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# A straightforward synthesis of (*E*)-δ-alkenyl-β,γ-unsaturated δ-lactones by a tandem ring-closing/cross-coupling metathesis process

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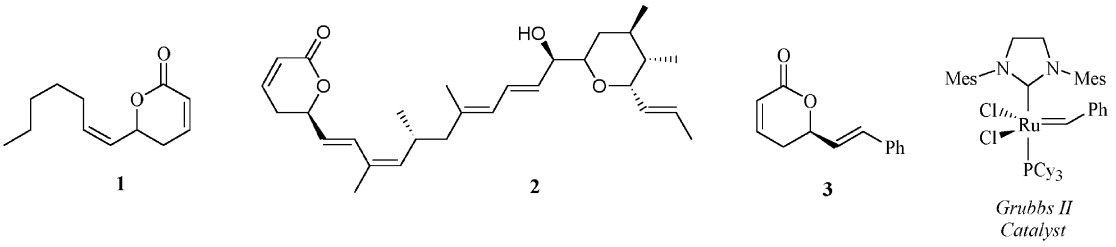
**Abstract**—The access to (*E*)-δ-alkenyl-β,γ-unsaturated δ-lactones starting from 3-*O*-(1,4-pentadienyl) 3-butenoate has been investigated by using a tandem process including two different metathesis reactions. By this way, new structures, isomers of natural compounds like argentilactone, were isolated in good yields. Reconjugation of the internal C=C bond can be achieved under basic conditions to give α-pyrones.


Numerous natural products possess as a core structure the 5,6-dihydro-2-pyrone (α-pyrone) subunit, bearing on position 6 an additional alkenyl chain (Scheme 1). For example, argentilactone **1** originally isolated from the rhizomes of *Aristolochia argentina*[1] and later extracted from the leaves of *Chorisia crispiflora*[2] exhibits *anti* leishmanial activity[3] and cytotoxic properties against mouse leukemia cells.[2] Due to these very promising biological properties, **1** has been already synthesized both in racemic[4] and enantiomeric pure form.[5] More complex molecules like ratjadone,[6] leptomycin,[7] callystatin A **2**,[8] goniothalamin **3**[9] and related styryl lactones, cryptofolione[10] or fostriecin,[11] possess also this heterocyclic structure and biological activities. Up to recently, many efforts have been devoted to their access. In this context, ring closure metathesis (RCM) of unsaturated esters has been successfully used to reach the lactone moiety thanks to powerful reagents like Grubbs type II catalyst.[12,13]

In connection with our interest into RCM applied to the synthesis of natural products,[14] we have investigated a straightforward access to 6-alkenyl-5,6-dihydro-2-pyrones from 1,4-pentadien-3-ol ester **4** according to Scheme 2.

By using twice a metathesis process,[15] we expected to build up the lactone framework via a RCM process but also to functionalize the lateral chain of the intermediate vinyl lactone **5** thanks to a subsequent CCM reaction with a conveniently chosen alkene **6**. This overall strategy could occur either under a sequential process if




**Scheme 1.**

*Keywords*: metathesis; lactones; ring-closure; cross-coupling; isomerisation.
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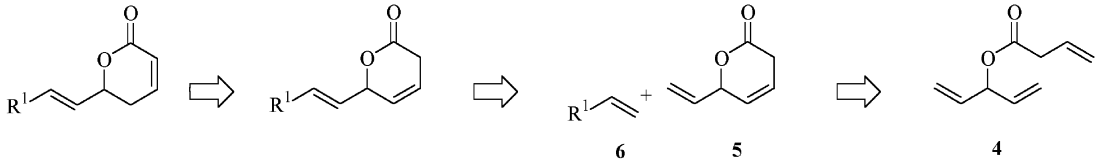
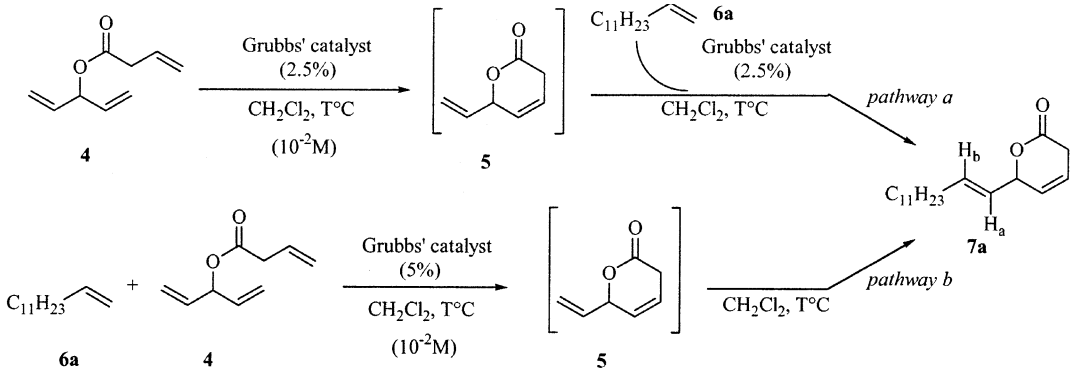
the alkene is introduced during the reaction, either under real tandem conditions if all partners are already present before addition of the catalyst.[16]

Pentadienyl ester **4** was easily prepared in good yield from commercially available vinylacetic acid and 1,4-pentadien-3-ol under DCC activation.[17] This substrate was first tested under sequential conditions with 1-tridecene **6a** ($R = C_{11}H_{23}$) as partner (Scheme 3, pathway a, Table 1).

When the reaction was conducted under highly diluted conditions[18] at rt and with only 2.5% of Grubbs' type II catalyst, ester **4** was totally converted into the intermediate vinyl lactone **5** in only 2 h (TLC control). After addition of the alkene (5 equiv.) and a new amount of catalyst (2.5%), **5** was isolated as the main product while substituted pyrone **7a** was only detected as traces (entry 1). By performing the same sequence at higher temperature, yields in **7a** increased considerably while the overall yield was still moderate (entry 2). As determined by $^1$H NMR ($J_{Ha-Hb} = 15.2$ Hz), only the thermodynamic *E*-isomer was formed during this process. The reaction was next performed under real tandem conditions (Scheme 3, pathway b, Table 1). Ester **4** was mixed in dichloromethane with tridecene (5 equiv.) and 5% catalyst. At rt and after 15 h, the two lactones **5** and **7a** were obtained in far better yields, respectively, 51 and 39% (entry 3). Finally, we succeed by performing the reaction at reflux of dichloromethane. In that case, **7a** was the sole compound isolated in 75% yield after only 4 h (entry 4). Longer time of reaction led to a decrease of the chemical yields reflecting probably a low thermal stability of the final product (entry 5). In order to decrease the amount of alkene introduced, the reaction was also tested with only 2 equivalents of tridecene (entry 6). By this way, **7a** was still isolated in an acceptable 68% yield. The same value was obtained by using less catalyst but with the same initial amount of alkene (5 equiv.). However, decreasing both the quantity of the organometallic species and of the alkene led to disappointing results (entry 8).




**Scheme 2.**

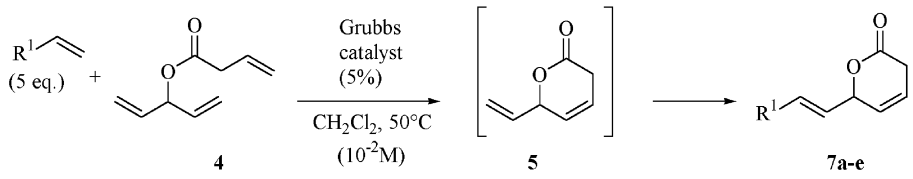



**Scheme 3.**

**Table 1.** Sequential and tandem RCM/CCM of ester **4** with 1-tridecene **6a**

| Procedure | Entry | *n* (equiv.) | Alkene conc. | Catalyst (mol%) | T (°C) | t (h) | Products | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **5**[c] | **7a**[c] | (*E*/*Z*[d]) |
| Sequential | 1 | 5 | $10^{-2}$ M | 2×2.5 | 25 | 20[a] | 51% | Traces | – |
| Sequential | 2 | 2 | $10^{-2}$ M | 2×2.5 | 50 | 4[b] | 38% | 18% | (Only *E*) |
| Tandem | 3 | 5 | $10^{-2}$ M | 5 | 25 | 15 | 51% | 39% | (Only *E*) |
| Tandem | 4 | 5 | $10^{-2}$ M | 5 | 50 | 4 | 17% | 75% | (Only *E*) |
| Tandem | 5 | 5 | $10^{-2}$ M | 5 | 50 | 15 | – | 57% | (Only *E*) |
| Tandem | 6 | 2 | $10^{-2}$ M | 5 | 50 | 4 | 19% | 68% | (Only *E*) |
| Tandem | 7 | 5 | $10^{-2}$ M | 2.5 | 50 | 4 | Not det. | 68% | (Only *E*) |
| Tandem | 8 | 2 | $10^{-2}$ M | 2.5 | 50 | 15 | 45% | 41% | (Only *E*) |

[a] Addition of the alkene after 2 h.
[b] Addition of the alkene after 2 h 30.
[c] Isolated yields of pure compounds.
[d] Determined by $^1$H NMR on the crude mixture.




**Scheme 4.**

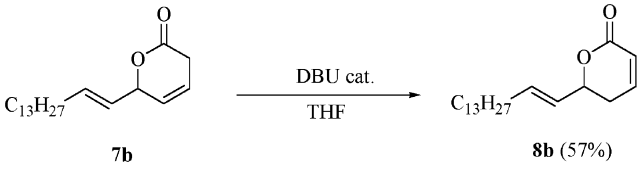
Compared to sequential procedures, tandem processes are much more attractive in term of feasibility and efficiency. Therefore, we have performed this reaction with other alkene counterparts **6b–d** under the most effective conditions (Scheme 4) and results are consigned in Table 2.

**Table 2.** Tandem RCM/CCM of ester **4** with various alkenes **6a–e**

| Entry | Alkene | 6 | Products | | |
|---|---|---|---|---|---|
| | | | 5[a] | 7[a] | (*E*/*Z*) |
| 1 | $R^1=C_{11}H_{23}$ | **6a** | – | **7a** (75%) | (Only *E*) |
| 2 | $R^1=C_{13}H_{27}$ | **6b** | 13% | **7b** (66%) | (Only *E*) |
| 3 | $R^1=C_5H_{11}$ | **6c** | – | **7c** (52%) | (Only *E*) |
| 4 | $R^1=CH_2$-Br | **6d** | 43% | **7d** (15%) | (Only *E*) |

[a] Isolated yields of pure compounds.

Except reaction with allyl bromide (entry 4), lactones **7** were obtained in convenient yields still as a single *E*-isomer.[19] Finally, the tedious reconjugation of the internal double bond was tested on **7b** and smoothly achieved by treatment with a catalytic amount of DBU[20] to deliver α-pyrone **8b** in 57% yield (Scheme 5).




**Scheme 5.**

In conclusion, we have described a very short access to (*E*)-δ-alkenyl-β,γ-unsaturated δ-lactones according to a tandem ring-closing/cross-coupling process performed in the presence of Grubbs type II catalyst. Work is now in progress to apply this strategy to the synthesis of more complex natural occurring α-pyrones and will be reported in due course.

**Typical procedure**: A solution of 3-*O*-1,4-pentadienyl butanoate **4** (0.152 g, 1 mmol) and 1-tridecene **6a** (0.910 g, 5 mmol) in dichloromethane (100 ml) was first bubbled with nitrogen flow. Grubbs type II catalyst (0.043 g, 0.05 mmol) was subsequently added at once and the resulting mixture was heated under nitrogen at 50°C for 4 h. After cooling and concentration, the solvent was removed and the crude mixture was purified by flash-chromatography (AcOEt/hexanes: 20/80) to give lactone **7a** (0.208 g, 0.75 mmol) as a pale yellow oil.

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