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Total Synthesis of Rugulovasine A

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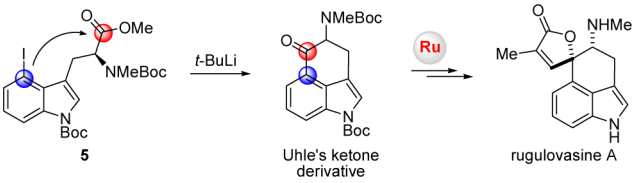
ABSTRACT



A concise total synthesis of rugulovasine A is achieved by using Uhle's ketone derivative as the key intermediate, which was synthesized by intramolecular cyclization via metal−halogen exchange. Two different routes to construct a spirocyclic butyrolactone subunit involving a Ru-catalyzed cyclocarbonylation and a special Ru-catalyzed double bond rearrangement were studied.

The indole alkaloids of the *Ergot* family have attracted the attention of synthetic chemists for decades because they possess various potent biological activities and a unique 3,4-fused indole structure, which is a synthetic challenge.[1,2] Rugulovasines A and B, containing a spirocyclic butyrolactone subunit, are two unique *Ergot* family indole alkaloids first isolated from the strains of *Penicillium concavo-rugulosum* in 1969 and then from *Penicillium islandicum* in 1976.[3] Different from most natural products that are commonly isolated as single enantiomers, rugulovasines A and B were isolated in racemic form and interconversion upon heating in polar solvents was observed (Figure 1). These interesting facts can be explained by a remarkable vinylogous Mannich reaction mechanism, which was convincingly proven by Rebek who not only finished the first total synthesis of rugulovasine A in optically pure form but also further

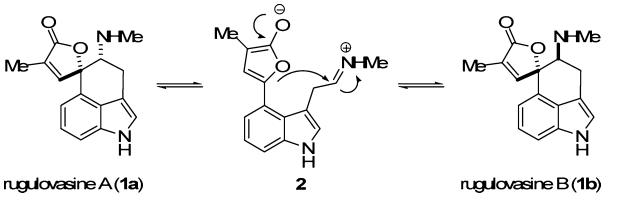


Figure 1. Structures of rugulovasines A and B.

investigated the thermodynamic and kinetic properties of the equilibrium between rugulovasines A and B.[4] Martin's group also reported the total synthesis of rugulovasines A and B in a biomimetic manner via inter- and intramolecular vinylogous Mannich reactions as the key steps.[5]

Different from the conventional "single-target" strategy of total synthesis, biosynthesis in nature usually constructs a wide range of natural products through the same intermediate.[6] Inspired by nature, we have recently accomplished the total synthesis of clavicipitic acid,[7,8]

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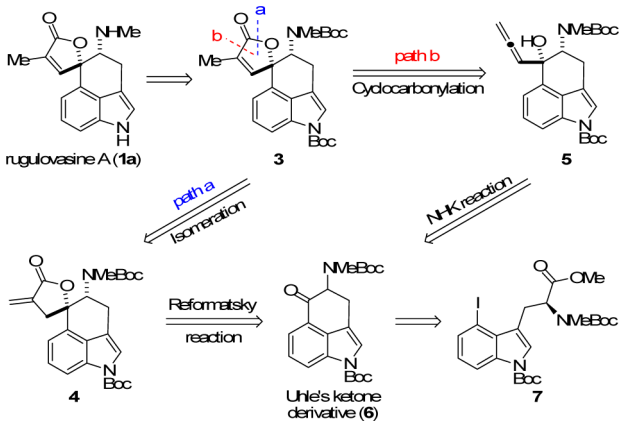
Scheme 1. Retrosynthetic Analysis of Rugulovasine A (**1a**)



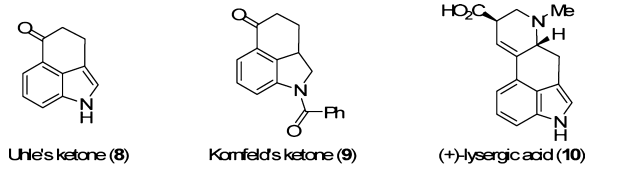
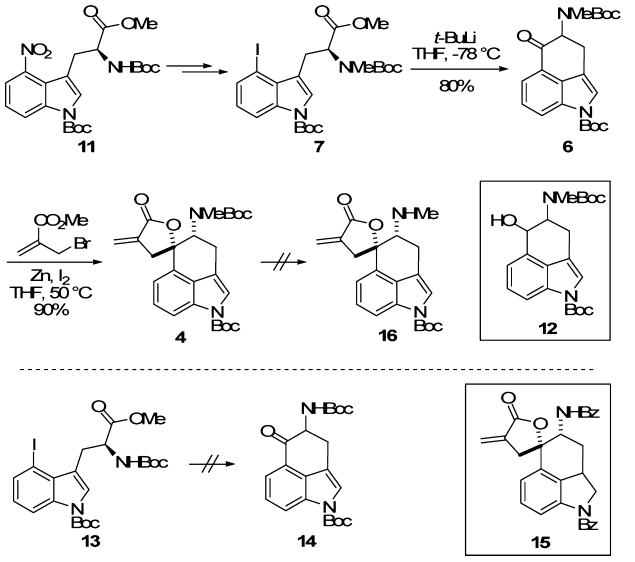


Figure 2. Structures of Uhle's ketone and Kornfeld's ketone.

aurantioclavine,[8] indolactam V,[9] and (+)-lysergic acid[10] all starting from the 4-nitrootryptophan derivative, which was prepared through a Pd-catalyzed indole synthesis by annulation of *o*-haloanilines and aldehydes developed by Jia and Zhu.[11] In order to further define this concept, we describe herein the total synthesis of rugulovasine A from the same 4-nitrotryptophan derivative.

Retrosynthetic analysis of **1a** is shown in Scheme 1. We envisioned that rugulovasine A could be accessed via deprotection of compound **3**. It was anticipated that the crucial spirocyclic butyrolactone ring of compound **3** could be prepared from Uhle's ketone derivative **6** via either Reformatsky reaction followed by double bond isomerization (Path a) or the transformation of **6** into allenyl alcohol **5** via NHK (Nozaki–Hiyama–Kishi) reaction followed by Ru-catalyzed cyclocarbonylation (Path b). The key tricyclic ketone **6**, a derivative of Uhle's ketone, could be obtained by intramolecular cyclization of 4-iodotryptophan derivative **7**. In fact, because Uhle's ketone (**8**) and Kornfeld's ketone (**9**) had been widely used as key intermediates in the synthesis of the ergot family of indole alkaloids (Figure 2), construction of these intriguing tricyclic ketones and their analogues had attracted the attention of many organic chemists.[12] In this context, an efficient method to obtain these tricyclic ketones is developed.

Scheme 2. Synthesis of Methylene Lactone **4**



The synthesis commenced with the optically pure L-4-iodotryptophan derivative **7**, which was synthesized from the known 4-nitrotryptophan **11** (Scheme 2).[8−10] Initial attempts to cyclize **7** using isopropylmagnesium bromide provided the desired product **6** in 20% yield along with alcohol **12** in 20% yield, which was produced by the reduction of ketone **6** with isopropyl magnesium.[13] Although oxidation of alcohol **12** could give ketone **6**, the overall yield was low. Further optimization of the reaction conditions showed that *t*-BuLi was the best base. Treatment of compound **7** with 2.2 equiv of *t*-BuLi afforded ketone **6** in 80% yield. It is worthwhile to note that ketone **6** was almost completely racemized under our optimized reaction conditions (see Supporting Information). Because the natural product rugulovasine A itself was isolated in racemic form, we did not make much effort to prepare optically pure ketone **6**. In addition, attempts to transform compound **13** to ketone **14** under the same conditions failed.

As the synthesis of the key tricyclic ketone **6** was successful, the stage was set for the construction of a spirocyclic butyrolactone subunit. We first investigated

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the synthetic route of Path a. Reformatsky reaction of ketone **6** with zinc and ethyl α-(bromomethyl)acrylate at 50 °C in THF afforded methylene lactone **4** smoothly as a single diastereomer in 90% yield.[14] Since lactone **4** existed as a mixture of rotamers due to the NMeBoc group, we could not obtain the X-ray crystal structure of lactone **4**. Therefore, the determination of its absolute configuration would have to wait for the completion of the synthesis of **1**. Unexpectedly, serious setback was encountered when we attempted to exploit a double bond rearrangement to form butenolide **3**. A variety of reported reagents such as $RhCl_3 \cdot 3H_2O$,[15] Grubbs II catalyst,[16] $Pd(OAc)_2$, and DBU[17] were investigated. However, no desired product was obtained (Table 1). Rebek reported a similar problem and proposed that the binding between the 2° amide of **15** and the metal center may be crucial for the isomerization when $RhCl_3$ was used.[4] However, attempts to remove NMe-Boc selectively to prepare compound **16** under a variety of conditions did not lead to the desired product.

We then turned our attention to Path b. Treatment of ketone **6** under the modified Nozaki–Hiyama–Kishi conditions developed by Jacques Goré ($CrCl_3$, $LiAlH_4$, and propargylbromide in THF/HMPA) provided the desired allenyl alcohol **5** in 66% yield (Scheme 3).[18] The fact that this reaction did not proceed when $CrCl_2$ was used instead of $CrCl_3$–$LiAlH_4$ implied lithium or aluminum might enhance the activity of organochromium species. Cyclocarbonylation of allenyl alcohol **5** was first carried out in dioxane with $Ru_3(CO)_{12}$ and Et_3N at 100 °C for 8 h under 30 atm of carbon monoxide. Spirocyclic butyrolactone **3** was obtained in 56% yield (brsm) with 50% starting material recovered.[19,20] When 2,4,6-collidine was used as the solvent, allenyl alcohol **5** was totally consumed and the desired butyrolactone **3** was obtained in 58% yield within 2 h. Moreover, the pressure of CO was greatly reduced from 30 to 1 atm.[21] The VT ^1H NMR experiment showed that compound **3** was indeed a mixture of rotamers of the Boc group instead of a pair of epimers (see Supporting Information). This result also implied that the conversion of **6** to **5** is strictly stereoselective.

With butyrolactone **3** in hand, the next step was to remove the two Boc groups. Deprotection of the two Boc groups simultaneously with TFA or TMSI led to complete decomposition of the product. Selective deprotection of NMe-Boc with TMSOTf in the presence of 2,6-lutidine gave amine **17** in 68% yield. However, subsequent deprotection of the Boc group on the indole nitrogen with Cs_2CO_3 in MeOH/THF provided the desired rugulovasine A (**1a**) in only 16% yield, which suggested that **1a** might not be stable under basic conditions. Further study revealed that the order of deprotection of the two Boc groups was critical. Thus, deprotection of **3** first with Cs_2CO_3 in THF/MeOH afforded compound **18** in 75% yield,[5] and the subsequent deprotection of the NMe-Boc group with TMSOTf and 2,6-lutidine gave rugulovasine A (**1a**) in 87% yield. All the spectroscopic data of **1a** were in agreement with those of natural and synthetic rugulovasine A reported in the literature.[3,5] Our results also confirmed that the addition reaction of ketone **6** provided the *cis* amino and hydroxyl compounds **4** and **5** due to the steric hindrance.

Based on the mechanism of cyclocarbonylation proposed by Takahashi, methylene lactone **4** could be isomerized to butyrolactone **3** in the presence of $Ru_3(CO)_{12}$ and Et_3N.[19] To examine this hypothesis, we treated methylene lactone **4** with $Ru_3(CO)_{12}$ and Et_3N in dioxane for 8 h at 100 °C to provide

Scheme 3. Synthesis of Rugulovasine A

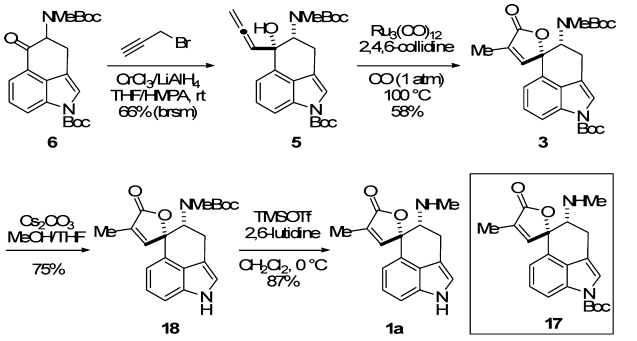

Table 1. Optimization of the Reaction Conditions

entry	conditions	yield (**3**)
1	$RhCl_3 \cdot 3H_2O$, EtOH, reflux	NR
2	DBU, $Pd(OAc)_2$, toluene, reflux	NR
3	DBU, toluene, reflux	NR
4	Grubbs II catalysis, CH_2Cl_2, reflux	NR
5	Grubbs II catalysis, H_2, CH_2Cl_2, reflux	NR
6	$Ru_3(CO)_{12}$, Et_3N, dioxane, 100 °C, 8 h	53%
7	$Ru_3(CO)_{12}$, Et_3N, dioxane, 100 °C, 4 h	82%
8	**$Ru_3(CO)_{12}$, Et_3N, dioxane, 100 °C, 2 h**	**95%**

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the desired butyrolactone **3** in 53% yield. Since we observed that prolonging the reaction time would reduce the yield because compound **3** was unstable under the cyclocarbonylation reaction conditions, shortening of the reaction time was investigated. We found that when the reaction was ran for 2 h at 100 °C, the desired butyrolactone **3** was obtained in 95% yield. This result showed that Path a is a more efficient route to provide rugulovasine A (Table 1) and $Ru_3(CO)_{12}$ might be used as a powerful olefin isomerization reagent.

In summary, we have accomplished the total synthesis of rugulovasine A from 4-indotryptophan derivative **7**. The synthesis features an intramolecular cyclization via a metal−halogen exchange to afford Uhle's ketone derivative, and a Ru-catalyzed cyclocarbonylation or a special Ru-catalyzed double bond rearrangement to construct the spirocyclic butyrolactone subunit. The $Ru_3(CO)_{12}$-mediated olefin isomerization could be widely used in the total synthesis of natural products.

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Supporting Information Available. Full experimental procedures, and ^1H and ^{13}C NMR spectra of compounds **6**, **4**, **5**, **3**, **18**, **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.