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Effects of temperature and concentration in some ring closing metathesis reactions

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Abstract—Ring closing metathesis (RCM) has emerged as a powerful tool to construct macrocyclic ring systems. However, the product distribution of monomer and oligomers is often a problem in the formation of medium to large rings. In the course of synthetic studies on the natural product radicicol and its analogs, we have found that the reaction temperature, along with concentration, has significant impact on the outcome of the product ratio. Specifically, carrying out the RCM reaction in refluxing toluene (110°C) at higher dilution affords improved yields of the monomeric macrocycle. Similar observations for another family of macrolactone natural products, the epothilones, are also reported.

Numerous macrocyclic natural products possess useful biological activities. Not surprisingly, many macrocyclization methods have been developed and applied toward their total chemical synthesis. In recent years, the use of ring closing metathesis (RCM) for macrocyclization has become increasingly popular.[1] During our studies on natural product-based drug development, we sought to produce a set of compounds altered by a single functionality from the parent molecule for SAR purposes. Recently, we have synthesized analogs of the natural products radicicol (**1**) and epothilone 490 (**2**) (Fig. 1). In each of these efforts, we took recourse to utilize RCM as a key step in macrocycle construction. Interestingly, we observed striking differences in the behavior of these substrates in the RCM step, notwithstanding their subtle structural alteration from the parent compounds. Herein, we report our findings, which show that tuning the reaction temperature and concentration has a significant impact on the outcome of the product ratio in the RCM, leading to improved yields in the closure step.

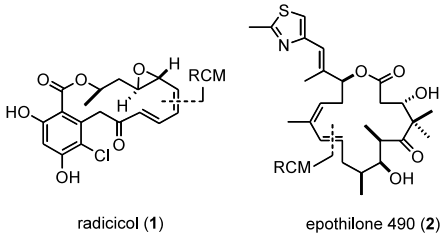

Figure 1. Structure of radicicol and epothilone 490.

The total synthesis of radicicol[2,3] has been achieved as a part of our program in anticancer drug development based on Hsp90 inhibitors.[4,5] We became interested in preparing a series of cyclopropyl analogs, isomeric at the C10′ methyl group and the C7′/C8′epoxide (radicicol numbering) (Scheme 1).[6]

The key steps in the synthesis of the parent compound **1** involved macrolide formation by RCM of precursor **3**. With compound **3**, which bears an epoxide at C7′/C8′ position, RCM occurred under mild reaction conditions (2 mM, CH_2Cl_2, 42°C) to give the monomeric macrocyclic product **6** in good yield (Scheme 1, entry 1). However, similar conditions (0.5 mM, CH_2Cl_2, 42°C) were applied to the cyclopropyl precursor **4**, the majority of the isolated products were dimeric 28-membered macrocycles (entry 2).[7] With higher reaction temperatures, the product distribution was improved to a ratio of ~1:1 (entry 4).[8] In an attempt to lower the substrate concentration, the precursor was added to the reaction mixture over 7 h ('infinite dilution' conditions, the well-known laboratory practice for promoting macrocyclizations).[9] In our case, however, the product distri-

Keywords: ring closing metathesis; RCM; product distribution; radicicol; epothilone.

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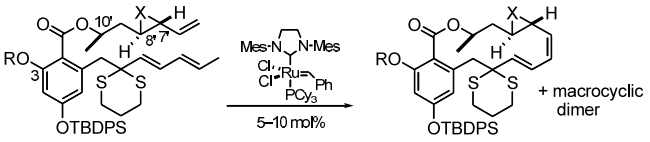
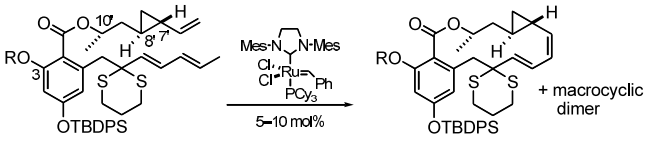


3, R = TBS, X = O
5, R = TBS, X = CH_2
9, R = H, X = CH_2

6, R = TBS, X = O
8, R = TBS, X = CH_2
11, R = H, X = CH_2



4, R = TBS
10, R = H

7, R = TBS
12, R = H

entry	substrate	conditions	concentration	yield of mono/dimers	
1	**3**	CH_2Cl_2, 42°C, 2 h	4 mM	60%	-
2	**4**	CH_2Cl_2, 42°C, 19 h	0.5 mM	16%	30%
3	**4**	PhMe, 42°C, 19 h	0.5 mM	27%	48%
4	**4**	PhH, 80°C, 35 min	0.5 mM	33%	36%
5	**4**	PhH, 80°C, over 7 h	infinite dilution (final 0.5 mM)	16%	30%
6	**4**	PhMe, 110°C, 10 min	0.2 mM	55%	-
7	ent-**5**	CH_2Cl_2, 42°C, 18.5 h	0.5 mM	20%	38%
8	ent-**5**	PhMe, 110°C10 min	0.2 mM	54%	-
9	ent-**9**	PhMe, 110°C, 5 min	0.2 mM	65%	19%
10	**10**	PhMe, 110°C, 5 min	0.2 mM	63%	18%

Scheme 1. Construction of the macrocycle via RCM under different reaction conditions in the radicicol series.

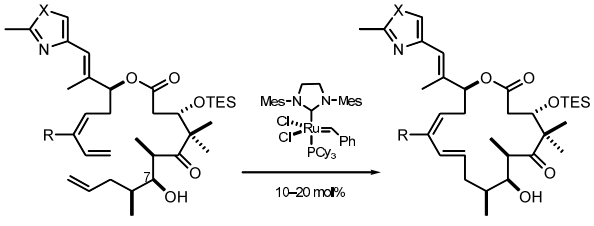
bution was not effected much by this operation, but was primarily sensitive to the final concentration (entry 5). The above observation can be attributed to the reversible nature of olefin metathesis.[10] Re-subjection experiments showed that the monomer re-opened to the acyclic precursor, while the dimers were inert under the reaction conditions.

Eventually, it was found that the product distribution is strikingly improved by adjustment of the reaction temperature. Thus, performing the reaction at 110°C in toluene and quenching after a short period of time resulted in clean conversion of **4** to the primary cyclization product **7** (entry 6).[11] The yields were significantly enhanced relative to runs at lower temperature at comparable concentrations. The different reaction conditions were also evaluated with the diastereoisomeric substrate ent-**5**, and were found to give comparable outcomes (entries 7 and 8). The substrates without a protecting group at the C(3)–OH behaved similarly (entries 9 and 10).

The observations described above may be explained by the difference of entropy in activation energy leading to each product. If the formation of the monomer is entropically favored over that of the dimer,[12] the kinetic ratio of the two products should shift toward the monomer at higher temperature. In fact, the ratio obtained after 5–10 min appears to be a kinetic ratio,[13] since runs with longer reaction times resulted in the formation of more dimer (vide infra). This indicates that the monomer might eventually revert to the thermodynamically favored dimers.

We have also recently described the total synthesis of epothilone 490, another naturally occurring macrolactone with a 1,3-diene unit.[14,15] A key step in the synthesis was the stereospecific RCM of compound **13**. The reaction occurred smoothly under standard reaction conditions (CH_2Cl_2, 40°C) to give **16** in 57% yield (Scheme 2, entry 1). However, while investigating the applicability of RCM to related congeners for SAR-level analysis, we encountered similar obstacles as seen in the radicicol series. Small changes in the substrate structure (compare **13** with **14** and **15**) led to a sharp drop in yield of the desired cyclic products when the reactions were carried out in CH_2Cl_2 at 40°C (entries 2 and 4). Applying the lessons from the aforementioned radicicol study, the yield of the monomers **17** and **18** was dramatically improved by conducting the metathesis reaction at higher temperature and dilution (entries 3 and 6). The desired macrolides **17** and **18** were isolated in 66 and 65% yield, respectively. We noted, however, that unlike the case in the radicicol system, longer reaction times did not change the product distribution.

The study described herein demonstrates the possibility of controlling the product distribution in RCM reactions by altering not only the reaction concentration, but also the reaction temperature.[16] Additionally, the excellent thermal stability of the second generation Grubbs catalyst is demonstrated.[17] Although it is too



13, R = Me, X = S
14, R = Et, X = S
15, R = Me, X = O

16, R = Me, X = S
17, R = Et, X = S
18, R = Me, X = O

entry	substrate	conditions	concentration	yield of monomer
1	**13**	CH_2Cl_2, 40°C, 5.5 h	2 mM	57%[a]
2	**14**	CH_2Cl_2, 40°C, 6 h	2 mM	20%
3	**14**[b]	PhMe, 110 °C, 20 min	0.5 mM	66%
4	**15**	CH_2Cl_2, 40°C, 6 h	2 mM	<20%
5	**15**	PhMe, 110 °C, 25 min	2 mM	30%
6	**15**	PhMe, 110 °C, 15 min	0.5 mM	65%

[a] Reference 13; [b] C(7)-OH protected as 2,2,2-trichlorcethyl carbonate (Troc)

Scheme 2. Construction of the macrocycle via RCM under different reaction conditions in the epothilone series.

early to assert the generality of the trend reported herein,[18] it was applicable to three independent, highly functional systems.[19]

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12. Although entropy is generally considered higher for smaller rings, the calculated values for those larger than 12-membered rings are comparable.[9b]
13. Typically, RCM produces a thermodynamic distribution of products, although there are some cases where kinetic distribution of products is reported.[10e]
14. Biswas, K.; Lin, H.; Njardarson, J. T.; Chappell, M. D.; Chou, T. C.; Guan, Y.; Tong, W. P.; He, L.; Horwitz, S. B.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 9825–9832.
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