One-Pot Hydrosilylation–RCM–Protodesilylation: Application to the Synthesis of ω-Alkenyl α,β-Unsaturated Lactones

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Abstract: A simple and efficient one-pot procedure has been developed for the synthesis of α,β-unsaturated lactones bearing a pendant *E*-olefin. This new methodology, which features a hydrosilylation, a ring-closing metathesis (RCM) and a protodesilylation reaction, allows to perform RCM on substrates containing an alkyne moiety. The utility of this methodology was further demonstrated in the total synthesis of (+)-goniothalamin and (–)-pironetin, two natural products with interesting biological activities.

Key words: hydrosilylation, ring-closing metathesis, protodesilylation, α,β-unsaturated lactones, goniothalamin, pironetin

ω-Alkenyl α,β-unsaturated lactones are present in a wide range of biologically active natural products such as (+)-goniothalamin,[1] (–)-pironetin,[2,3] (–)-callystatin A,[4] (–)-cryptocaryalactone,[5] or phoslactomycin B[6] (Figure 1).

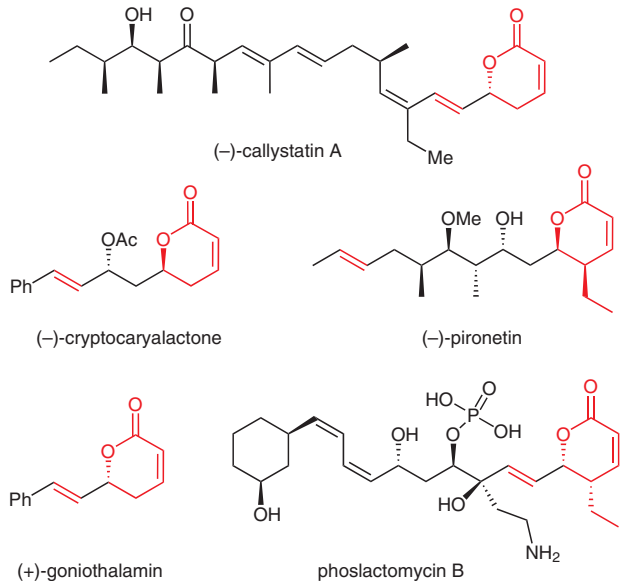

Figure 1 Structure of various natural products containing an ω-alkenyl α,β-unsaturated lactone

Whilst ring-closing metathesis (RCM) has proven to be a useful reaction to access the α,β-unsaturated lactone motif **II** from the corresponding diene **I** (Scheme 1, eq 1),[7] it appears that this reaction fails when applied to alkyne-containing substrates such as **III** (Scheme 1, eq 2). In Kobayashi's synthesis of phoslactomycin B for instance, RCM performed on **V** using Grubbs first- and second-generation catalyst under various conditions appeared to be completely unsuccessful (Scheme 1, eq 3).[8] This failure is supposedly due to a chelation that occurs between the alkyne moiety and the catalyst which inhibits the reaction.

One way to prevent catalyst deactivation in a RCM process, which involves an alkyne-containing substrate, is to protect the triple bond. This can either be done by introducing a bulky silylated group as shown by Panek[9] in his synthesis of (–)-callystatin A, or by complexating the alkyne moiety using hexacarbonyldicobalt.[10] These methods, however, have the disadvantage of requiring either unnecessary steps or harsh conditions that are not compatible with most substrates.[11]

In our quest to develop chemoselective methods to synthesize polyfunctional compounds of type **VII** starting from readily accessible substrates such as **III**, we became interested in a simple and efficient one-pot procedure featuring a hydrosilylation, a RCM, and a protodesilylation (Scheme 2).

In order to establish the viability of the sequence, each step was carried out separately on a model substrate of type **III**: compound **1a** (Scheme 2). Hence, compound **1a** [R^1 = Pr, R^2 = H, n = 0] was first hydrosilylated under the conditions developed by Trost and Ball[12] using $HSi(OEt)_3$ in the presence of 1 mol% of $[Cp^*Ru(MeCN)_3]PF_6$ in CH_2Cl_2. These conditions led to the corresponding silylated product of type **VIII** (**3a**), which was obtained in 90% yield as a mixture of regioisomers but with complete chemoselectivity. The latter was then subjected to standard RCM conditions {Grubbs second-generation catalyst [Ru]-**II** (5 mol%), CH_2Cl_2, 40 °C} to afford the corresponding α,β-unsaturated δ-lactone **IX** (**4a**) in a moderate 45% yield. Finally, compound **4a** was protodesilylated under the conditions developed by Fürstner et al.[13] using AgF in a MeOH–H_2O–THF (1:1:10) mixture at room temperature to afford the desired (*E*)-ω-alkenyl α,β-unsaturated lactone in 72% yield. Hence, compound **2a** could be obtained in three steps and 29% overall yield (Scheme 2).

In order to avoid the time and yield loss usually associated with the isolation and purification of intermediates in a multistep sequence, a one-pot, three-step reaction was examined.[14] Thus, **1a** was treated with 1 mol% of $[Cp^*Ru(MeCN)_3]PF_6$ in the presence of $HSi(OEt)_3$ (1.2

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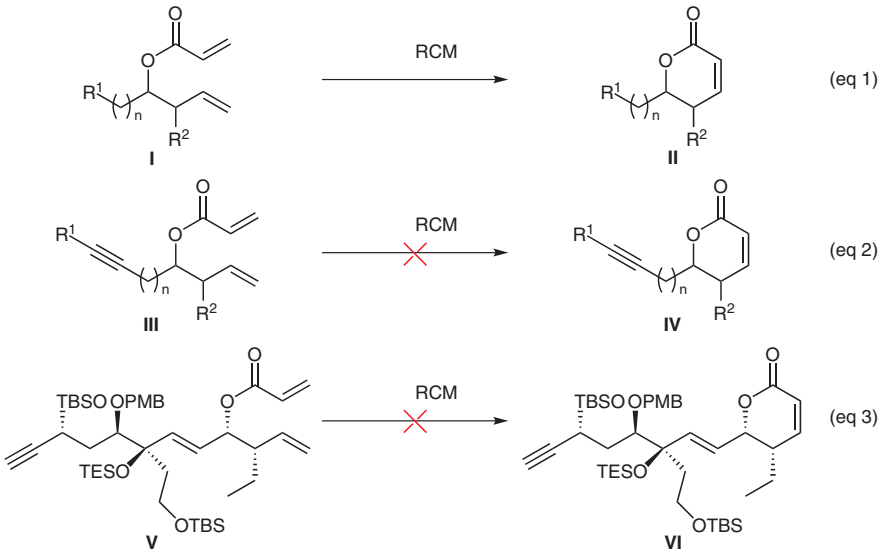
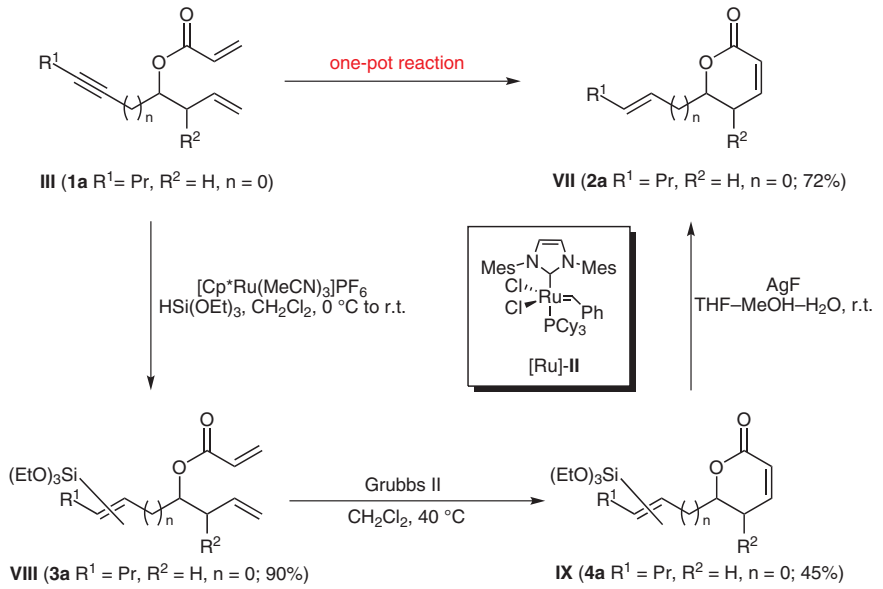


Scheme 1 Synthesis of α,β-unsaturated lactones via RCM



Scheme 2 One-pot hydrosilylation–RCM–protodesilylation

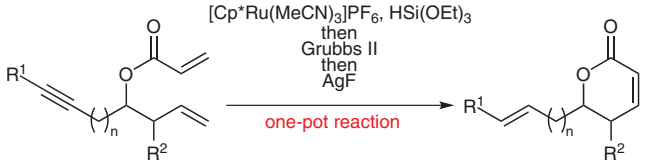
equiv) in CH_2Cl_2. After complete conversion of the starting material,[15] [Ru]-**II** (5 mol%) was added and stirring was continued at 40 °C. Once the RCM was over,[15] the reaction mixture was allowed to reach room temperature before AgF (2.4 equiv) was added along with MeOH (0.01 M), H_2O (0.01 M), and THF (0.1 M). Stirring was then continued in the absence of light until complete consumption of the silylated intermediate.[15] To our delight, the desired (*E*)-ω-alkenyl α,β-unsaturated lactone **2a** was isolated in 80% yield which compared favorably with the 29% yield obtained previously in a sequential fashion.[16]

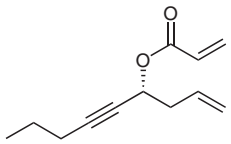
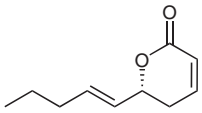
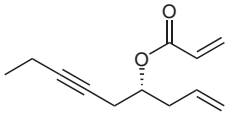
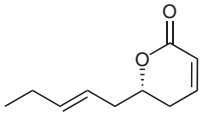
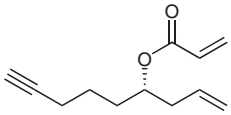
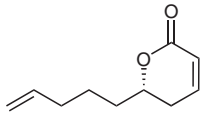
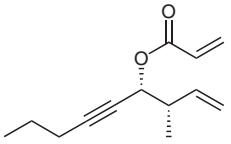
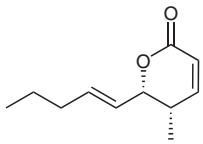
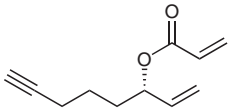
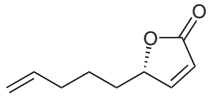
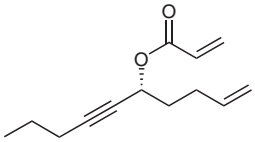
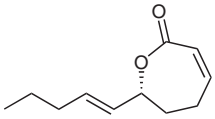
With these conditions in hand, a close examination of the reaction scope was then undertaken with a set of alkyne-containing dienes. The results are reported in Table 1.

As a general trend, all the ω-alkenyl α,β-unsaturated lactones were obtained in good yields ranging from 35–82%, and complete control of the stereoselectivity of the exocyclic double bound as (*E*)-alkenyl products were exclusively formed. The alkyne position (Table 1, entries 1–3) or the substitution pattern at the α-position of the ester (Table 1, entries 1 and 4) did not seem to tremendously affect the reactivity. It is noteworthy that while five-membered ring lactones could be obtained though in a slightly lower yield (Table 1, entry 5), the access to seven-membered ring lactones failed at the RCM stage (Table 1, entry 6).

Following these initial results, we were particularly interested in applying this synthetic methodology to α,β-unsaturated δ-lactone-containing natural products.

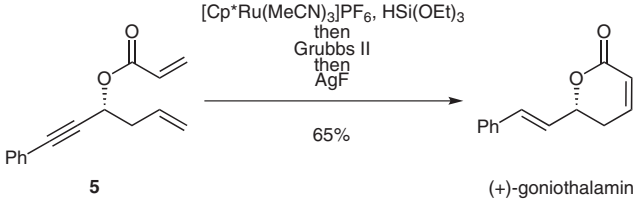
Table 1 One-Pot Hydrosilylation–RCM–Protodesilylation Scope[a]



Entry	Olefin		Product		Yield (%)[b]	*E*/*Z* (%)[c]
1		(±)-**1a**		(±)-**2a**	80	>20/1
2		(±)-**1b**		(±)-**2b**	82	>20/1
3		(±)-**1c**		(±)-**2c**	50	–
4		(±)-**1d**		(±)-**2d**	60	>20/1
5		(±)-**1e**		(±)-**2e**	35	–
6		(±)-**1f**		(±)-**2f**	–	–

[a] Reactions conditions: $HSi(OEt)_3$ (1.2 equiv), CH_2Cl_2, 0 °C, $Cp^*Ru(MeCN)_3PF_6$ (1 mol%), 0 °C to r.t., Grubbs II (5 mol%), 40 °C, AgF (2.4 equiv), MeOH–H_2O–THF, r.t.
[b] Isolated yield.
[c] The *E*/*Z* ratio was determined by ^1H NMR of the crude reaction mixture.

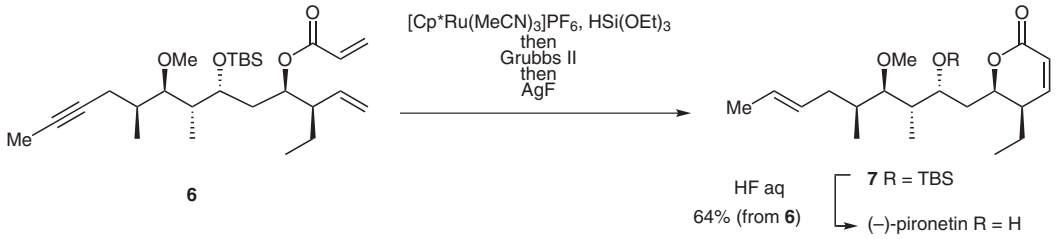
Our first target was (+)-goniothalamin,[1] which exhibits interesting antifungal,[17] immunosuppressive, and anti-inflammatory activities.[18] Hence, by applying our one-pot, three-step sequence to compound **5**, we were able to isolate the desired natural product in 65% yield (Scheme 3). Its spectroscopic and physical data were in accordance with those reported for the natural product {$[\alpha]_D^{20}$ +168.2 (*c* 1.40, $CHCl_3$); lit. $[\alpha]_D^{22}$ +170.3 (*c* 1.38, $CHCl_3$)}.[19]



Scheme 3 Total synthesis of (+)-goniothalamin

We next turned our attention to (–)-pironetin,[2,3] another α,β-unsaturated δ-lactone-containing natural product which displays plant-growth regulatory[20] as well as immunosuppressive activities (Scheme 4).[21] Hence, by subjecting compound **6**[22] to our one-pot hydrosilylation–RCM–protodesilylation reaction conditions, we were able to access simultaneously the α,β-unsaturated δ-lactone and the olefin with the *E*-configuration in 78% isolated yield. A final deprotection of the alcohol at C6 using aqueous HF led to the desired natural product in 82% yield (Scheme 4). The spectroscopic and physical data of the synthesized (–)-pironetin were in accordance with those reported for the natural product {$[\alpha]_D^{20}$ –133.6 (*c* 0.35, $CDCl_3$); lit. $[\alpha]_D^{22}$ –137.5 (*c* 0.34, $CDCl_3$)}.[2,3]

In conclusion, we have developed a new straightforward methodology which allows not only to perform RCM on alkyne-containing substrates, but also to reduce the triple bond in a stereoselective fashion. With this highly



Scheme 4 Total synthesis of (–)-pironetin

chemoselective one-pot procedure, ω-alkenyl α,β-unsaturated lactones were obtained in moderate to good yields under mild conditions. Finally, this methodology was used as a key step in the total syntheses of (+)-goniothalamin and (–)-pironetin, two natural products with interesting biological activities. Further applications of this methodology to targets of major interest will be described in due course.

Acknowledgment

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(15) The reaction was monitored by TLC.
(16) **General Procedure for the One-Pot Hydrosilylation–RCM–Protodesilylation**
To a solution of alkyne (1 equiv) in CH_2Cl_2 (0.1 M solution) at 0 °C was added triethoxysilane (1.2 equiv) followed by $Cp^*Ru(MeCN)_3PF_6$ (0.01 equiv). The flask was immediately allowed to warm to r.t. and stirred until complete conversion of the starting material. Grubbs' second-generation catalyst was then added (0.05 equiv), and the reaction mixture was stirred at 40 °C until complete conversion. The reaction mixture was then allowed to reach r.t. before AgF (2.4 equiv) was added followed by MeOH (0.01 M), H_2O (0.01 M), and THF (0.1 M). Stirring was continued in the absence of light until complete consumption of the silylated intermediate, and the reaction mixture was filtered through Celite, extracted with CH_2Cl_2, dried over $MgSO_4$, and evaporated under reduced pressure. The crude residue was purified by flash column chromatography on SiO_2 using a gradient of eluents to afford the desired lactone.
Representative Characterization Data for Selected Products
Compound **2a**: IR: 2960, 2920, 2870, 1720, 1380, 1240, 980, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.81 (dt, *J* = 9.6, 4.3 Hz, 1 H), 6.07 (dt, *J* = 9.6, 1.8 Hz, 1 H), 5.82 (dtd, *J* = 15.4, 5.8, 1.0 Hz, 1 H), 5.58 (ddt, *J* = 15.4, 6.6, 1.5 Hz, 1 H), 4.87 (q_{app}, *J* = 7.3 Hz, 1 H), 2.45–2.39 (m, 2 H), 2.04 (q_{app}, *J* = 6.8 Hz, 2 H), 1.41 (h_{app}, *J* = 7.3 Hz, 2 H), 0.90 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2 (s), 144.7 (d), 135.5 (d), 126.9 (d), 121.6 (d), 78.3 (d), 34.2 (t), 29.8 (t), 21.9 (t), 13.6 (q). ESI-HRMS: *m/z* calcd for $C_{10}H_{14}NaO_2$ $[M + Na]^+$: 189.0891; found: 189.0886.
Compound **2c**: IR: 2920, 1720, 1640, 1390, 1250, 820 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.87 (ddd, *J* = 9.8, 5.0, 3.0 Hz, 1 H), 6.01 (dt, *J* = 9.8, 2.0 Hz, 1 H), 5.78 (ddt, *J* = 17.2, 10.1, 6.6 Hz, 1 H), 5.01 (dq_{app}, *J* = 17.2, 2.0 Hz, 1 H), 5.01 (dq_{app}, *J* = 10.1, 3.3 Hz, 1 H), 4.41 (m, 1 H), 2.35–2.29 (m, 2 H), 2.14–2.01 (m, 2 H), 1.86–1.71 (m, 1 H), 1.70–1.56 (m, 2 H), 1.56–1.42 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5 (s), 144.0 (d), 137.0 (d), 120.4 (d), 114.0 (t), 76.8 (d), 32.3 (t), 31.2 (t), 28.4 (t), 22.9 (t). ESI-HRMS: *m/z* calcd for $C_{10}H_{14}NaO_2$ $[M + Na]^+$: 189.0891; found: 189.0886.
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