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Selective formation of dihydropyran derivatives by a tandem domino ring-closing metathesis/cross-metathesis

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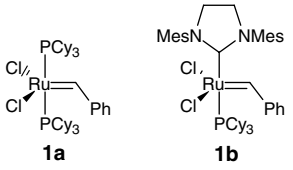
Abstract—A ring-closing metathesis (RCM)/cross-metathesis (CM) domino reaction has been applied to esters and unsymmetrical ether prepared from 1,5-hexadien-3-ol. For the first time, dihydropyran derivatives have been obtained via a regioselective cyclization. This reaction was performed in high yield and *E* stereoselectivity.

With the discovery of well-defined catalysts **1a** and **1b** (Fig. 1), which can react with highly functionalized substrates, metathesis[1,2] is more and more applied even for the total synthesis of natural products.[3,4] Due to the mildness of the experimental conditions, tandem metathesis processes have been also obviously considered: the catalyst used for a first metathesis coupling is able to promote a second reaction from the intermediate generated during the first step.[5]

In this context, we already reported two different tandem ring-closing/cross-metathesis reactions from β,γ- or α,β-unsaturated 3-*O*-1,4-pentadienyl esters leading, respectively, to δ-lactones[6] and γ-lactones.[7] In the latter case, the reaction proceeded via an efficient alkylidene transfer. Although tandem metathesis reactions are nowadays well recognized methods to reach rapidly and easily complex structures, a major challenge is still to investigate the regioselectivity issue when different competitive cyclizations are possible.



1a **1b**

Figure 1.

Therefore, we previously studied a similar process starting from 3-*O*-1,5-hexadienyl esters (Scheme 1).[7] In that case, the diene which should interact with the ester part is not symmetrical and two competitive ring-closing metatheses could be expected leading to the formation of two regioisomers. The reaction showed a moderate ring-size selectivity while both five- and six-membered ring lactones were obtained with a noticeable preference for the γ-lactone (**6**/**5** = 2/1).

We have subsequently performed a tandem RCM/CM process with acrylate **7** in the presence of 1-hexene (Scheme 2). The reaction delivered unsaturated lactones in higher chemical yields and with a better selectivity still in favour of the γ-lactone (**9**/**8** = 3/1).[8] These results are closed to those observed by Quinn et al. who observed the exclusive formation of butenolides from the related acrylates of C_2-symmetric alcohols.[9]

The difference in the chemical yields between the two processes described above can be correlated with the steric hindrance generated by the alkyl substituent on **4**, which could prevent the formation of the metallacyclobutane. Furthermore, the intermediate for the five-membered ring formation in the case of **4** should be more sterically encumbered than the six-membered one. These reasons could explain the lower yields for the butenolide isolated from ester **4**.

Keywords: Ring-closing metathesis; Cross-coupling metathesis; Allyl ethers; Cyclization.
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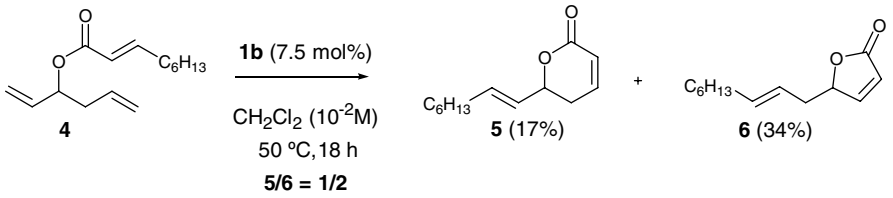
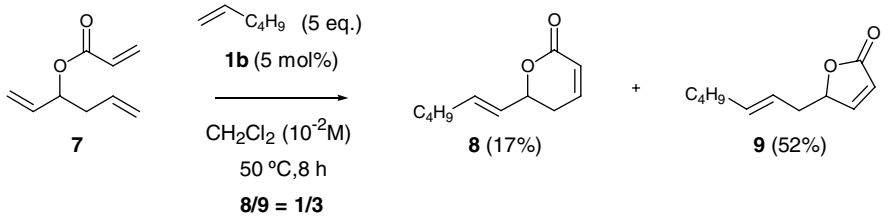


Scheme 1. Formation of δ-lactones (**5**) and γ-lactones (**6**) by a RCM/CM process from 2-nonenoate **4**.



Scheme 2. Formation of δ-lactones (**8**) and γ-lactones (**9**) by a RCM/CM process from acrylic ester **7**.

We next examined the regioselectivity issue of the RCM/CM domino process applied to ether derivatives. We envisaged that an important modification of our substrate could modify the regioselectivity of the reaction. Moreover, starting from a hexadienyl ether, and in the case of a regioselective pathway, we could apply this strategy to a direct synthesis of the isolated pyran of laulimalide as depicted in Figure 2. It should be noted that the heterocyclic subunit has been already obtained by RCM while the exocyclic chain was functionalized by a Stille coupling.[10]

The access to five- or six-membered cyclic ethers has been widely investigated by RCM and applied in total synthesis. In the context of the synthesis of (−)-mucocin,[11] Crimmins et al. used a tandem relay strategy[12] from a triene derivative to circumvent the lack of regioselectivity and to obtain an efficient access to a dihydrofuran. Furthermore, Basu and Waldmann studied the regioselectivity during the ring-closure of allyl and conjugated pentadienyl ethers.[13] In a recent article,[14] Schmidt and Nave described the reactivity of hexadienyl ethers derived from D-mannitol and the selective formation of dihydrofurans versus dihydropyrans by modifying the nature of alkoxy group. For this ether series, the formation of the five-membered ring was again preferred.

All these recent published data urged us to disclose herein our preliminary investigations performed on allylether **10** prepared from 1,5-hexadien-3-ol.[15] The expected RCM/CM reaction was first tested with 5-bromopentene **15a** as the alkene partner (R = –$(CH_2)_3$Br) for the second coupling (Scheme 3). Performed in the presence of catalytic amounts of Grubbs catalyst **1a**, the only compound isolated in a low yield was dihydropyran **11** functionalized by a 5-bromopentenyl lateral chain (Table 1, entry 1).

With the more active catalyst **1b** (entry 2), the reaction again delivered six-membered ring **11** in far better yield. Another compound was isolated from the reaction mixture and identified as dimeric dihydropyran **13** and present according to the ^{13}C NMR spectrum as a nearly 1:1 mixture of diastereomers (Fig. 3).

To ascertain that the formation of the six-membered ring was preferred, the process was generalized with other alkenes **15b–e** by using the same experimental conditions, and results are summarized in Table 1.[16] Only traces of **13** were detected by TLC control on the crude reaction mixture, while the *E* configuration of the new C=C bond was determined by analysis of the ^{1}H NMR spectra for all isolated compounds **11**. With terminal alkenes, the reaction occurred in yields up to 78% and with a total *E* selectivity for **11b**, **c** and **e**, which

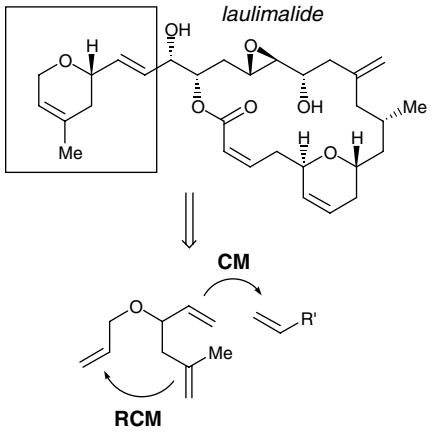
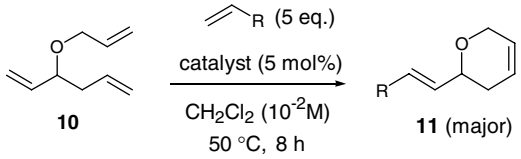
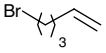
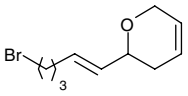
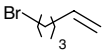
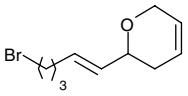
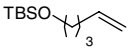
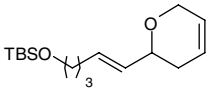
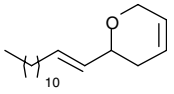
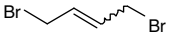
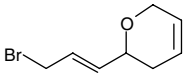
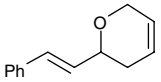
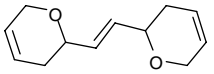
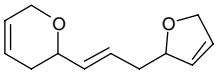


Figure 2. RCM/CM approach for a subunit of laulimalide.



Scheme 3. Regioselective formation of dihydropyran **11** from ether **10**.

Table 1. Tandem RCM/CM of ether **10** with alkenes **15a–e**

Entry	Alkene		Catalyst[a]	Product		Yield[b] (%)
1		**15a**	**1a**		**11a**	9
2		**15a**	**1b**		**11a**	78
3		**15b**	**1b**		**11b**	69
4		**15c**	**1b**		**11c**	73
5		**15d**	**1b**		**11d**	40
6		**15e**	**1b**		**11e**	61
7	No alkene		**1b**		**13**	24
					**14**	23

[a]Reaction performed in the presence of 5 mol % of catalyst.
[b] Isolated yields.

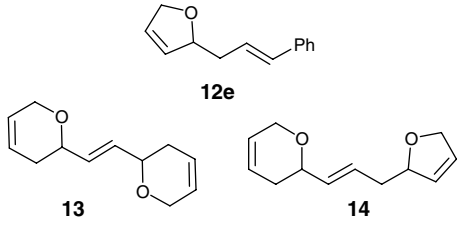


Figure 3.

reflects the thermodynamic conditions of this tandem metathesis process. Similarly, a *E* configuration was attributed both to compounds **11a** and **11d**. Even styrene, which is not an efficient partner in RCM/CM of esters,[6] gave the functionalized 2-styryl dihydropyran **11e** in 61%. In this case, the dihydrofuran **12e** was also isolated in a 12% yield (Fig. 3) maybe due to a deactivating effect of the phenyl group which could disturb the equilibrium of the process.

In the absence of alkene (entry 7), two compounds **13** and **14** were isolated. Compound **13** corresponds to the self-coupling of 2-vinyldihydropyran while **14** results from the cross-coupling of the same intermediate with a 2-allyldihydrofuran obtained by the competitive pathway. Even when the reaction is performed without any alkene, a preferred formation of the pyran ring is observed.

In conclusion, we have developed a short access to 2-alkylidene dihydropyrans by using a RCM/CM starting from 1,5-hexadien-3-ol allyl ether. The reaction occurred in yields up to 78% with always high regio and *E* stereo selectivities. To the best of our knowledge, this is the first example of a regioselective RCM performed on trienic ether bearing three terminal double bonds. We currently investigate the synthesis of the laulimalide subunit using this strategy.

Experimental procedure: A nitrogen stream was bubbled through a dichloromethane solution of ether **10** (69 mg, 0.5 mmol) containing the chosen alkene **15** (5 equiv). Grubbs type II catalyst (5 mol %) was added at once and the resulting solution was heated for 8 h at 50 °C. After cooling, the solvent was removed by concentration and the mixture was purified by flash-chromatography (SiO_2—eluent: EtOAc/PE = 10/90).

Acknowledgments

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8. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$–0.96 (m, 3H), 1.11–1.43 (m, 4H), 1.96–2.14 (m, 2H), 2.34–2.57 (m, 2H), 4.87 (q, $J = 7.3$ Hz, 1H), 5.53–5.65 (m, 1H), 5.83 (dt, $J = 15.3(E)$-6.8 Hz, 1H), 6.04 (dt, $J = 9.8$–1.7 Hz, 1H), 6.88 (dt, $J = 9.8$–4.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 22.5, 30.1, 31.1, 32.0, 78.6, 121.7, 126.9, 136.0, 145.1, 164.5.
   Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$–0.96 (m, 3H), 1.11–1.43 (m, 4H), 1.96–2.14 (m, 2H), 2.34–2.57 (m, 2H), 5.03 (t, $J = 6.4$ Hz, 1H), 5.35 (dt, $J = 15.3(E)$-7.3 Hz, 1H), 5.60 (dt, $J = 15.3(E)$-6.8 Hz, 1H), 6.13 (dd, $J = 5.7$–2.0 Hz, 1H), 7.44 (dd, $J = 5.7$–1.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.1$, 22.3, 31.5, 32.4, 36.4, 83.2, 122.0, 122.2, 136.3, 156.4, 173.3.
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16. Compound **11a**: 78%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.93$ (quin, $J = 7.1$ Hz, 2H), 2.12–2.30 (m, 4H), 3.39 (t, $J = 6.9$ Hz, 2H), 3.98 (quin, $J = 4.7$ Hz, 1H), 4.20 (sl, 2H), 5.58–5.93 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.9$, 31.4, 32.2, 33.4, 65.9, 73.9, 124.1, 126.5, 130.2, 132.2. HRMS (CI) calcd for $C_{10}H_{15}BrO$–$H^+ = 229.0228$, found 229.0221.
   Compound **11b**: 69%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.04$ (s, 6H), 0.90 (s, 9H), 1.50–1.80 (m, 2H), 1.94–2.37 (m, 4H), 3.62 (t, $J = 6.4$ Hz, 2H), 3.98 (dt, $J = 6.2$–3.7 Hz, 1H), 4.20 (sl, 2H), 5.55 (dd, $J = 15.4(E)$-6.2 Hz, 1H), 5.68–5.87 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = -5.0$, 18.6, 26.2, 28.9, 31.4, 32.5, 62.8, 65.9, 74.2, 124.3, 126.5, 131.0, 132.3. HRMS (CI) calcd for $C_{16}H_{30}O_2Si$–$H^+ = 281.1937$, found 281.1936.
   Compound **11c**: 73%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.89$ (t, $J = 7.1$ Hz, 3H), 1.17–1.46 (m, 18H), 1.93–2.18 (m, 4H), 3.98 (dt, $J = 6.2$–3.7 Hz, 1H), 4.24 (sl, 2H), 5.52 (dd, $J = 15.4(E)$-6.2 Hz, 1H), 5.14–5.96 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.4$, 23.0, 29.4, 29.5, 29.7, 29.8, 29.9, 30.0, 30.1, 31.4, 32.2, 32.7, 66.0, 74.3, 124.3, 126.5, 130.6, 133.0. HRMS (EI) calcd for $C_{18}H_{32}O = 264.2453$, found 264.2450.
   Compound **11d**: 40%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.05$–2.16 (m, 2H), 3.96 (d, $J = 7.2$ Hz, 2H), 4.03–4.12 (m, 1H), 4.23 (sl, 2H), 5.70–5.89 (m, 3H), 5.90–6.03 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.9$, 32.5, 66.0, 72.9, 123.9, 126.6, 127.3, 135.6. HRMS (CI) calcd for $C_8H_{11}BrO$–$H^+ = 200.9915$, found 200.9917.
   Compound **11e**: 61%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.06$–2.30 (m, 2H), 4.18 (quin, $J = 4.8$ Hz, 1H), 4.27 (s, 2H), 5.75 (dm, $J = 10.3$–1.2 Hz, 1H), 5.85 (dm, $J = 10.3$–2.5 Hz, 1H), 6.24 (dd, $J = 16.0(E)$-5.8 Hz, 1H), 6.62 (d, $J = 16.0$ Hz, 1H), 7.17–7.40 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 31.4$, 66.0, 74.1, 124.2, 126.6, 126.8, 127.9, 128.8, 130.2, 130.8, 137.1. HRMS (CI) calcd for $C_{13}H_{14}O$–$H^+ = 185.0966$, found 185.0960.
   Compound **12e**: 12%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.51$ (t, $J = 6.5$ Hz, 2H), 4.58–4.76 (m, 2H), 4.98 (m, 1H), 5.85 (dd, $J = 6.2$–1.3 Hz, 1H), 5.93 (dd, $J = 6.4$–1.6 Hz, 1H), 6.24 (dt, $J = 15.8(E)$-7.2 Hz, 1H), 6.48 (d, $J = 15.8$ Hz, 1H), 7.17–7.40 (m, 5H).
   Compound **13**: 24%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.98$–2.23 (m, 4H), 4.00–4.10 (m, 2H), 4.23 (sl, 4H), 5.72 (dm, $J = 10.3$ Hz, 2H), 5.78–5.87 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 2 diastereomers: $\delta = 31.2$ and 31.3, 66.0 and 66.1, 73.4 and 73.7, 124.2, 126.6, 131.6 and 131.9.
   Compound **14**: 23%. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.96$–2.20 (m, 2H), 2.23–2.40 (m, 2H), 4.00 (quin, $J = 4.8$ Hz, 1H), 4.20 (sl, 2H), 4.53–4.70 (m, 2H), 4.85 (sl, 1H), 5.47–5.96 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 30.1$, 31.4, 66.0, 74.1, 75.6, 85.9, 124.3, 126.7, 127.2, 127.9, 139.7, 133.6.