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First total synthesis of oteromycin utilizing one-pot four-step cascade reaction strategy

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ABSTRACT

The first total synthesis of oteromycin was investigated. Our previously reported convergent strategy for the synthesis of α-acyl-γ-hydroxy-γ-lactams was first applied for the total synthesis, however, the final deprotection of the methoxyaminal moiety could not be achieved since an unexpected intramolecular Diels–Alder (IMDA) reaction occurred. Therefore, a novel one-pot four-step cascade reaction starting from α-selenolactam was investigated. The efficient synthetic strategy was successfully developed to afford the desired oteromycin, and its complete structure elucidation including the stereochemistry at C24 position was also accomplished.

Oteromycin (**1a**) is an antagonist of the endothelin receptor (ET_B), first isolated from fungus strains MF5810 and MF5811 by Singh et al. in 1995.[1] In 1999, Hazuda et al. reported that the compound also exhibits inhibitory activity against HIV-1 integrase.[2] Oteromycin (**1a**) has a unique structure consisting of a phenylalanine-derived α-acyl-γ-hydroxy-γ-lactam with a hydrophobic decalin skeleton (Fig. 1). However, the absolute configuration and relative stereochemistry at C24 position of oteromycin have not been determined. On the other hand, similar α-acyl-γ-hydroxy-γ-lactams **2–5** have been discovered[3–6] in recent years, and have garnered considerable interest for their various and promising biological activities. Each of these compounds exhibits a different biological activity according to structural variations on the decalin skeleton and on the substituent at the γ-position of the lactam ring. However, their detailed bioactivity spectra and precise modes of action have not been identified. Therefore, we developed a novel convergent synthetic method for this type of compounds,[7a] and recently achieved the first total synthesis of antitumor compound myceliothermophin A (**2**) and related compounds.[7b] In this Letter, we report the first total synthesis of oteromycin (**1a**) as the second achievement in this series of work.

We expected that oteromycin **1a** could be synthesized by a similar strategy developed in the total synthesis of myceliothermophins. That is, the target compound **1a** would be obtained via the aldol reaction of *N*-Teoc-protected γ-methoxylactam **9** with decalin aldehyde **8**, and the following oxidation and deprotection steps (Scheme 1).

Therefore, trienylborane **17** was first prepared as a substrate for the Suzuki–Miyaura coupling reaction by a similar method to that reported by Moses and co-workers[8] (Scheme 2).

Next, the decalin aldehyde **8** was synthesized (Scheme 3). The Suzuki–Miyaura coupling reaction of vinyl iodide **18** with trienylborane **17** was performed to obtain the conjugated tetraene **19**. The vinyl iodide **18** was previously prepared from (+)-citronellal in the total synthesis of myceliothermophin A.[7b] Oxidation of tetraene **19** using sulfur trioxide–pyridine (SO_3–Py) complex gave the corresponding aldehyde **20**. With the cyclization precursor in hand, the Lewis acid-mediated intramolecular Diels–Alder (IMDA) reaction was attempted. To the best of our knowledge, the construction of decalin skeleton utilizing the IMDA reaction of such acid-sensitive conjugated tetraene-type precursor has only been reported by Roush and co-workers in the total synthesis of superstolide A.[9] In this report, the IMDA reaction was carried out in 2,2,2-trifluoroethanol at 70 °C, and the corresponding decalin compound was obtained in moderate stereoselectivity. On the other hand, we dared to perform the reaction in the presence of Lewis acid catalyst under the low temperature (−78 °C), and the desired *endo*-type cyclization product **8** was successfully obtained with almost perfect stereoselectivity.

An aldol reaction of decalin aldehyde **8** with independently synthesized *N*-Teoc-protected γ-methoxylactam **9**[10] proceeded smoothly, and the following four step conversions gave the corresponding γ-methoxylactam **22** (Scheme 4).

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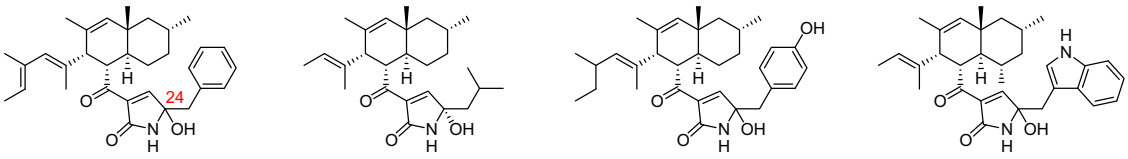
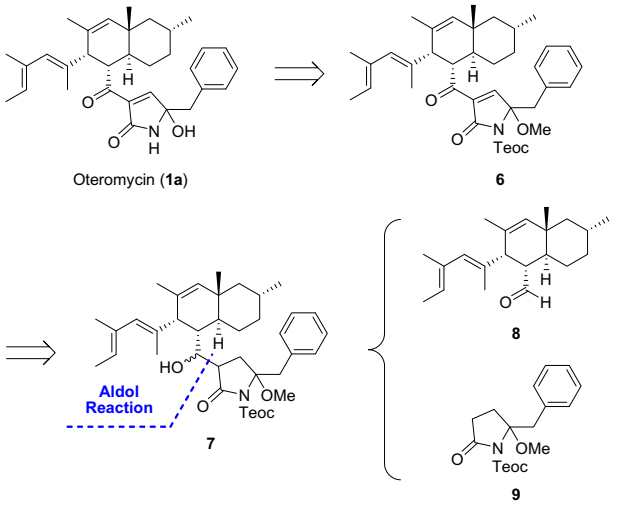
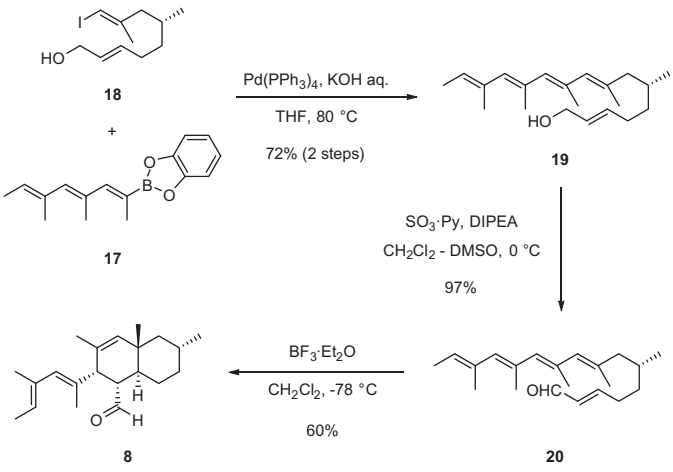


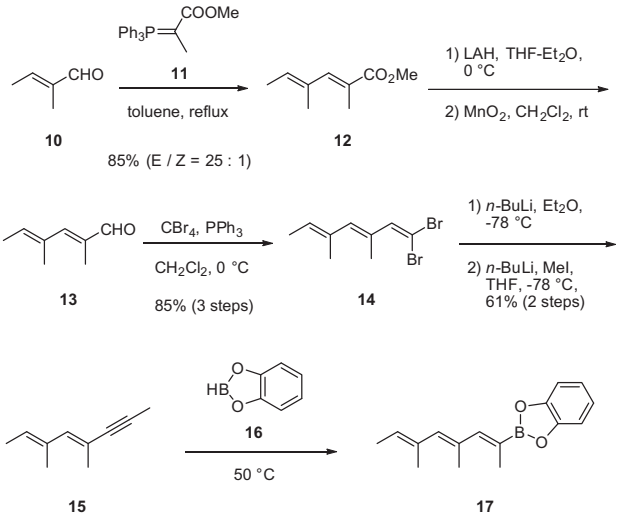
Figure. 1. Structures of α-acyl-γ-hydroxy-γ-lactams bearing decalin skeletons.



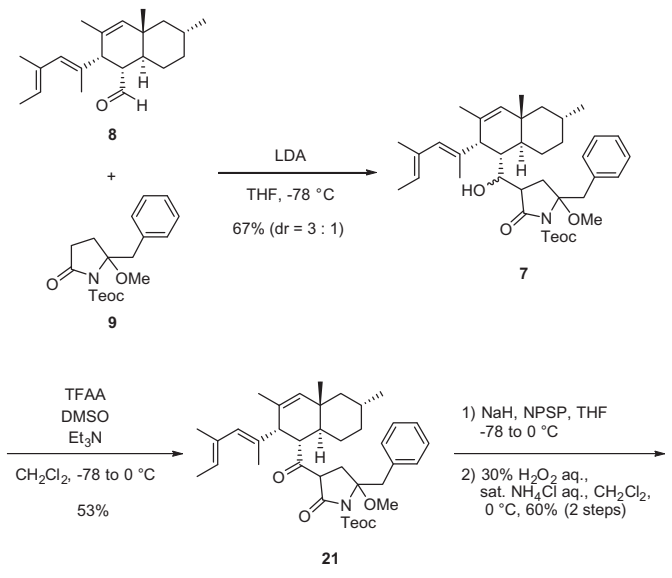
Scheme 1. Synthetic strategy for oteromycin (**1a**).



Scheme 3. Constrcution of decalin aldehyde (**8**).



Scheme 2. Preparation of trienylborane (**17**).



Scheme 4. Synthesis of the precursor of oteromycin (**22**).

Therefore, as the final step, a hydrolysis of the methoxyaminal moiety of γ-methoxylactam **22** was attempted (Scheme 5). However, the desired oteromycin (**1a**) was not obtained, despite carrying out the hydrolysis under mild conditions using hydrofluoric acid in acetonitrile at −15 °C. In this reaction condition, pentacyclic compound **24a**[11] and its geometrical isomer **24b** were exclusively produced as a 3:1 mixture. It is probably because the unexpected IMDA reaction of γ-methoxylactam **22**[12] proceeded in an