

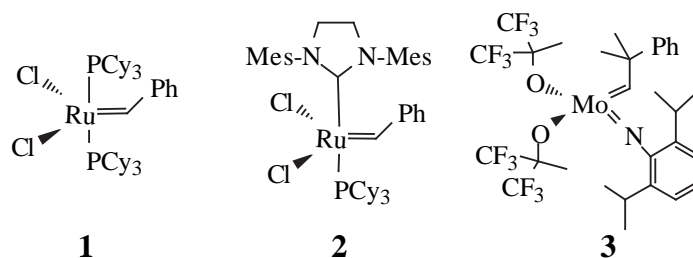
RING CLOSING METATHESIS REACTION OF DIENES WITH ACRYLATE
MOIETY LEADING TO 5- TO 7-MEMBERED LACTONES AND
CYCLIZATION TO 14-MEMBERED RINGS

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Abstract–Dienes with acrylate moiety have been subjected to olefin metathesis reactions using $(\text{PCy}_3)_2\text{Cl}_2\text{Ru}=\text{CHPh}$ (**1**) and $(\text{PCy}_3)\text{Cl}_2[\text{H}_2\text{imid}(\text{Mes})_2]\text{Ru}=\text{CHPh}$ (**2**). 5- to 7-Membered α,β -unsaturated lactones were obtained in good yields. Formation of 14-membered compounds was attempted using different substrates.

A number of large ring heterocycles have successfully been synthesized using the ring closing metathesis (RCM) reaction as a key step.¹⁻⁷ RCM reaction has now been one of the method of choice for synthesis of natural products.¹⁻⁷ Although considerable amounts of examples have been reported, different positions for cyclizations lead to different yields.⁸ Yields of the electron deficient olefins are relatively low or do not cyclize to the desired compounds, presumably due to the slow formation of the metalacyclobutanes of the acrylate terminal olefins. Recently, Grubbs developed the new generation olefin metathesis catalyst (**2**).⁹ We became interested in comparing **1** with **2** for RCM reactions and studied the possibility of cyclizations having acrylate moiety in the molecule. At the same time, the effect of the ring size was also investigated, although Ghosh¹⁰⁻¹² and Grubbs¹³ have recently reported similar RCM reactions. Cyclization to 14-membered compounds has also been investigated using catalyst (**1**, **2**, or **3**).

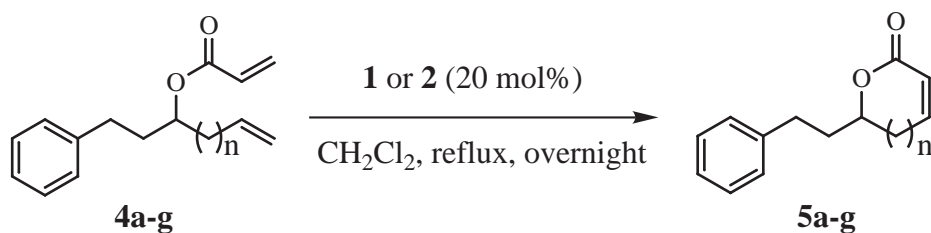


Compounds (**4a** and **4b**) were treated with 20 mol% of Grubbs' catalyst (**1**) in refluxing CH_2Cl_2 to provide 5- and 6-membered α , β -unsaturated lactones (**5a** and **5b**) in 76% and 61% yields, respectively (Table 1, entries 1, 3). In these reactions, we obtained similar results regardless of the presence or absence of $\text{Ti}(\text{O}^i\text{Pr})_4$ (entries 2, 4). Compound (**4c**) did not provide 7-membered α , β -unsaturated lactone (**5c**) using catalyst (**1**) (entry 5). When the concentration was raised to 10 mM, the desired product (**5c**) was produced in 5% (entry 6). However, when compound (**4c**) was treated with 20 mol% of catalyst (**2**) in refluxing CH_2Cl_2 (1 mM), compound (**5c**) was obtained in 72% yield (entry 7). Interestingly, as in entry 8, in the case of 10 mM, **5c** was produced in 6% yield, and instead the dimers were formed. Compound (**4d-g**) did not provide 8-, 9-, 10-, and 13-membered α , β -unsaturated lactones (**5d-g**) using catalyst (**1**) (entries 9, 11, 13, 17). These compounds were treated with catalyst (**2**) to afford dimeric compounds (**6d-g** and **7d-g**) (entries 10, 12, 14, 18).¹⁴ Even if the concentration of these reactions were changed, the desired product was not formed (entries 15, 16).

We next studied the possibility of cyclizations into 14-membered compounds. Table 2 illustrates the results of reactions of dienes (**8-13**). Compound (**8**) has the diacrylate functional group and the cyclization was not induced using **1**, presumably due to the slow reaction between acrylate ruthenium carbene and the second acrylate group (entry 1). Compound (**9**) was treated with 20 mol% of catalyst (**1**) in CH_2Cl_2 (1 mM) at room temperature to provide 14-membered lactone (**15**) in 73% yield (entry 2). Compound (**15**) was formed as the single isomer and the geometry of the double bond was *E*, because the allylic methylenes appeared at δ 31.2 and 31.6 in the ^{13}C NMR spectrum.^{8c} Compound (**10**) was treated with 20 mol% of catalyst (**2**) in 1 mM refluxing CH_2Cl_2 to afford 14-membered trisubstituted alkene (**16**) in 21% yield (entry 3). Compound (**16**) was also formed as the single isomer and the geometry was *E*, because the olefinic methyl group appeared at δ 15.4 and no NOE was observed between the methyl group and the olefinic proton. This reaction did not undergo using catalyst (**1**) or Schrock's catalyst (**3**). Keto ester (**11**) was treated with 20 mol% of catalyst (**2**) in 1 mM refluxing CH_2Cl_2 to give 14-membered trisubstituted alkene (**17**) in 14% yield (entry 4).¹⁵ Compound (**12**) was treated with 6 mol% of catalyst (**1**) in 10 mM refluxing CH_2Cl_2 to provide a mixture of *E/Z* isomer (**18**) (1.6:1.0 or 1.0:1.6) in 42% yield. Finally, compound (**13**) was treated with 30 mol% of catalyst (**3**) in 4 mM benzene at 60 °C to afford dimeric compound (**19**) in 52% yield (entry 6).

In conclusion, we have carried out the RCM reactions of dienes with acrylate moiety. 5- to 7-Membered α , β -unsaturated lactones were obtained in good yields. However, 8- to 13-membered rings were not produced, instead dimeric compounds were obtained. These results were different from those of a similar system recently reported by Grubbs *et al.*¹³ It is worth mentioning that $\text{Ti}(\text{O}^i\text{Pr})_4$ was not necessary in these reactions (Table 1, entries 1-4), although many reports pointed out that the use of $\text{Ti}(\text{O}^i\text{Pr})_4$ was essential for cyclization reactions.^{10-13, 16, 17} It is also true that catalyst (**2**) is much more reactive than catalyst (**1**).⁹ It was possible to cyclize compound (**10**) into 14-membered lactone (**16**) with the

Table 1. Cyclization of acrylate derivatives (**4a-4g**).



entry	n	substrate	conc. (mM)	catalyst	product (isolated yield %)
1	0	4a	10	1	5a (76)
2 ^{a)}	0	4a	10	1	5a (79)
3	1	4b	10	1	5b (61)
4 ^{a)}	1	4b	10	1	5b (69)
5	2	4c	1	1	5c (0)
6	2	4c	10	1	5c (5)
7	2	4c	1	2	5c (72)
8	2	4c	10	2	5c (6), 6c (18), 7c (11)
9	3	4d	1	1	5d (0)
10	3	4d	1	2	6d (41), 7d (9)
11	4	4e	1	1	5e (0)
12	4	4e	1	2	6e (30), 6f (20)
13	5	4f	1	1	5f (0)
14	5	4f	1	2	6f (9), 7f (13)
15	5	4f	10	1	5f (0)
16	5	4f	10	2	6f (15), 7f (27)
17	8	4g	1	1	5g (0)
18	8	4g	1	2	6g (24), 7g (24)

a) $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.3 eq.) was added.

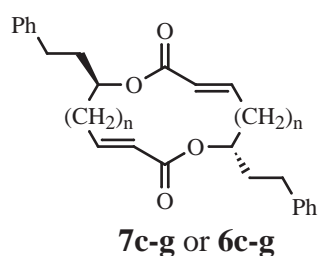
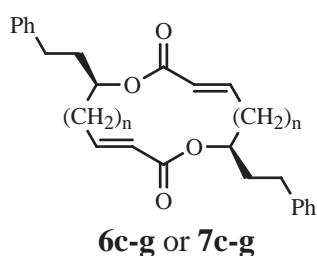
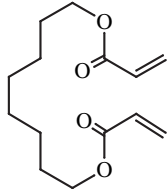
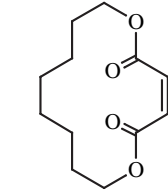
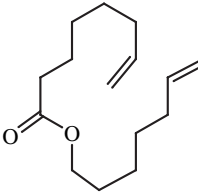
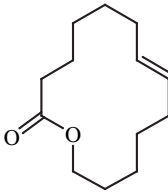
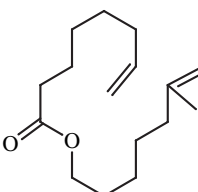
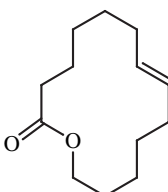
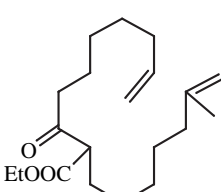
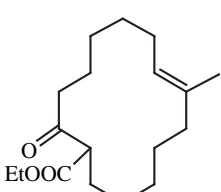
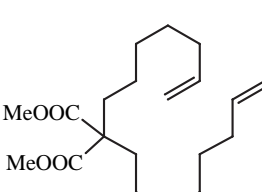
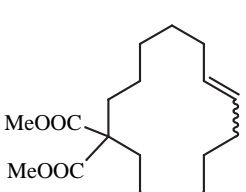
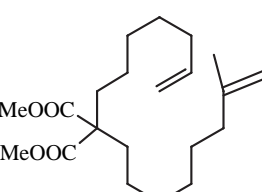
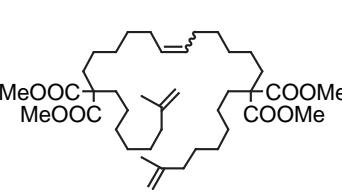


Table 2. Cyclization to 14-membered compounds.¹⁾

entry	substrate	product	catalyst (mol%)	solvent	conc. (mM)	isolated yield (%)
1	 8	 14	1 (20)	CH ₂ Cl ₂	10	0
2	 9	 15	1 (20)	CH ₂ Cl ₂	10	73
3	 10	 16	2 (20)	CH ₂ Cl ₂	1	21
4	 11	 17	2 (20)	CH ₂ Cl ₂	10	14
5	 12	 18 (1.6:1)	1 (6)	CH ₂ Cl ₂	10	42 ²⁾
6	 13	 19	3 (30)	benzene	4	52 ²⁾

1) The reaction mixture was stirred under reflux overnight.

2) mixture of *cis/trans* isomers.

trisubstituted double bond by use of catalyst (**2**), although the isolated yield was only 21%. A similar substrate (**11**) was successively cyclized into compound (**17**) on treatment with **2**. The major difference should be attributed to the presence of the hetero atom in the skeleton in the case of **10**. Heterocycles seem to be easier to be formed by RCM reactions (the better yield in entry 2 than in entry 5 and in entry 3 than in entry 4).⁴ We are currently working on the synthesis of natural products having α,β -unsaturated lactones under these reaction conditions.

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14. These products showed the quasi molecular ion peaks at m/z 461 ($[M+H]^+$, **6d**), 489 ($[M+H]^+$, **6e**), 517 ($[M+H]^+$, **6f**), and 601 ($[M+H]^+$, **6g**) in their CIMS spectra, respectively.
15. Compound (**17**) was isolated as a single isomer. The ¹³C NMR indicated the geometry as *E* (δ 15.2 for Me).
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