Published in final edited form as:

Angew Chem Int Ed Engl. 2011 February 25; 50(9): 2141–2143. doi:10.1002/anie.201005044.

Allylmalonate as an Activator Subunit for Initiation of Relay Ring-Closing Metathesis (RRCM) Reactions

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We have previously described a total synthesis of (+)-gigantecin (**5**, Scheme 1) in which the importance of sequencing competitive ring-closing vs. cross metathesis events was revealed. [1] The most significant results (Scheme 1) were that the direct RCM reaction of key substrate **2** [using the Hoveyda-Grubbs 2nd generation initiator (**HG2**)] gave the 11-membered alkene **1** rather than the desired silacycloheptene derivative that would have arisen from closure of C15 with C16. By contrast, initial cross metathesis of **2** with **3** to form the C7/C8 bond was followed by RCM to give **4**, which was carried on in straightforward fashion to **5**.

Relay metathesis, of both the ring-closing (RRCM)[2] and cross metathesis (Relay-CM)[3] flavors, is an alternative strategy for redirecting the outcome(s) of competitive metathesis pathways in complex polyfunctional substrates. We felt that polyene intermediates like **2** and **4** held further promise as vehicles for exploring new aspects of the RRCM process. Here we report observations that extend both the utility and our understanding of RRCM.

We wondered if we could use RRCM to solve the regioselectivity problems outlined in Scheme 1, we considered arming the C15/C15' (or C16/C16') vinyl group in **2** with a relay activator unit as shown generically in **6** (or **7**, Scheme 2). The goal was to have the process implied by arrows *a* then *b* in **6** (or *a'* then *b'* in **7**) dominate, thereby closing the C15/C16 bond selectively over that of the C8/C16 (cf. numbering in **2**). Also shown in Scheme 2 is a set of relay activated, terminal allyl-containing substrates **8a-e** that we prepared (along with the malonate derivative **9b**, Scheme 3) in order to test this idea. Each substrate was exposed to a variety of olefin metathesis conditions, differing principally in the choices of initiators, solvents, and temperature. Reaction progress and outcome were monitored by ESI-MS and ¹H NMR analyses. In most cases complete consumption of starting material **8** was observed and most, if not all, of the identified product(s) were macrocyclic alkenes in which ethylene, but not the relay unit, had been lost. The preponderance of evidence pointed to reaction pathways via *c* and *d* in **6** (and *c'* in **7**), rather than the desired RRCM process via *a*/*b* (or *a'*/*b'*). In turn, this suggested that at least in the setting of the family of complex polyenes **8**, the rate constant of the critical relay event (*a/a'*) within the relay subunits (cf. **I-III**, Scheme 2) was too slow to compete with the undesired macrocyclizations. This led us to then study the allylmalonate ester derivatives **9a** and **9b**. Although we had used malonate 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, including incisive mechanistic studies[4]), this structural subunit had not been explored previously as the expendable relay activator moiety. The tetraene substrate **9a** contains a capping terminal *n*-butyl group on C8'. Treatment of **9a** with **HG2** in hot methylene chloride resulted in clean formation of the two RRCM products **10a** and **10b** in a 4:1 ratio

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(tabular inset, Scheme 3). Even more exciting was the observation that the malonate ester **9b**, now containing the C8/C8' *terminal vinyl group* and, therefore, a direct analog of the substrates **8a-e**, also cleanly cyclized to **10b** in 88% yield following purification.[5] Surprisingly, we did not detect the symmetrical C8-C8 dimer what would arise from cross metathesis of two molecules of **10** in either of these experiments.

Two factors likely contribute to the far greater efficiency of the RRCM with malonate ester derivatives **9a-b** compared with any of **8a-e** (Scheme 2). First, a buttressing/Thorpe-Ingold/gem-dimethyl-like effect should accelerate the initial stage of the relay event (i.e., k_{on} for **11a** to **11b**, Scheme 4). Second, ejection of the dimethyl cyclopentene-1,1-dicarboxylate moiety from the coordination sphere of the ruthenium center (cf. **11d** to **11e**, Scheme 4) should be faster than the corresponding decomplexation of the relay by-products for substrates **8a-e**. This second point deserves addition commentary.

The reversible nature of many individual steps in olefin metathesis, including dissociation of the product alkene from the metal center, has been examined fundamentally and in detail by Piers and co-workers.[6] We suggest that the slowest step in some RRCM reactions is loss of the relay alkene (a cyclopentene derivative here) from **11d** [i.e., k_{off} for **11d** (or an associative counterpart involving the C16/C16' vinyl group)[4]]. In this scenario it could be that the steric repulsion between the added bulk of the geminal dicarboxylates with moieties in the metal ligand sphere reduces the avidity of Ru-alkene binding. This would serve to speed ejection of the relay-generated remnant from **11d** relative to the analogous event in the reactions emanating from any of **8a-e**. Regardless of the mechanistic details of the transformation of **9b** to **10b**, the practical advantage of the malonate relay activator in the setting of tetraene **9** is unmistakable and suggests a potentially wider utility of this subunit to combat premature macrocyclization[7],[8] or truncation,[2] processes that have plagued a number of applications of the RRCM strategy.[2]

In the context of a different study, we made an observation that bears on the question of ease of ejection of the relay remnant from the ruthenium coordination sphere. Triene **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 additional, minor by-products were isolated and shown to be the macrocyclic dienes (*E*)-**13**, (*Z*)-**13**, and **15**. The last is most intriguing, since it is, formally, the constitutional isomer of **13** in which the allylic methyl substituent has moved from C9 to C7. We suggest that diene **15** was produced via the *reinsertion process* indicated by **16a-d**. Wenzel and Grubbs have reported the dynamic nature of a π -bound alkene to a ruthenium *N*-heterocyclic carbene (NHC) in a simpler system.[11]

In summary, the studies reported here shed light on regioselectivity issues associated with the application of the RRCM strategy in a complex molecular setting. A practical solution to overcome competitive premature macrocyclizations within **8** was uncovered. In particular the efficiency and selectivity of RRCM reactions of substrates **9a/b**, each armed with an allylmalonate relay moiety, was achieved. This example demonstrates that the structure of the relay moiety can be crucial in structurally complex RRCM substrates. We propose that faster ejection of dimethyl cyclopentene-1,1-dicarboxylate, the remnant from the relay event, contributes to the dramatic benefit (**9b** to **10b**, 88% yield) afforded by use of the allylmalonate relay.

Acknowledgments

This investigation was supported by a grant awarded by the National Cancer Institute (CA76497) of the United States National Institutes of Health.

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Scheme 1.
Sequenced Metatheses Leading to (+)-Gigantecin.[1] TIPS = triisopropylsilyl.

Scheme 2.
RRCM with Various Relay Activator Units.

Scheme 3.

RRCM with Allyl Malonate as the Relay Activator. **HG2** = second generation Hoveyda-Grubbs initiator, [Ru=CH(*o*isopropoxyPh)(Cl)₂(H₂IMes)].

Scheme 4.
Mechanistic Cascade for the Relay Stage of RRCM. $[Ru^*] = Ru(Cl)_2(H_2IMes)L_n$.

Scheme 5.

Rearranged Macrocyclic Diene **15**, Formed during the RRCM Reaction of Triene **12**. **G1** = first generation Grubbs initiator [Ru=CHPh(Cl)₂(PCy₃)₂].