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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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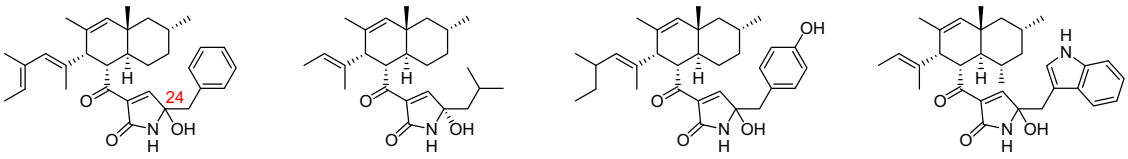
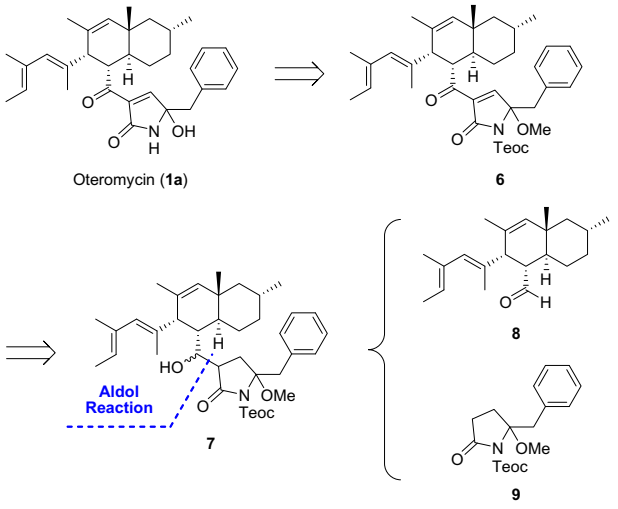
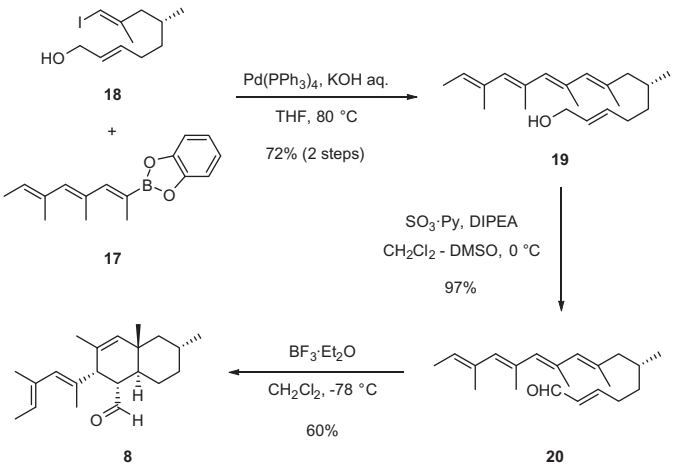


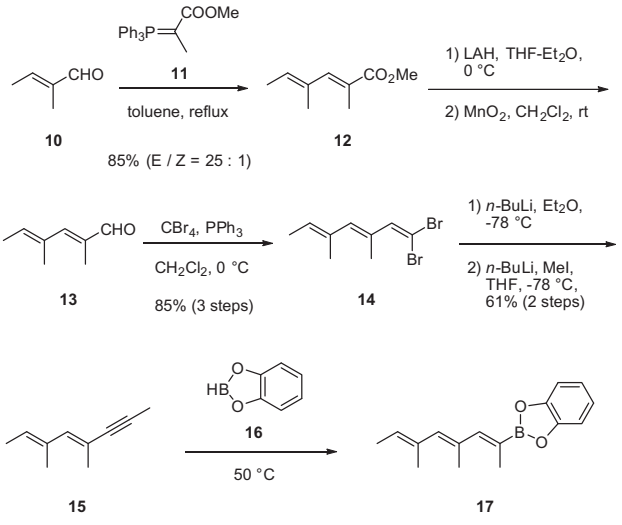
Figure. 1. Structures of α-acyl-γ-hydroxy-γ-lactams bearing decalin skeletons.



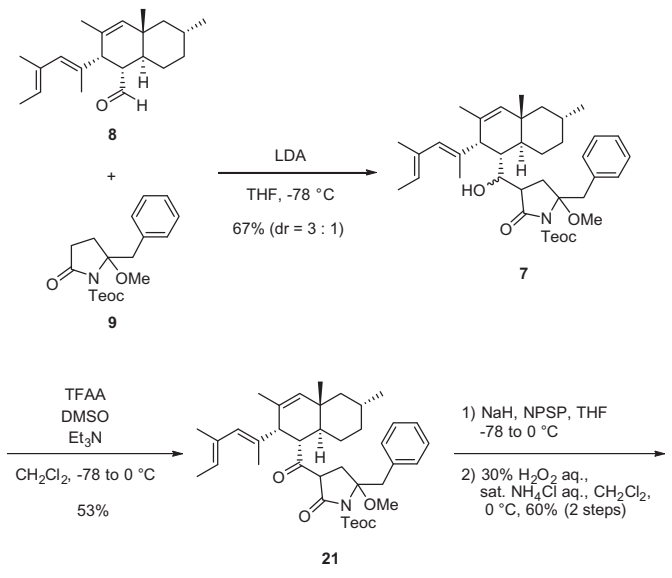
Scheme 1. Synthetic strategy for oteromycin (**1a**).



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

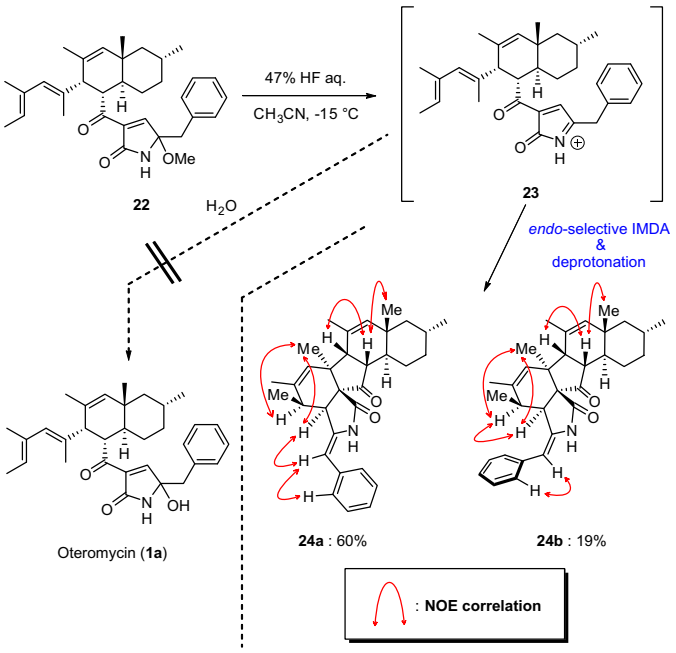


Scheme 2. Preparation of trienylborane (**17**).



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

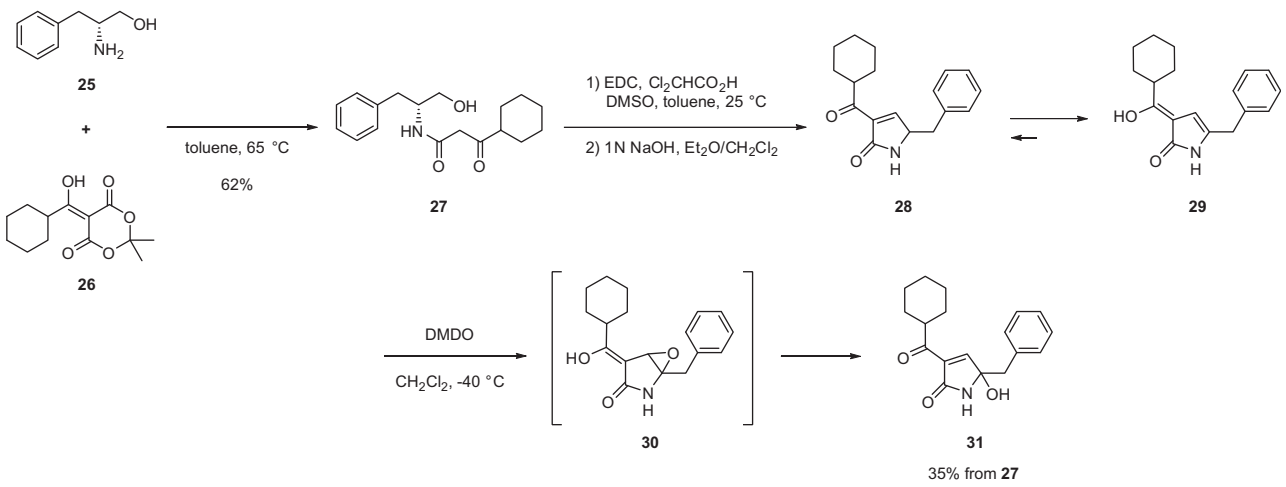


Scheme 5. Hydrolysis of γ-methoxylactam (**22**).

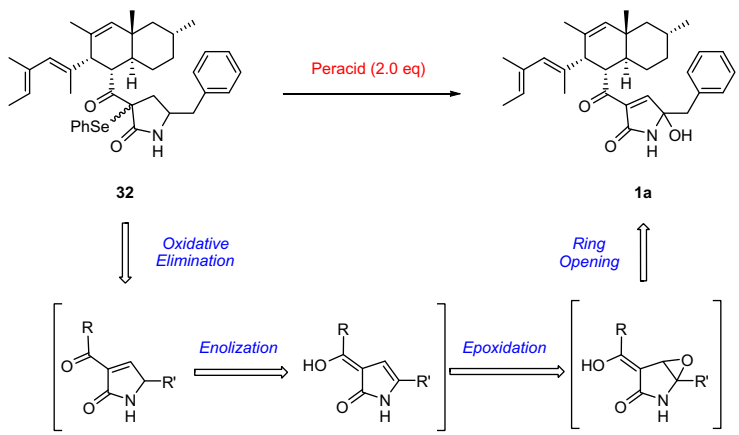
endo-selective manner via the initially-formed and highly reactive iminium ion intermediate **23** with the diene side chain on its decalin skeleton, and subsequent deprotonation gave the corresponding pentacyclic compounds **24a** and **24b**. This result indicated that our previously developed strategy for the total synthesis of myceliothermophin A (**2**) and related compounds[7b] was not applicable to oteromycin (**1a**). Therefore, to complete the total synthesis of this elusive target, we undertook the development of a second generation synthetic strategy not via the above described iminium ion intermediate **23**.

In 2004, Snider et al. reported an interesting biomimetic strategy for the synthesis of α-acyl-γ-hydroxy-γ-lactam **31**.[13,14] The synthetic method featured an epoxidation of the enol form of **29** derived from α-acyl-α,β-unsaturated lactam **28** and the subsequent ring opening reaction (Scheme 6). However, this method has not been applied to the total synthesis of natural products. This is probably because of the relative instability of the α-acyl-α,β-unsaturated lactam, which must be synthesized under strong basic conditions and isolated before the next step.

Therefore, we planned a novel synthetic strategy based on a one-pot cascade process including the in situ generation of α-acyl-α,β-unsaturated lactam and its subsequent transformation into the desired α-acyl-γ-hydroxy-γ-lactam. We hypothesized that the treatment of α-phenylselenolactam **32** with two equivalents of peracid would give the desired α-acyl-γ-hydroxy-γ-lactam



Scheme 6. Snider's approach for the synthesis of α-acyl-γ-hydroxy-γ-lactams.



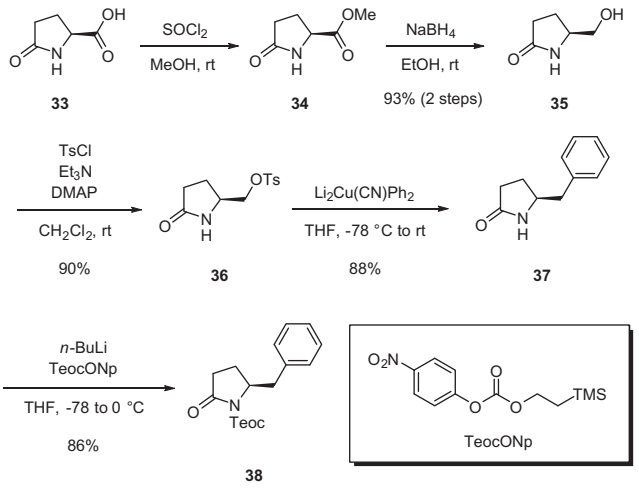
Scheme 7. A novel one-pot four-step cascade reaction strategy for the synthesis of oteromycin (**1a**).

through the following four stages: (i) the formation of α-acyl-α, β-unsaturated lactam via the oxidative elimination of the phenylselenyl group; (ii) enolization; (iii) regioselective epoxidation between the β- and γ-positions; and (iv) γ-hydroxylactam formation via ring opening (Scheme 7).

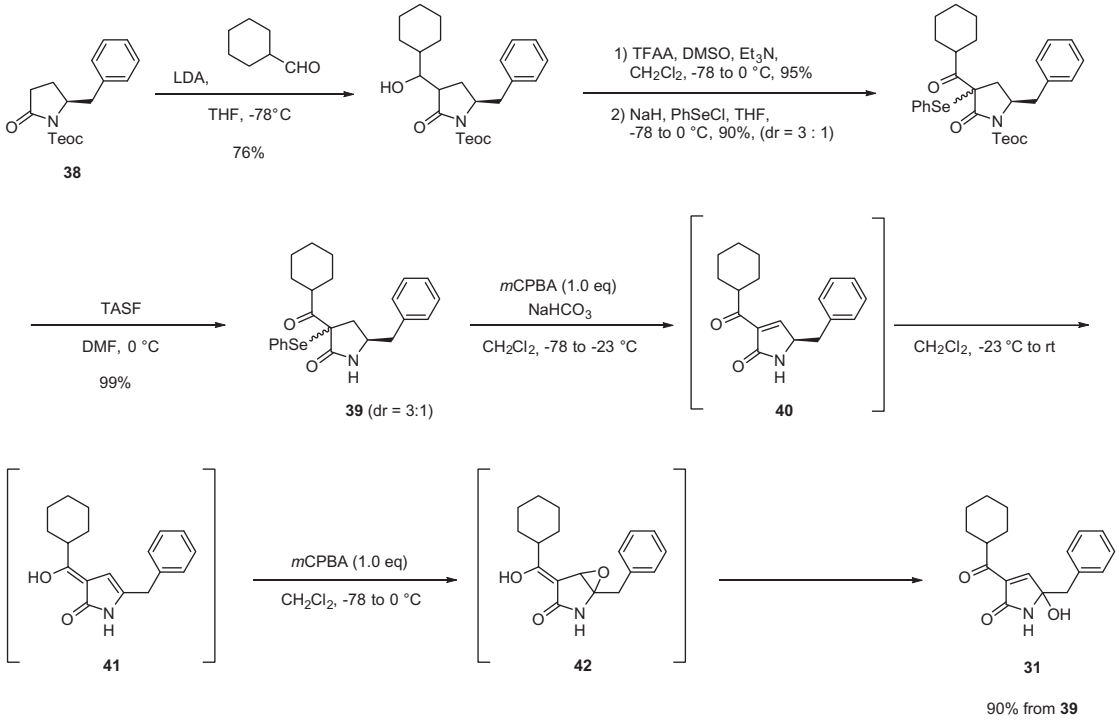
Accordingly, we prepared a chiral lactam fragment **38** as shown in Scheme 8. L-Pyroglutamic acid **33** was treated with $SOCl_2$ in MeOH to give the corresponding methyl ester **34**. The carbonyl group of ester **34** was reduced by $NaBH_4$, and the resulting hydroxyl group was then converted into tosylate **36**. The substitution reaction of tosylate **36** with cyanocuprate was performed to introduce the phenyl group. The nitrogen atom of the obtained γ-benzyllactam **37** was protected by a Teoc group to afford the desired chiral lactam fragment **38**.

Next, we tried to develop the second generation synthetic strategy through the synthesis of model compound **31** (Scheme 9). An aldol reaction of *N*-Teoc protected γ-lactam **38** with cyclohexanecarbaldehyde was performed, and the subsequent 3 step reactions gave the α-selenolactam **39** as a key intermediate. By a treatment of two equivalents of *m*-chloroperoxybenzoic acid (*m*CPBA), α-selenolactam **39** was successfully converted into the desired α-acyl-γ-hydroxylactam **31** via the above described four-step cascade reaction (Scheme 9). Thus, a new efficient synthetic strategy for α-acyl-γ-hydroxylactams was successfully developed.

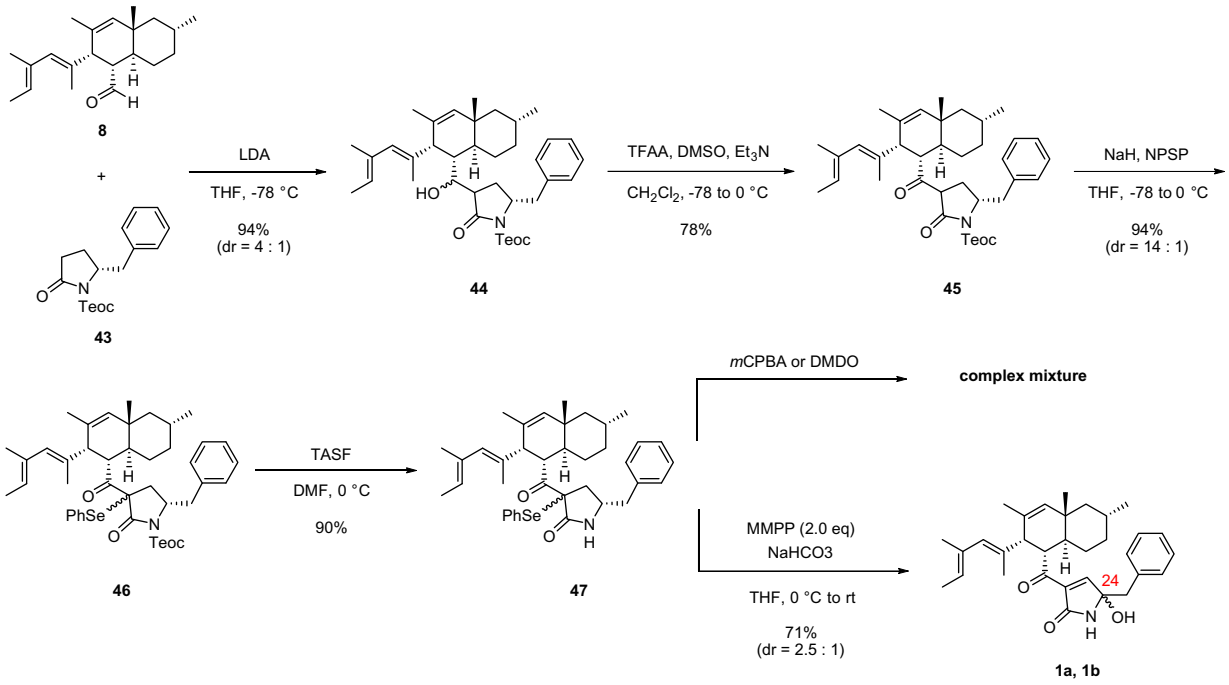
The result of our new approach for the total synthesis of oteromycin (**1a**) is summarized in Scheme 10. After the aldol reaction of chiral lactam **43**[15] with decalin aldehyde **8**, the resulting hydroxyl group was oxidized to obtain the corresponding α-acyllactam **45**. The introduction of a phenylselenyl group at the α-position and removal of the Teoc group gave the corresponding α-selenolactam **47**. However, the desired oteromycin (**1a**) was not obtained by a treatment of **47** with *m*CPBA, and the reaction mixture was immediately complicated. It is probably due to the unexpected epoxidation of highly reactive diene moiety, and subsequent polymeric reactions. The use of dimethyldioxirane (DMDO), which was used in Snider's model synthesis, also caused serious complications. Therefore, in order to realize more chemoselective epoxidation, magnesium monoperoxyphthalate (MMPP) was employed as a milder peracid. As a result, the desired four-step cascade reaction[16] successfully proceeded, and the corresponding γ-hydroxylactams **1a** and **1b** were obtained as a mixture of two diastereomers at the C24 position (dr = 2.5:1). It is clearly indicated that MMPP was a useful reagent for the synthesis of α-acyl-γ-hydroxylactam bearing highly reactive carbon–carbon unsaturated bonds. The obtained diastereomers **1a** and **1b** were easily separated by silica gel column chromatography, and all the spectral data of the major isomer **1a** were in good accordance[17] with those reported by Singh and co-workers. The absolute stereochemistry of oteromycin (**1a**) was also confirmed as shown in Figure 1 by agreement of the sign of optical rotation. However, despite detailed analysis of various spectral data, the stereochemistry at the C24 position could not be determined.



Scheme 8. Preparation of lactam fragment **38**.



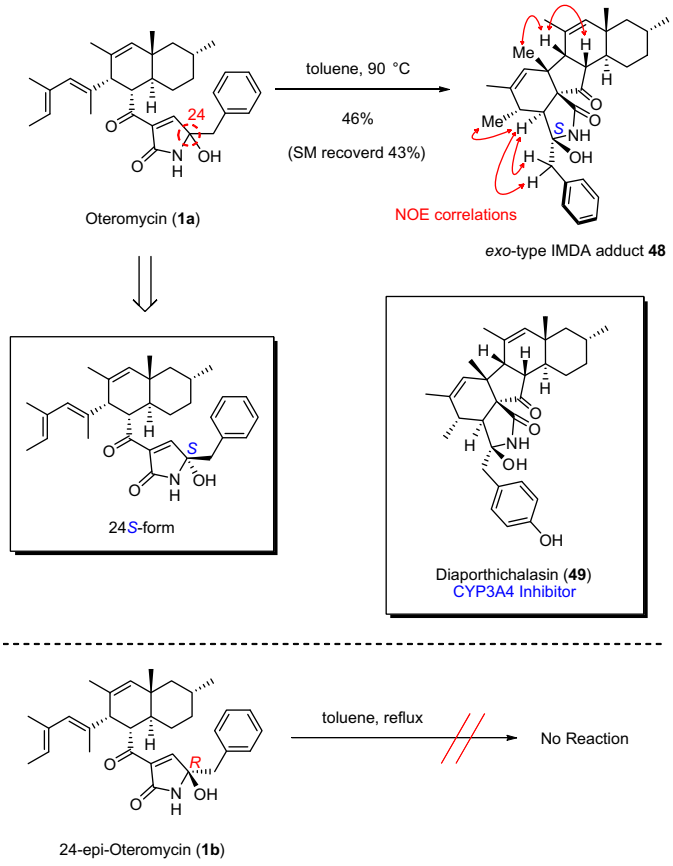
Scheme 9. A second generation synthetic approach for α-acyl-γ-hydroxy-γ-lactams (**31**).



Scheme 10. Completion of total synthesis of oteromycin (**1a**).

Therefore, if we can perform the IMDA reaction between the diene side chain on the decalin skeleton and the α,β-unsaturated lactam of oteromycin (**1a**) without the elimination of the C24 hydroxyl group under thermal conditions, it will be possible to determine the stereochemistry at the C24 position by NOE studies of the resulting pentacyclic compound. Accordingly, we tried the above described thermal reaction of oteromycin (**1a**). As a result, the desired IMDA reaction proceeded in toluene at 90 °C to give the corresponding pentacyclic compound **48** as a single stereoisomer[18] (Scheme 11). In this reaction, unreacted starting material **1a** was recovered in 43% yield without epimerization at C24 position. Based on the NOE spectra of pentacyclic compound **48**, the stereochemistry of the C24 position was determined to be of *S*-configuration. Surprisingly, in contrast to the above described IMDA reaction of γ-methoxylactam **22** via the iminium ion intermediate **23**, the reaction stereoselectively proceeded to give the *exo*-type pentacyclic compound **48**, and its carbon framework and relative stereochemistry were completely consistent with that of CYP3A4 inhibitor diaporthichalasin (**49**).[19] On the other hand, 24-*epi*-oteromycin **1b** was also subjected to a similar reflux condition. However, the IMDA reaction did not proceed, and the starting compound **1b** was quantitatively recovered without epimerization at C24 position. These results indicated that no epimerization had occurred in the process of the IMDA reaction of **1a**.

In conclusion, the first total synthesis of oteromycin (**1a**) based on a second generation synthetic strategy utilizing a one-pot four-step cascade reaction starting from α-selenolactam was successfully achieved. However, the stereochemistry at the C24 position could not be determined in spite of detailed analysis of various spectral data. Therefore, the IMDA reaction between the diene side chain on the decalin skeleton and the α,β-unsaturated lactam was attempted to observe the definitive NOE correlations in the resulting pentacyclic compound. As a result, the ambiguous stereochemistry at C24 position was established to be the *S*-configuration. Thus, a complete structure elucidation of oteromycin (**1a**) was also accomplished.



Scheme 11. The stereochemical elucidation of oteromycin.

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10. *N*-Teoc-protected γ-methoxylactam **9** was synthesized by a similar manner to that of *N*-Boc-protected one. (See Ref. 7a).
11. *Physical data of endo-type pentacyclic compound **24a***: $[\alpha]_D^{22} = -62$ ($c = 0.050$, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) δ 7.50 (1H, s), 7.35–7.31 (2H, m), 7.21–7.16 (3H, m), 6.20 (1H, s), 5.61 (1H, s), 5.38 (1H, s), 4.02 (1H, d, J = 10.5 Hz), 3.35 (1H, d, J = 9.5 Hz), 2.95 (1H, m), 2.64 -2.59 (1H, dd, J = 12.5, 11.0 Hz), 2.57 (1H, m), 1.80 (3H, s), 1.72 (3H, s), 1.65–1.61 (1H, m), 1.54 (3H, s), 1.51–1.46 (1H, m), 1.37–1.30 (1H, m), 1.14 (3H, d, J = 7.6 Hz), 0.98 (3H, s), 0.83 (3H, d, J = 5.1 Hz), 0.83–0.93 (4H, m) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 212.2, 173.3, 138.4, 138.0, 136.8, 136.4, 132.6, 131.0, 129.2, 127.7, 126.6, 105.3, 48.5, 47.0, 44.2, 44.1, 43.9, 43.9 36.0, 35.9, 33.1, 30.0, 27.7, 25.8, 23.4, 22.9, 21.3, 20.3, 16.9, 16.2 ppm; IR (ATR) ν_{max} = 2923, 2349, 2145, 1670, 1219, 1029, 822, 718 cm^{-1}; HRMS (EI) calcd. for $C_{32}H_{39}NO_2$ 469.2981, found 469.2986.
12. Interestingly, thermal IMDA reaction of γ-methoxylactam **22** did not proceed at higher temperature (in toluene, reflux). It is supported that the observed IMDA reaction under the acidic condition proceeded via more reactive iminium ion intermediate **23**.
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14. Similar interesting oxidative approaches to synthesize the non-α-acyl-type γ-hydroxy-γ-lactams (5-hydroxypyrrol-2(5*H*)-ones) were reported by two groups: (a) Boukouvalas, J.; Xiao, Y.; Cheng, Y. X.; Loach, R. P. *Synlett* **2007**, *20*, 3198; (b) Kiren, S.; Hong, X.; Leverett, C. A.; Padwa, A. *Tetrahedron* **2009**, *65*, 6720; (c) Boukouvalas, J.; Loach, R. P.; Ouellet, E. *Tetrahedron Lett.* **2011**, *52*, 5047.
15. In this reaction, the chiral lactam **43** was used because the yield of the aldol reaction with decalin aldehyde **8** (94%) was superior to that of using its enantiomer **38** (47%).
16. *Experimental procedure of one-pot four-step cascade reaction for the synthesis of oteromycin (**1a**)*: To a solution of lactam **47** (10.0 mg, 0.0159 mmol) in THF (1.5 mL) was added $NaHCO_3$ (2.81 mg, 0.0333 mmol) at 0 °C. After stirring for 30 min at 0 °C, MMPP (15.7 mg, 0.0318 mmol) was added, and then the resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution at 0 °C, and the resulting mixture was extracted with AcOEt. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, filtrated, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Hexane/AcOEt = 2:1) to afford the desired oteromycin (**1a**) (4.0 mg, 51%) as a white amorphous with its diastereomer **1b** (1.6 mg, 20%) as a white amorphous.
17. Physical data of synthesized oteromycin (**1a**): $[\alpha]_D^{20} = -116$ ($c = 0.2$, MeOH); lit. $[\alpha]_D^{22} = -60$ ($c = 0.5$, MeOH) (See Ref. 1), ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.40 (1H, d, J = 1.9 Hz), 7.24–7.35 (6H, m), 6.10 (1H, brs), 5.48 (1H, brs), 5.39 (1H, brs), 5.20 (1H, q, J = 6.8 Hz), 3.73 (1H, dd, J = 7.8, 12.2 Hz), 3.17 (1H, d, J = 13.6 Hz), 3.12 (1H, brd, J = 8.0 Hz), 3.04 (1H, d, J = 13.6 Hz), 1.62 (3H, brd, J = 7.1 Hz), 1.61 (3H, s), 1.49 (3H, d, J = 1.0 Hz), 1.46 (3H, s), 1.41–1.80 (5H, m), 0.91–0.98 (3H, m), 0.90 (3H, s), 0.86 (3H, d, J = 6.1 Hz) ppm; ^{13}C NMR (100 MHz, CD_2Cl_2) δ 196.3, 167.7, 154.3, 137.0, 136.8, 135.8, 134.7, 134.1, 133.8, 130.8, 130.0, 128.8, 127.7, 124.7, 86.0, 51.4, 50.2, 48.8, 43.8, 40.3, 36.1, 35.4, 27.8, 24.7, 22.9, 22.0, 20.6, 16.6, 15.1, 13.6 ppm; IR (ATR) ν_{max} = 3310, 2949, 2912, 1723, 1606, 1497, 1451, 1377, 1212, 1086, 1038, 955, 858, 702 cm^{-1}; HRMS (FAB) calcd for $C_{32}H_{42}NO_3$: 488.3165; found: 488.3160 $[M+H]^+$.
18. *Physical data of exo-type pentacyclic compound **48***: $[\alpha]_D^{23} = -133$ ($c = 0.060$, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO) δ 8.67 (1H, s), 7.32–7.23 (5H, m), 5.74 (1H, s), 5.33 (1H, s), 5.09 (1H, s), 2.99 (2H, s), 2.73 (1H, d, J = 8.3 Hz), 2.48 (1H, s), 2.09–1.99 (2H, m), 1.83 (3H, s), 1.58 (3H, s), 1.48 (3H, s), 1.64–1.23 (3H, m), 0.99 (1H, q, J = 12.9 Hz), 0.90–0.77 (2H, m), 0.75 (3H, d, J = 7.8 Hz), 0.74 (3H, s), 0.72 (3H, d, J = 7.3 Hz), 0.58 (1H, t, J = 12.2 Hz), 0.46 (1H, dq, J = 12.4, 3.4 Hz) ppm; ^{13}C NMR (100 MHz, DMSO) δ = 218.7, 174.6, 137.9, 136.4, 134.6, 130.6, 128.0, 127.9, 126.5, 126.0, 87.7, 63.5, 50.0, 49.4, 48.6, 47.7, 44.9, 43.6, 40.9, 35.5, 35.3, 28.7, 26.6, 25.4, 24.9, 22.9, 22.6, 22.3, 19.9, 19.4 ppm; IR (ATR) ν_{max} = 3284, 2947, 2920, 1733, 1683, 1496, 1455, 1376, 1227, 1119, 859, 702 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{42}NO_3$ $[M+H]^+$ 488.3159, found 488.3158.
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