α,β-Unsaturated δ-Valerolactones through RCM–Isomerization Sequence

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Abstract: α,β-Unsaturated δ-lactones are accessible via a sequential ring-closing metathesis (RCM) double-bond migration reaction starting from butenoates of allyl alcohols. This approach proceeds efficiently with lower catalyst loadings and higher initial substrate concentrations compared to the alternative RCM of acrylates derived from homoallylic alcohols.

Key words: ruthenium, lactones, tandem reactions, metathesis, esters

The ring-closing metathesis (RCM) of acrylates **2** derived from homoallylic alcohols yields α,β-unsaturated δ-lactones (α-pyrones, **1**). This transformation has not only been used for the total synthesis of numerous natural products, such as umuravumbolide[1] or strictifolione,[2,3] but also to obtain intermediates en route to the synthesis of other naturally occurring compounds, such as ricciocarpin A[4] or laulimalide[5,6] (Figure 1).

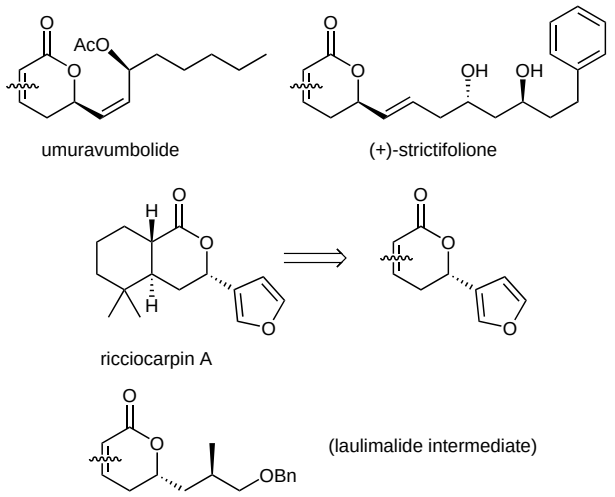
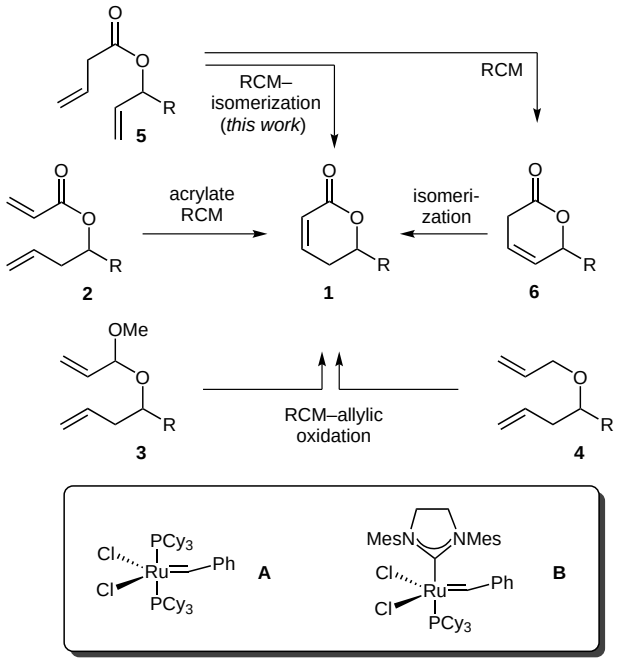


Figure 1 Natural products synthesized through RCM of acrylates

Unfortunately, the high synthetic value of acrylate RCM is somewhat tainted by the comparatively low reactivity of electron-deficient alkenes in olefin-metathesis reactions.[7] This problem has been addressed by using either first-generation Grubbs catalyst $[Cl_2(PCy_3)_2Ru{=}CHPh]$ (**A**) in combination with Lewis acids, for example, Ti(O*i*-Pr)$_4$,[8] or the more reactive second-generation catalyst **B**.[9] Although this catalyst can be used without addition of a Lewis acidic co-catalyst, occasionally very high catalyst loadings of up to 20 mol% were reported for the synthesis of α-pyrones.[10] A further drawback is the necessity to apply high- or pseudo-high-dilution conditions in these transformations, because exceeding a certain critical initial substrate concentration, normally ca. 0.01 M, will inevitably lead to incomplete conversion and very low isolated yields, presumably due to irreversible inhibition of the catalyst.[11] For these reasons, tactics were developed to circumvent this difficult metathesis step: for instance, Metz et al. demonstrated that the RCM of a mixed acrolein acetal **3**[12,13] proceeds without any solvent using very small amounts of the first-generation catalyst **A**. Mo(VI)-catalyzed or Cr(VI)-mediated oxidation of the intermediate dihydropyran acetal yields the desired α-pyrone **1**.[4] A sequence of RCM and allylic oxidation has also been applied to allyl ethers **4**, either as a two-step procedure, using stoichiometric amounts of Cr(VI) reagents for the allylic oxidation,[14,15] or as a Ru-catalyzed tandem sequence.[16,17] We thought that the problems arising from the insufficient reactivity of electron-deficient C–C double bonds might also be solved by using butenoates **5** instead of acrylates **2** as RCM precursors. Subsequent isomerization of the intermediate β,γ-unsaturated lactones **6** to α,β-unsaturated lactones should be facile because a conjugated π-system is established in this step (Scheme 1).



Scheme 1 Synthetic routes to α-pyrones (**1**) based on RCM

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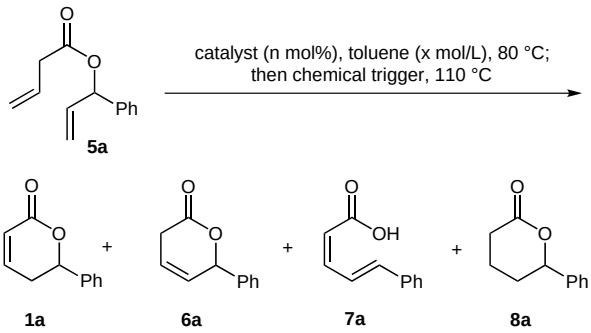
Compared to the number of examples reported in the literature for RCM of acrylates **2** to α-pyrones **1** there are only few examples for the cyclization of butenoates **5** to lactones **6**.[18–22] An organocatalytic synthesis of unsaturated lactones **6** has very recently been reported,[23] and previous syntheses rely on tartrate- or carbohydrate-derived aldehydes which are *Z*-selectively olefinated and subsequently cyclized.[24] It has been shown that unsaturated lactones **6** undergo a base-mediated double-bond migration to α-pyrones **1**, with DBU[20–22,24–27] or KO*t*-Bu[23] being the most commonly used reagents. In order to avoid the use of these basic reagents and to reduce the number of workup steps, we investigated an assisted tandem RCM–isomerization approach to accomplish the synthesis of α-pyrones from butenoates. Like assisted tandem catalytic transformations in general,[28] the RCM–isomerization sequence[29,30] relies on the presence of a 'chemical trigger'[28] which is required to induce in situ the transformation of a Ru carbene into a Ru hydride,[31] which then catalyzes the double-bond isomerization step. Snapper et al.[32] and we have introduced a variety of chemical triggers for the synthesis of cyclic enol ethers via a catalytic RCM–isomerization sequence of allyl ethers. In particular, our group proposed inorganic hydrides,[33] 2-propanol plus sodium hydroxide,[34] ethyl vinyl ether,[35,36] or triethylsilane[36] as additives to achieve the crucial in situ conversion of the carbene into a hydride complex.

At the beginning of this study we investigated the possibility to replace the more expensive second-generation catalyst **B** by the first-generation catalyst **A**. It has previously been noted that the use of **A** for substrates **5** requires the addition of $Ti(O\textit{i}\text{-}Pr)_4$.[18] As this Lewis acid might inhibit most of our isomerization-inducing additives, we investigated phenol as a co-catalyst,[37] unfortunately to no avail as the isolated yield of **6a** was only 42% (Table 1, entry 1). In contrast, with the second-generation catalyst **B** a yield of 93% was obtained with a much lower catalyst loading of just 1.0 mol% and at significantly higher initial substrate concentration (Table 1, entry 2). This prompted us to use **B** in all further experiments. In the next step, we investigated various chemical triggers: while no isomerization was observed with $NaBH_4$ (Table 1, entry 3), even at an increased catalyst loading, the two basic additives sodium hydroxide with 2-propanol and sodium hydride lead to a rapid base-induced ring-opening reaction which gives 2*Z*,4*E*-dienoic acids in good yields and high stereoselectivities (Table 1, entries 4 and 5).[38] With ethyl vinyl ether, we could indeed detect significant amounts of isomerized lactone **1a**, however, conversion was incomplete, and an unidentified byproduct was formed in significant amounts (Table 1, entries 6 and 7). For these reasons triethylsilane was tested. With one equivalent, the desired isomerization was indeed accomplished, but a small amount of saturated lactone **8a** was formed as a byproduct upon heating the reaction mixture after addition of the silane for 1.5 hours (Table 1, entry 8). This problem became more pronounced when dichloromethane was used as a solvent (Table 1, entry 9), presumably because the reaction time had to be increased to 48 hours at 40 °C. The observation of a concomitant hydrogenation of the C–C double bond was not fully unexpected in light of a report by Cossy and Dalko, who described a one-flask RCM–reduction sequence using triethylsilane in fivefold excess.[39] Gratifyingly, we were able to suppress the undesired formation of **8a** completely by reducing the amount of triethylsilane to 0.2 equivalents, resulting in an isolated yield of α-pyrone **1a** of 85% (Table 1, entry 10).

Table 1 Optimization of Conditions

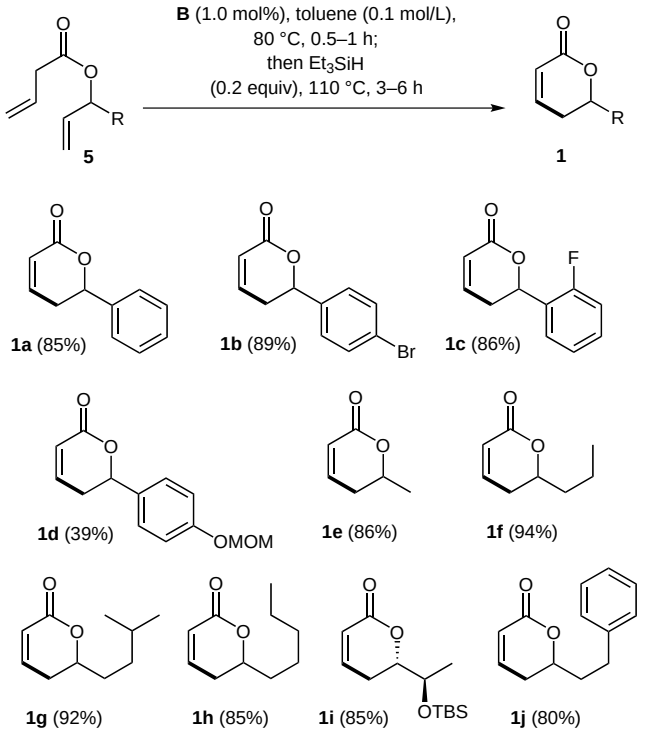


Entry	Catalyst (mol%)	*c* (mol/L)	Chemical trigger (equiv)	Yield of **6** (%)
1[a]	**A** (5.0)	0.01	none	**6a** 42
2	**B** (1.0)	0.10	none	**6a** 93
3[b]	**B** (5.0)	0.05	$NaBH_4$ (0.5)	**6a**
4	**B** (5.0)	0.05	2-PrOH; NaOH (0.5)	**7a** 44
5	**B** (2.0)	0.10	NaH (1.2)	**7a** 80
6[c]	**B** (5.0)	0.05	H_2C=CHOEt (3)	**6a**/**1a**
7[c]	**B** (5.0)	0.05	H_2C=CHOEt (10)	**6a**/**1a**
8[d]	**B** (2.0)	0.10	Et_3SiH (1.0)	**1a** 71
9[e]	**B** (2.0)	0.10	Et_3SiH (1.0)	**1a** 76
10	**B** (1.0)	0.10	Et_3SiH (0.2)	**1a** 85

[a] Phenol (0.5 equiv) was added to the RCM reaction.
[b] No product apart from **6a** was detected.
[c] Heating to reflux for 16 hours after addition of H_2C=CHOEt; **6a** and **1a** are formed in a 1:1 ratio, along with unidentified byproducts.
[d] Approximately 10% of **8a** as a byproduct.
[e] CH_2Cl_2 was used as a solvent, heating to 40 °C after addition of silane for 48 h; approximately 25% of **8a** as a byproduct.

We applied these optimized conditions to several other butenoates **5b**–**j**, which were synthesized from the corresponding allylic alcohols as described previously.[38] In most cases, the desired α-pyrones **1** were obtained in high yields and excellent selectivity. In all cases, no products resulting from hydrogenation or ring opening of the lactone could be detected. There is also no indication that γ,δ-unsaturated isomers, that is, cyclic enol ethers, are formed, which might have been an additional complication in those cases where the substituent R is sterically less

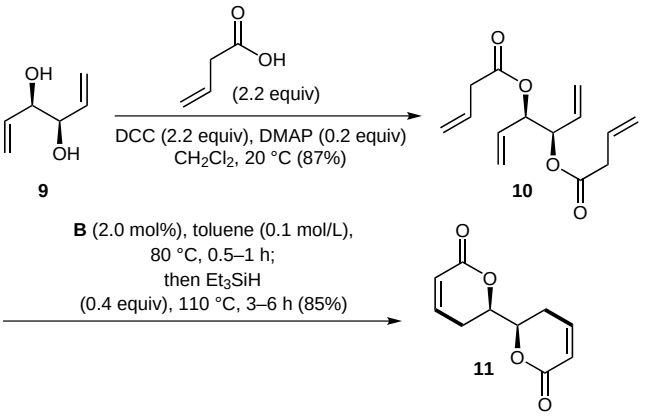
demanding, such as **1e** with R = Me. Haloarenes (e.g., **1b** and **1c**) tolerate the reductive reaction conditions, as we did not find any products resulting from a reductive dehalogenation (Scheme 2).



Scheme 2 Synthesis of α-pyrones **1** from butenoates **5**; bonds formed through RCM are highlighted in bold

Finally, we investigated the possibility to extend a double RCM reaction by a sequential double isomerization reaction. Double or multiple RCM reactions have emerged as a valuable approach for the rapid assembly of bi- or polycyclic molecules.[40] However, in order to obtain synthetically useful yields of bicyclic products and to avoid laborious separation of the target molecule from unreacted starting material or monocyclic intermediates, it is necessary that all RCM steps proceed in very high yields and selectivities. This prerequisite is even more important for the envisaged tandem double RCM–isomerization, because every molecule will undergo four transformations, calling for a yield >99% for each Ru-catalyzed step if a conversion of more than 95% to the target molecule is intended (Scheme 3).

We realized a double tandem RCM–isomerization starting from enantiomerically pure diene **9**, which is available in few steps from D-mannitol.[41,42] Esterification with vinyl acetic acid was achieved using Steglich's conditions[43] and resulted in the formation of diester **10** in 87% yield. For a full conversion of **10** to the dumbbell-type bislactone **11**, our standard conditions were modified by increasing the catalyst loading to 2 mol% and the amount of triethylsilane to 0.4 equivalents. Compound **11**, obtained in 85% yield, is a C_2-symmetric bisoxacyclic building block. The dumbbell-type bispyran pattern present in **11** is found in a number of natural products.[44,45]



Scheme 3 Tandem double RCM–isomerization of tetraene **10**; Bonds formed through RCM are highlighted in bold

In summary, we disclose herein that triethylsilane is a suitable additive in RCM reactions to trigger the in situ conversion of the metathesis catalyst to an isomerization catalyst. This opens up a route to circumvent the disadvantageous acrylate RCM for the synthesis of α-pyrones.[46]

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(46) **Representative Example: Synthesis of 1i**
A solution of **5i** (200 mg, 0.7 mmol) in toluene (7.0 mL) was preheated to 80 °C, and catalyst **B** (6.0 mg, 1.0 mol%) was added. After the starting material was fully consumed (TLC, approx. 30 min), Et_3SiH (22 μL, 0.14 mmol) was added, and the solution was heated to reflux for 1 h. All volatiles were evaporated, and the residue was purified by chromatography on silica (eluent: hexane–MTBE = 5:1) to give α-pyrone **1i** (152 mg, 85%) as a colorless oil. $[\alpha]^{24}_{D}$ +117.3 (*c* 0.56, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.90 (ddd, *J* = 9.6, 5.8, 2.7 Hz, 1 H), 6.00 (dm, *J* = 9.7 Hz, 1 H), 4.19 (dt, *J* = 11.1, 5.0 Hz, 1 H), 4.00 (qm, *J* = 6.3 Hz, 1 H), 2.57–2.35 (2 H), 1.22 (d, *J* = 6.3 Hz, 3 H), 0.88 (9 H), 0.09 (3 H), 0.08 (3 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.5 (0), 145.1 (1), 121.1 (0), 81.7 (1), 69.3 (1), 25.8 (3), 24.3 (2), 20.2 (3), 18.0 (0), –4.5 (3), –4.7 (3). IR (neat): ν = 2957 (m), 2931 (m), 2897 (w), 1723 (s), 1383 (m), 1249 (s), 1075 (s). ESI-MS: *m/z* = 239 (5), 257 (35), 279 (100) $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $C_{13}H_{24}NaO_3Si^+$ $[M + Na]^+$: 279.1392; found: 279.1375. Anal. Calcd (%) for $C_{13}H_{24}O_3Si$ (256.41): C, 60.9, H, 9.4. Found: C, 60.7; H, 9.6.

