined in Scheme 1. By arming either the C15=C15′ or the C16=C16′ alkene in **2** with a relay activator unit (e.g. **6** or **7**, Scheme 2) we hoped the process



Scheme 2. RRCM with various relay activator units.

implied by arrows a and b in **6** (or arrows a′ and b′ in **7**) would dominate, thus resulting in the formation of the C15=C16 bond selectively over the C8=C16 bond (see arrow d). Also shown in Scheme 2 is a set of the relay activated terminal-alkene-containing substrates **8a–e** that we prepared along with the allylmalonate derivative **9b** (Scheme 3) to test this theory. The substrates **8a–e** were exposed to a variety of olefin metathesis conditions that differed principally in the choice of initiators, solvents, and temperature. The reaction progress and outcome were monitored by ESIMS and ^{1}H NMR analysis. In most cases complete consumption of the starting material **8** was observed. Most of the identified products were macrocyclic alkenes in which ethylene, and not the relay unit, had been lost. The preponderance of evidence pointed towards the reaction pathway represented by arrows c and d for **6** and arrow c′ for **7**, rather than the desired RRCM process represented by arrows a and b or arrows a′ and b′. This evidence suggested that for the complex

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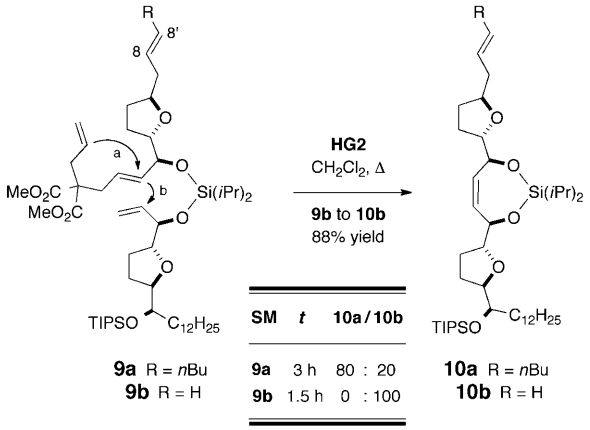
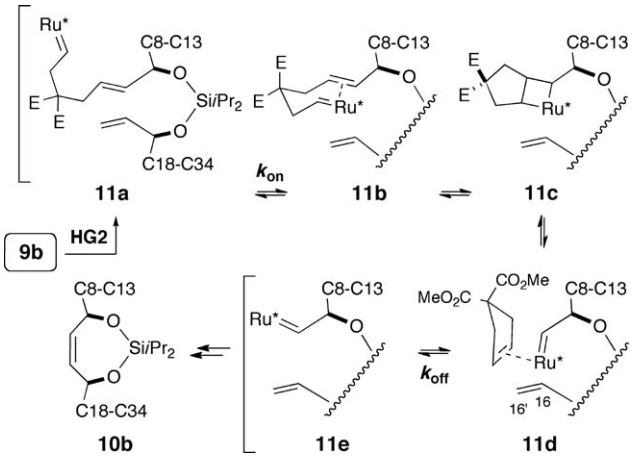


Scheme 3. RRCM with allylmalonate as the relay activator. **HG2** = second-generation Hoveyda–Grubbs initiator; [Ru = CH(*o*-isopropoxyPh)$(Cl)_2(H_2IMes)$]. SM = starting material.



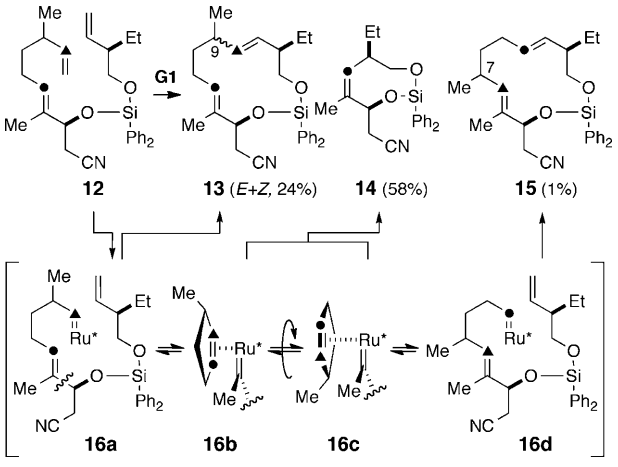
Scheme 4. Mechanism for the relay stage of RRCM. [Ru*] = $Ru(Cl)_2(H_2IMes)L_n$.

polyenes **8**, which contain the relay subunits **A**–**C** (Scheme 2), the rate of the critical relay event (a/a′) was too slow to compete with the undesired macrocyclizations. This led us to study the allylmalonate ester derivatives **9a** and **9b** (Scheme 3). Although we had used allylmalonate ester derivatives in our initial demonstrations of RRCM,[2] and dimethyl diallylmalonate itself has served as an important test substrate for many aspects of olefin metathesis,[4] this structural subunit had not yet been explored as an expendable relay-activator moiety. Treatment of **9a**, which contains a terminal *n*-butyl group on C8′, with **HG2** in hot methylene chloride resulted in the formation of the two RRCM products **10a** and **10b** in a 4:1 ratio (Scheme 3, tabular inset). Pleasingly, the allylmalonate ester **9b**, which contains a C8=C8′ terminal alkene and is therefore a direct analogue of **8a**–**e**, cyclized to give **10b**, in an 88% yield.[5] Surprisingly, we did not detect the symmetrical C8=C8 dimer what would arise from the cross-metathesis of two molecules of **10** in either of these experiments.

There are two possible explanations for the greater efficiency of the RRCM with the allylmalonate ester derivatives **9a**–**b** (Scheme 3) compared with the substrates **8a**–**e** (Scheme 2). First, a gem-dimethyl-like effect (Thorpe–Ingold) should accelerate the initial stage of the relay event for the substrates **9a**–**b** (k_{on} for **11a**→**11b**, Scheme 4). Second, ejection of the dimethyl cyclopentene-1,1-dicarboxylate moiety from the coordination sphere of the ruthenium center (**11d**→**11e**, Scheme 4) should be faster than the corresponding decomplexation of the relay by-products for the substrates **8a**–**e**. This second point deserves further explanation.

The reversible nature of several important steps in olefin metathesis, including dissociation of the product alkene from the metal center, has been examined in detail by Piers and coworkers.[6] We suggest that the rate-determining step in some RRCM reactions is the decomplexation of the relay alkene, in this case a cyclopentene derivative from **11d** (i.e., k_{off} for **11d**, or an associative counterpart involving the C16=C16′ alkene).[4] Here we suggest that the steric repulsion between the bulky geminal dicarboxylate groups and the other moieties in the metal-ligand sphere reduces the avidity of Ru–alkene binding. This scenario would result in a faster rate of decomplexation of the cyclopentene from **11d** relative to the analogous events in the possible reactions of **8a**–**e**. The practical advantage of the allylmalonate relay activator has been demonstrated here and we believe that this subunit could potentially have wider utility as a tool to combat macrocyclization[7,8] or truncation[2] processes that have plagued the application of the RRCM strategy.[2]

We performed additional studies to investigate the ease of ejection of the relay alkene from the ruthenium coordination sphere. The compound **12** produced the hindered *Z*-alkene **14**[2,9,10] along with several by-products upon treatment with the first-generation Grubbs precatalyst (Scheme 5). These by-products were isolated and shown to be the macrocyclic dienes (*E*)-**13**, (*Z*)-**13**, and **15**. Interestingly, **15** is a constitutional isomer of **13** in which the allylic methyl substituent has moved from C9 to C7. We suggest that diene **15** was produced through the reinsertion process indicated by **16a**–**d**. Wenzel and Grubbs have reported the dynamic nature of an alkene



Scheme 5. Rearranged macrocylic diene **15** that was formed during the RRCM reaction of compound **12**. **G1** = first-generation Grubbs initiator; [Ru = $CHPh(Cl)_2(PCy_3)_2$].

that is π-bound to the ruthenium in an N-heterocyclic carbene (NHC) complex in a simpler system.[11]

In summary, the studies reported here shed light upon the regioselectivity issues associated with the application of the RRCM strategy in complex molecules. A practical solution to overcome the competitive macrocyclizations seen for the substrates **8a–e** was found. In particular, the efficient and selective RRCM reactions of the substrates **9a** and **9b**, which contain an allylmalonate relay moiety, were achieved. This result demonstrates the importance of the relay moiety in structurally complex RRCM substrates. We propose that the faster ejection of the dimethyl cyclopentene-1,1-dicarboxylate, which is the by-product from the relay event, contributes to the dramatic benefit (**9b** into **10b**, 88% yield) afforded by use of the allylmalonate relay subunit.

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[5] An additional three steps involving cross-metathesis of the cyclic silaketal **10b** with butenolide **3** (to provide **4**), selective hydrogenation, and global desilylation afforded (+)-gigantecin (**5**, 62% over the three steps). See Ref. [1] and see J. Jeon, Ph.D. Thesis, University of Minnesota, Minneapolis, MN, **2009**.

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