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Total synthesis of (+)-UCS1025A based on a sequential Michael-retro Michael strategy featuring one-pot six-step cascade reaction

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ABSTRACT

The asymmetric total synthesis of UCS1025A is accomplished by establishing a novel and efficient method for the construction of a tricyclic pyrrolizidinone skeleton based on a sequential Michael-*retro* Michael strategy. The key step is a one-pot six-step cascade reaction including oxidation of a primary alcohol to the corresponding carboxylic acid, a *retro* thio-Michael reaction, and an intramolecular oxy-Michael reaction. This newly-developed synthetic strategy inspired by "masked" electrophilic character of tricyclic pyrrolizidinone is efficient and high-yielding compared to that developed in previously-reported total syntheses.

Introduction

Natural organic compounds having tricyclic pyrrolizidinone skeletons have been developed in recent years (Fig. 1), and currently receive frequent attention for their interesting pharmacological properties. For example, UCS1025A (**1**) is a potent telomerase inhibitor,[1] while CJ-16,264 (**2**) has antibacterial activity toward multi-drug resistant bacteria.[2] Pyrrolizilactone (**3**) is a new small molecule inhibitor of proteasome, and shows cytotoxicity against cancer cell lines such as HL-60 and HeLa.[3]

The most interesting structural feature of these compounds is the "Masked" Michael acceptor, i.e. their electrophilic α,β-unsaturated lactam moiety which is temporarily protected by intramolecular oxy-Michael reactions with a carboxylic acid moiety. In addition, the "Masked" Michael acceptor easily reacts with thioglycol under weak basic conditions to produce the corresponding thio-Michael-type adduct.[4] The unique electrophilic character of tricyclic pyrrolizidinones may be closely related to their reported biological activities. Several synthetic studies of these compounds have been conducted, and total syntheses of UCS1025A (**1**) have been reported previously by four groups.[5–8] We are particularly interested in the uncleared molecular function of tricyclic pyrrolizidinones *in vivo*, and have sought to develop a new and efficient method for the synthesis of tricyclic pyrrolizidinone cores. In this paper, we describe an asymmetric total synthesis of UCS1025A (**1**) based on a novel sequential Michael-retro Michael strategy including a one-pot six-step cascade reaction process.

Result and discussion

Our sequential Michael-retro Michael strategy for the synthesis of UCS1025A (**1**) is shown in Scheme 1. Previously-reported bicyclic compound **4**[11] can be converted to the corresponding unsaturated lactam **5** by chemoselective reduction of the ester group. Intramolecular oxy-Michael reaction of unsaturated lactam **5** with the resulting primary alcohol can then proceed under basic conditions. The generated enolate anion **5′** is expected to react with a benzotriazole-type activated ester **6**[8–10] having a decalin skeleton to form the desired α-acylated lactam **7**. Treating lactam **7** with an appropriate base causes abstraction of the α-proton and a subsequent *retro* oxy-Michael reaction to afford the primary alcohol **8**. After oxidation of alcohol **8** to the corresponding carboxylic acid **9**, the intramolecular oxy-Michael reaction occurs spontaneously to afford the desired tricyclic pyrrolizidinone **10**. Finally, UCS1025A (**1**) can be obtained by removal of the TBS group. The global aims of this strategy are the following: (i) to minimize the protection/deprotection steps by utilizing sequential Michael-retro Michael reactions which are inspired by "masked" electrophilic character of tricyclic pyrrolizidinone, (ii) to develop a new and readily available lactam fragment which can easily be enolized by treating with commonly used base such as lithium diisopropylamide (LDA).

Based on the strategy described unsaturated lactam **5** (Scheme 2). A racemic bicyclic compound (±)-**4** was prepared

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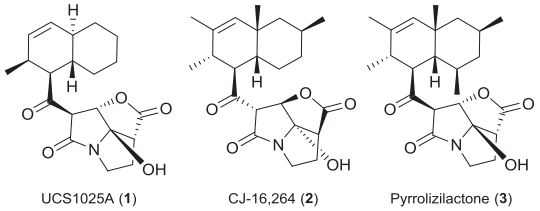


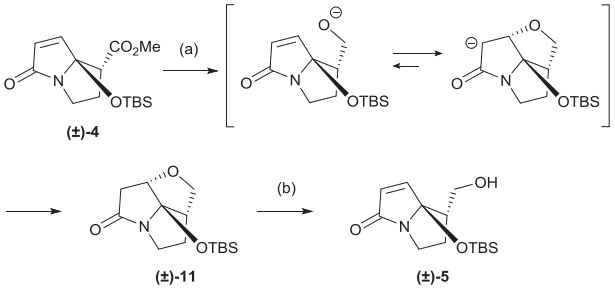
Fig. 1. Structures of UCS1025A (**1**) and other tricyclic pyrrolizidinones.

according to procedures first reported by Hoye et al.[11] and improved by Danishefsky et al.[5] Selective reduction of the ester group was examined using various reducing agents. Notably, the desired reduction to primary alcohol (±)-**5** and the following intramolecular oxy-Michael reaction subsequently proceeded by using $NaBH_4$-$CaCl_2$[12,13] in ethanol to afford a tricyclic compound (±)-**11** in high yield (96%). The desired unsaturated lactam (±)-**5** was then obtained via *retro* oxy-Michael reaction of the tricyclic compound (±)-**11** by treatment with LDA as a base.

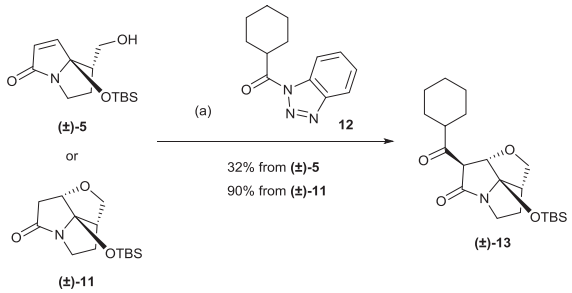
Next, we attempted to introduce an acyl group to the α-position of unsaturated lactam (±)-**5** by Claisen-type condensation (Scheme 3). In this study, active ester **12** was chosen as a model substrate of a decalin fragment. First, a mixture of unsaturated lactam (±)-**5** and active ester **12** was treated with LDA. Although the expected cascade reaction proceeded, the yield of α-acylated lactam (±)-**13** was unsatisfactory (32%). On the other hand, when the above-synthesized tricyclic compound (±)-**11** was properly used as an alternative precursor of enolate anion, the desired α-acylated lactam (±)-**13** was obtained in high yield (90%). Thus we developed a new and readily available and easily enolizable lactam fragment (±)-**11** for the synthesis of tricyclic pyrrolizidinone.

We next sought to prepare the optically-active form of tricyclic compound (−)-**11** (Scheme 4). The ester group of racemic bicyclic compound (±)-**4** was hydrolyzed, and the obtained carboxylic acid (±)-**14** was then converted to *N*-acyl-oxazolidinone **17** via the corresponding acyl chloride (±)-**15** by introducing the Evans-type chiral auxiliary (−)-**16**.[14] The obtained mixture of two diastereomers **17a**, **17b** was easily separated by silica gel column chromatography. The desired diastereomer **17a** was subjected to the above developed reduction conditions ($NaBH_4$-$CaCl_2$ in ethanol), and the desired tricyclic compound (−)-**11** was obtained in good yield in an optically pure form.

Preparation of decalin fragment (+)-**6** was carried out next (Scheme 5). Paintner et al. reported the synthesis of decalin carboxylic acid with the opposite absolute configuration (−)-**18** as



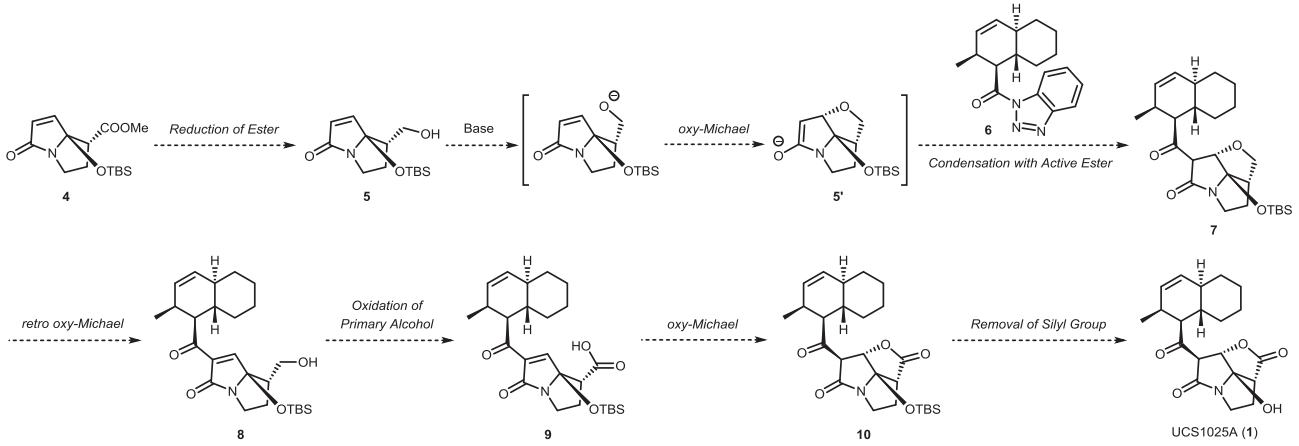
Scheme 2. Synthesis of unsaturated lactam (±)-**5**. Reagents and conditions: (a) $NaBH_4$, $CaCl_2$, EtOH, 0 °C to RT, 96%; (b) LDA, THF, −78 to 0 °C, 61%.



Scheme 3. Introduction of α-acyl group. Reagents and conditions: (a) compound **12**, LDA, THF, −78 to 0 °C.

an intermediate for the synthesis of tetrodecamycin.[15] As such, we prepared the desired enantiomer (+)-**18** in a similar manner utilizing an asymmetric intramolecular Diels-Alder reaction of *N*-acyl-oxazolidinone. The desired active ester with chiral decalin core (+)-**6** was obtained via two steps of functional manipulation as reported by Kan et al.[8]

With both fragments (−)-**11** and (+)-**6** in hand, Claisen-type condensation was conducted under the above described reaction conditions to build the carbon framework of UCS1025A (**1**). In this manner, the desired α-acylated lactam **7** was successfully obtained in good yield as a mixture of keto-enol tautomers (keto: enol = 1:2) (Scheme 6). The α-acylated lactam **7** was then subjected to different basic conditions in order to carry out the *retro* oxy-Michael reaction, but the desired primary alcohol **8** could not be obtained. Therefore, an alternative synthetic pathway is required to complete the construction of the tricyclic pyrrolizidinone core of UCS1025A (**1**). We assumed that the *retro* oxy-Michael and oxy-



Scheme 1. Sequential Michael-retro Michael strategy for the synthesis of UCS1025A (**1**).