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# Tandem Ring-Closing Metathesis/ Isomerization Reactions for the Total Synthesis of Violacein

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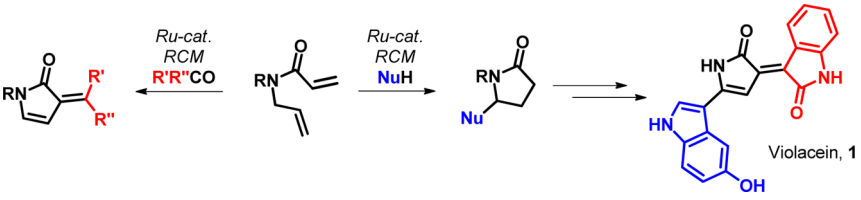
## ABSTRACT




**A series of 5-substituted 2-pyrrolidinones was synthesized through a one-pot ruthenium alkylidene-catalyzed tandem RCM/isomerization/ nucleophilic addition sequence. The intermediates resulting from RCM/isomerization showed reactivity toward electrophiles in aldol condensation reactions which provided a new entry for the total synthesis of the antileukemic natural product violacein.**

Ruthenium-catalyzed ring-closing metathesis (RCM) is a robust and reliable method for the synthesis of cyclic alkenes.[1] The combination of RCM with concurrent chemical transformations, frequently referred to as tandem sequences, provides access to complex molecular structures in a single synthetic step.[2] Over the past decade, several successful examples of "autotandem" and "assisted tandem"[3] RCM/isomerization reactions have been reported[4] along with tandem reactions, where RCM successfully has been coupled to other chemical transformations such as hydrogenation,[5] oxidation,[4e,6]

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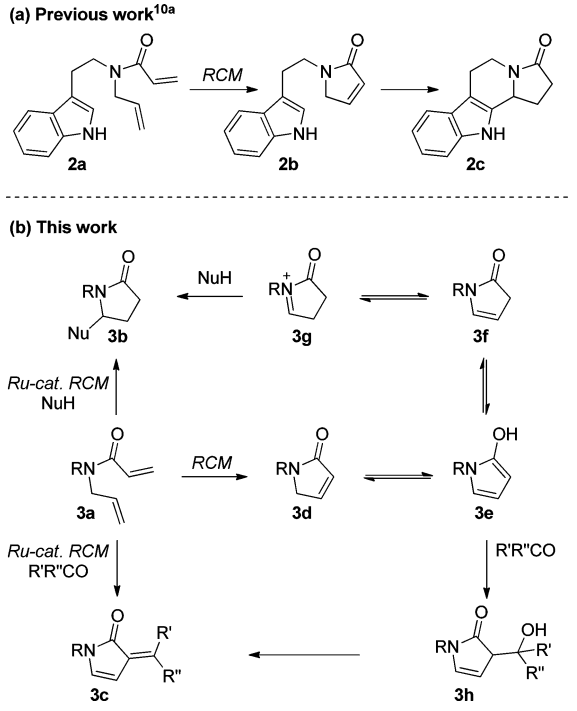
Kharasch addition,[7] cyclopropanation,[8] Pauson–Khand reaction,[9] and iminium cyclization.[10]

Here, we report an extension of a recently developed tandem RCM/isomerization/*N*-acyliminium cyclization sequence (Scheme 1a)[10a] where focus is directed toward intermolecular reactions of *N*-acyliminium ions with electron-rich carbon nucleophiles. In particular, we demonstrate that the Ru-catalyzed tandem reaction of dienes **3a** and indoles is useful for the rapid synthesis of pharmacologically interesting 5-substituted 2-pyrrolidinones **3b** (Scheme 1b).

Previous experiments had indicated the intermediacy of enols **3e**, presumably arising through favorable tautomerization events,[10a,11] and we envisioned how intermediates **3d** could also serve as precursors for aldol condensations with aldehydes and ketones to give pyrrolones **3c** (Scheme 1b).

**Scheme 1.** Tandem RCM/Isomerization Reaction Sequences




The pyrrolone and pyrrolidinone motives are well-known and widespread cores in biologically active molecules (Figure 1).

Much focus has recently been directed toward natural pigments for use in food and healthcare products, and one relevant compound is the bacterial pigment violacein (**1**),[12] which would be directly accessible from this synthetic scheme. Violacein belongs to the bisindole class of natural compounds, which are biosynthesized from two molecules of L-tryptophan. Other members of this class comprise the topoisomerase inhibitor rebeccamycin **1a** and the kinase inhibitor staurosporine **1b**, the latter being widely used as

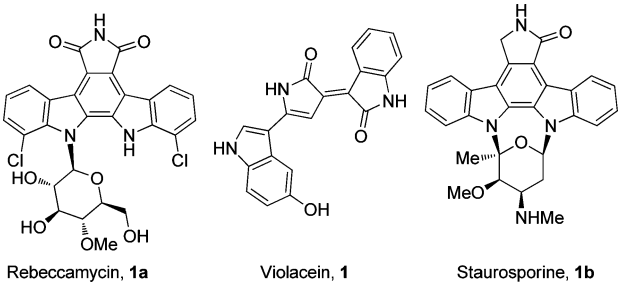



**Figure 1.** Bisindole natural products with pyrrolone motives.

an inducer of apoptosis for cell-based assays.[13] In addition, violacein displays a wide array of biological activities, including antibacterial, antifungal, antileukemic, antiparasitic, and antiviral properties.[12]

We initiated our efforts toward the development of a tandem RCM/isomerization/nucleophilic addition sequence (**3a** → **3b**) by investigating all relevant reaction parameters, i.e., temperature, catalyst, and solvent (see Table 1 for selected results). The Grubbs second-generation catalyst gave full conversion of both the diene **4a** and the intermediate RCM product **4b** to the tandem product **5a** at temperatures above 65 °C (entries 6–8), whereas no formation of tandem product was detected below 65 °C. Experiments at room temperature indicated that the RCM proceeded faster in THF and toluene (entries 2 and 3) than in $CH_2Cl_2$ (entry 1). In the search for the mildest possible reaction conditions, we conducted a catalyst screen in THF at 65 °C (entries 9–12), which revealed the *o*-tolyl-Hoveyda–Grubbs second-generation catalyst as most efficient.

Next, the substrate scope of the reaction was explored with a range of dienes and nucleophiles (Table 2). In general, good yields were obtained with electron-rich indoles as nucleophiles (entries 1–10). In the reaction with indole-5-boronic acid, the deboronated product **5a** was also observed, indicating the loss of boric acid (entry 11). In reactions with electron-deficient indoles (entries 12–16), the intermediate RCM product **3d** was typically completely consumed before the indole was fully converted. This indicated a side reaction of **3d**, and various dimers thereof were identified in the reaction mixture. The yields of the desired tandem products **5l–p** were increased by the addition of TFA to the reaction mixture upon completion of the RCM, which presumably facilitated the formation of the *N*-acyliminium ion **3g**.

Besides indoles, other nucleophiles, namely an alcohol and an electron-rich benzene, were employed in the tandem reaction, and these also benefitted from the addition of TFA (entries 17 and 18).

The importance of the electronic nature of the R group in diene **3a** became evident in the case where R = Boc (entry 5). The RCM proceeded smoothly, but no formation of the tandem product was observed until the addition

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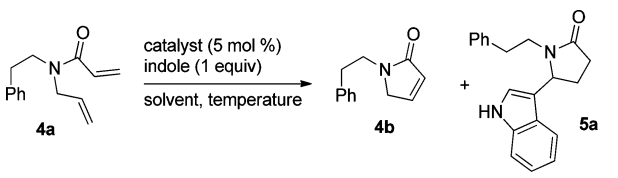
**Table 1.** Solvent and Catalyst Optimization for a Tandem RCM/Isomerization/Nucleophilic Addition Sequence (Selected Results)




| | | | | 4a:4b:5a[a] | |
|---|---|---|---|---|---|
| entry | catalyst | solvent | temp (°C) | 2 h | 21 h |
| 1 | Grubbs 2nd | $CH_2Cl_2$ | rt | 67:33:0 | 49:51:0 |
| 2 | Grubbs 2nd | THF | rt | 0:100:0 | 0:100:0 |
| 3 | Grubbs 2nd | toluene | rt | 35:65:0 | 0:100:0 |
| 4 | Grubbs 2nd | *m*-xylene | rt | 52:48:0 | 41:59:0 |
| 5 | Grubbs 2nd | $CH_2Cl_2$ | 40 | 0:100:0 | 0:100:0 |
| 6 | Grubbs 2nd | THF | 65 | 0:100:0 | 0:0:100 |
| 7 | Grubbs 2nd | toluene | 110 | 0:23:77 | 0:0:100 |
| 8 | Grubbs 2nd | *m*-xylene | 139 | 0:7:93 | 0:0:100 |
| 9 | Grubbs 1st | THF | 65 | 62:38:0 | 42:11:47 |
| 10 | Hoveyda–Grubbs 1st | THF | 65 | 40:35:25 | 9:1:90 |
| 11 | Hoveyda–Grubbs 2nd | THF | 65 | 0:100:0 | 0:35:65 |
| 12 | (*o*-tolyl)-Hoveyda–Grubbs 2nd | THF | 65 | 0:35:65 | 0:0:100 |

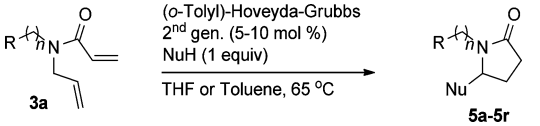
[a] As determined by RP-HPLC at 215 nm.

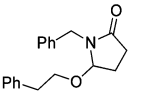
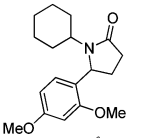
of TFA ensured Boc-deprotection. This indicated a decreasing tendency to form the *N*-acyliminium ion **3g** when the R group on the diene was electron-withdrawing.

Previous experiments suggested to us that isomerization of the double bond to the *N*-acyliminium intermediate **3g** did not proceed via a ruthenium hydride mechanism[10a,11] but rather through a favorable tautomerization. We envisioned that if the double bond in **3d** did in fact undergo isomerization via tautomer **3e** (Scheme 1b) it should be feasible to trap this intermediate with an electrophile, e.g., in aldol reactions. Gratifyingly, the reaction indeed proceeded in tandem with RCM from dienes **6** in the presence of Grubbs second-generation catalyst and various carbonyl electrophiles. A cleaner and faster tandem RCM/tautomerization/aldol condensation sequence was generally observed when a mild Lewis acid, such as $B(OH)_3$, was used as co-catalyst, presumably to facilitate the tautomerization.

We briefly looked into the substrate scope for the tandem sequence by employing different dienes **6** and electrophiles (aldehydes and ketones) to give pyrrolone tandem products **7a**–**e** (Table 3). Given that a significant number of distinct synthetic transformations (ring-closing metathesis, tautomerization, and aldol condensation) occur, the isolated yields of the rapidly degrading tandem products **7a**–**e** were satisfactory. With a set of new synthetic methodologies at hand, we turned our attention to the total synthesis of violacein (**1**) (Scheme 2).

**Table 2.** Substrate Scope of a Tandem RCM/Isomerization/Nucleophilic Addition Sequence




| entry | R | *n* | NuH[a] | product (yield (%))[b] |
|---|---|---|---|---|
| 1 | Ph | 2 | indole | **5a** (70) |
| 2 | Ph | 1 | indole | **5b** (60)[c] |
| 3 | Cy | 0 | indole | **5c** (77) |
| 4 | 2-napht | 1 | indole | **5d** (80)[c] |
| 5 | Boc/H | 0 | indole | **5e** (46)[d] |
| 6 | Ph | 2 | 1,2-dimethylindole | **5f** (65) |
| 7 | Ph | 2 | 5-methylindole | **5g** (74) |
| 8 | Cy | 0 | 5-methoxyindole | **5h** (70) |
| 9 | Cy | 0 | 4-methoxyindole | **5i** (67) |
| 10 | Cy | 0 | 5-benzyloxyindole | **5j** (74) |
| 11 | Ph | 2 | indole-5-boronic acid | **5k** (36) |
| 12 | Ph | 1 | indole-5-carboxylic acid | **5l** (46)[e] |
| 13 | Cy | 0 | 4-cyanoindole | **5m** (55)[e] |
| 14 | Ph | 1 | 6-nitroindole | **5n** (26)[e] |
| 15 | Ph | 1 | 4-bromoindole | **5o** (25)[e] |
| 16 | Ph | 1 | 5-iodoindole | **5p** (36)[e] |
| 17 | Ph | 1 | 2-phenylethanol |  **5q** (59)[e] |
| 18 | Cy | 0 | 1,3-dimethoxybenzene |  **5r** (27)[f] |

[a] All indoles reacted via the 3-position. [b] Isolated yield after flash column chromatography. Detailed reaction conditions are provided in the Supporting Information. [c] Grubbs 2nd generation was used in combination with $B(OH)_3$ (1 equiv). [d] TFA (11 equiv) was added upon completion of the RCM reaction to yield the Boc-deprotected tandem product. [e] Grubbs 2nd generation was used, and TFA (1 equiv) was added upon completion of the RCM reaction. [f] TFA (1 equiv) was added upon completion of the RCM reaction.

In the first step, we used the tandem RCM/isomerization/nucleophilic addition sequence to construct the pyrrolidinone core of violacein. The double bond was reintroduced in the tandem product **9** by way of phenylselenation, $H_2O_2$ oxidation and elimination of the selenide,[14] thereby setting the stage for attachment of the oxindole moiety via a Ti-catalyzed tautomerization/aldol condensation with isatin. In this case, where the pyrrolone substrate **10** had a substituent in the 5-position, the yield of the reaction sequence was 88% as compared to 17% isolated yield of product **13** from the unsubstituted pyrrolone substrate **12** (Scheme 3).

The total synthesis was completed by deprotection of **11** with TFA to provide violacein (**1**) in 49% isolated yield

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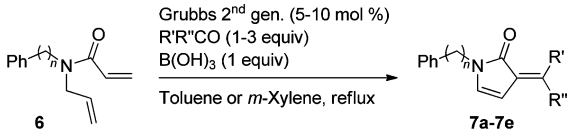
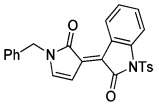
**Table 3.** Tandem RCM/Tautomerization/Aldol Condensation




| entry | *n* | electrophile | product (R', R") (yield (%))[a] |
|---|---|---|---|
| 1 | 1 | heptanal | **7a** (H, $C_6H_{13}$) (44) |
| 2 | 2 | heptanal | **7b** (H, $C_6H_{13}$) (33) |
| 3 | 1 | benzaldehyde | **7c** (H, $C_6H_5$) (12) |
| 4 | 2 | benzaldehyde | **7d** (H, $C_6H_5$) (17) |
| 5 | 1 | *N*-tosylisatin |  **7e** (36) |

[a] Isolated yield after flash column chromatography. Detailed reaction conditions are provided in the Supporting Information.

(> 80% purity) upon crystallization.[15] The final product was extremely difficult to handle, primarily due to unfavorable solubility properties in most common solvents and LC/MS analysis indicated that the crude yield was significantly higher than the isolated yield.

In conclusion, we have developed a new tandem RCM/isomerization/nucleophilic addition sequence which provides access to 5-substituted 2-pyrrolidinones in a single step from *N*-allylacrylamides. Furthermore, we found that 3-substituted 2-pyrrolones can be synthesized using similar tandem reactions from the same substrates, indicating that the isomerization step proceeds through a synthetically versatile tautomer intermediate. The utility of the tandem RCM/isomerization/nucleophilic addition sequence was further illustrated by a total synthesis of the natural product violacein.

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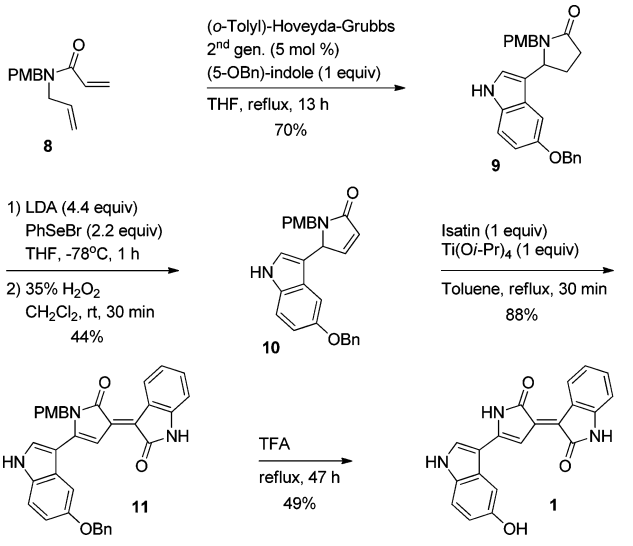
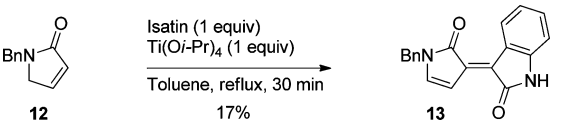
**Scheme 2.** Synthesis of Violacein via a Tandem RCM/Isomerization/Nucleophilic Addition Sequence




**Scheme 3.** Titanium-Catalyzed Tautomerization/Aldol Condensation of Pyrrolone **12** and Isatin




**Supporting Information Available.** Comprehensive data from optimization of tandem RCM/isomerization/nucleophilic addition, experimental procedures, and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.