

Cyclization of *N*-Allyl-5-allyl-5-hydroxylactams to 8*a*-Hydroxy-1,5,8,8*a*-tetrahydro-2*H*-indolizin-3-ones Using Grubbs' Catalyst

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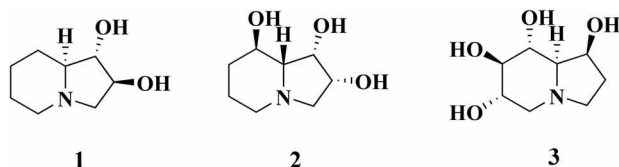
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A short and highly efficient synthetic method to prepare synthetically useful tetrahydroindolizinone derivatives from the ring-closing metathesis of *N*-allyl-5-allyl-5-hydroxylactams is described.

Key Words : Grubbs' catalyst. Ring-closing metathesis (RCM). Tetrahydroindolizinone. *N*-Acyliminium ion

Introduction

Indolizidine alkaloids which contain 1-azabicyclo[4.3.0]-nonane skeleton play important role in medicinal chemistry. Diabetes, anti-cancer, anti-viral and anti-AIDS activities have also been reported for polyhydroxylated indolizidine alkaloids.¹ Lentiginosine 1,² swainsonine 2³ and castanospermin 3^{3d,4} are naturally occurring indolizidine alkaloids which are known to inhibit enzymatic glycosidase hydrolysis.



Ring-closing metathesis (RCM) has recently emerged as a powerful method to synthesize a variety of ring systems.⁵ A lot of related syntheses of indolizidine and pyrrolizidine moieties using RCM have been reported in the literature.⁶

Here, we show this methodology can be extended to the synthesis of fused bicyclic systems which contain a nitrogen atom at the angular position, a carbonyl group and a hydroxyl group. These bicyclic systems available from the ring-closure metathesis of *N*-allyl-5-allyl-5-hydroxylactams **4** could be potentially useful for the synthesis of more complex indolizidine derivatives. Although a number of examples of metathesis have been described,⁵⁻⁷ only one example was reported involving the participation of hetero-substituted hydroxyolefins.⁸ It is reported that the presence of free polar groups close to the double bonds inhibits the RCM reaction with Grubbs' catalyst in most cases.⁹ We

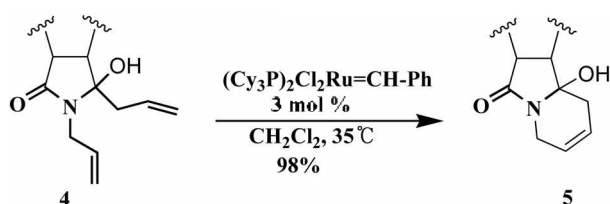
employed bis-alkenyl substituted hydroxylactams **4** and showed that RCM underwent smoothly to afford unsaturated cyclic olefins **5** in moderate to good yields (Scheme 1).

Results and Discussion

For the synthesis of fused bicyclic systems **5**, *N*-allyl cyclic imides **8** which were readily obtained from succinimide, phthalimide, maleic anhydride, and tartaric anhydride were used as starting materials. We previously reported that the zinc mediated Barbier type allylation of cyclic imides in the presence of a catalytic amount of PbBr_2 went very efficiently.¹⁰ The resulting hydroxylactams were transformed into the corresponding fused bicyclic systems **5** in good yields using intramolecular ring-closing olefin metathesis. The unsaturated hydroxylactams could also serve as a potentially valuable synthetic intermediate for the synthesis of certain natural products containing an azabicyclic system.¹¹

The RCM reaction was performed using 3 mol% of Grubbs' ruthenium catalyst **6** or **7** (Fig. 1). We used Grubbs' 1st generation catalyst **6** for the RCM of **4c**, **4d** and 2nd generation catalyst **7** for **4a** and **4b**. After stirring in dichloromethane at 35 under Ar atmosphere for 4h, the cyclized products were isolated in high yields (Scheme 2).

The results are summarized in Table 1. When RCM of hydroxylactam **4a** and of **4b** were carried out in dichloromethane at 35 in the presence of 3 mol% Grubbs 1st generation catalyst **6**, almost starting material **4a** and **4b** were recovered. The use of Grubbs' 2nd generation catalyst **7** gave increased isolated yields of **5a** and **5b** in 55% and 45%, respectively. In case of **4b**, higher dosage of catalyst **6** (10 mol%) gave **5b** in 85% yield. The RCM of hydroxylactam **4c** and **4d** were carried out in dichloromethane at 35 in the



Scheme 1

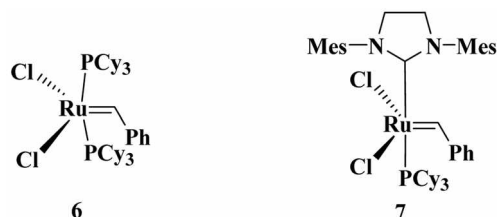


Figure 1. Grubbs' catalysts used for RCM reactions.

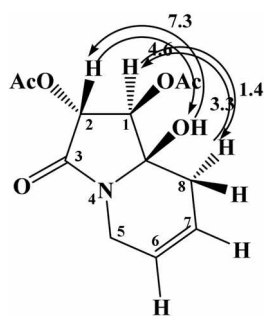
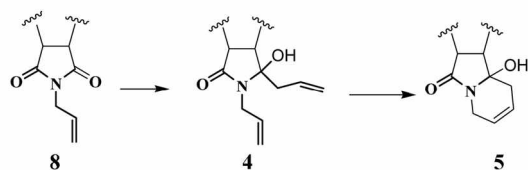


Figure 2. Nuclear Overhauser effect of **5c**.

Table 1. Alkylation of cyclic imides and ring-closing metathesis of *N*-allyl-5-allyl-5-hydroxylactams



entry	cyclic imide	bis-alkene	yield (%)	Grubbs' catalysis	products	yield (%)
a			92	7		55
b			88.2	6		85
c			60	6		98
d			95	6		98

presence of 3 mol% Grubbs 1st generation catalyst **6**, the cyclized products **5c** and **5d** were isolated in almost quantitative yield.

The stereochemical assignment of **5c** was carried out using nuclear Overhauser effect, as illustrated in Figure 2. Irradiation of the angular hydroxyl hydrogen led to a 7.3% increment in the H2 signal and no increment in the H1 signal. Accordingly, irradiation of the hydrogen at C2 led to a 4.6% increment in the hydroxyl hydrogen signal, indicating that **5c** possesses *R*-configurations at 8a position.

In order to check the versatility of our tetrahydroindo-

Table 2. Addition of carbon nucleophiles to 5-hydroxytetrahydroindolizones **5**

Entry	hydroxylactams	Nucleophiles	Products 9	isolated yield (%)
1	5b	allyltributyltin		39
2	5b	trimethylsilyl cyanide		25
3	5c	trimethylsilyl cyanide		38
4	5d	trimethylsilyl cyanide		26
5	5d	allyltributyltin		72

^a reaction condition: 1 eq. BF₃·OEt₂ in CH₂Cl₂, -78 °C, then slowly warmed up to rt, 1 day

lizinone derivatives. intermolecular alkylations with different carbon nucleophiles were accomplished under mild conditions using Lewis acid.^{9a,12} The reactions first tested were with allyltrimethylsilane, trimethylsilyl cyanide as carbon nucleophiles and BF₃·OEt₂ to generate the *N*-acyliminium ion. Thus, to a solution of **5** and a carbon nucleophile in dichloromethane was added BF₃·OEt₂ at -78 °C, stirred for 2 h, then the reaction mixture was allowed to warm to room temperature. The yields were relatively low because of dehydration to conjugated dienes.^{10a} The results are summarized in Table 2.

As described here, we have developed a simple method for the cyclization of *N*-allyl-5-allyl-5-hydroxylactams, using RCM to construct tetrahydroindolizone derivatives. This synthetic approach is short and highly efficient. Substitution of hydroxyl group in compounds **5b-d** by carbon-based nucleophiles via *N*-acyliminium ion intermediate promoted by Lewis acid were also achieved in order to prove synthetic versatility. The methodology described herein has potential applicability in the synthesis of complex natural and non-natural indolizidine compounds because of the presence of the double bond, carbonyl group and hydroxyl group available for further functionalization.

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