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## 学位論文審査の要旨

博士 (環境科学)

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### 学位論文題名

Total Synthesis of Dolastatin 16  
(ドラスタチン16の全合成)

The use of marine antifouling paints in ships and submersible structures to prevent biofouling causes a dilemma for both economic and environmental reasons. Marine antifouling paints help to reduce additional fuel consumption resulting from increased drag caused by the attachment of colonizing organisms. However, as marine antifouling paints' function is facilitated by their toxic nature, non-target organisms might also be adversely affected. A notorious example is the masculinization of female gastropods by tributyltin, the prevalent antifouling agent since the 1970s. Consequently, the International Maritime Organization ordered the complete ban of TBT paints in 2008. A promising alternative to toxic biocide-based antifouling agents are marine antifouling compounds, secondary metabolites released by marine organisms to prevent fouling of their outer surfaces. Among newly discovered compounds, dolastatin 16, a macrocyclic depsipeptide first isolated from the sea hare *Dolabella auricularia*, was revealed to exhibit potent antifouling activity against the cypris larva of the barnacle *Amphibalanus amphitrite* ( $EC_{50}$  0.003  $\mu\text{g/mL}$ ), without exhibiting biocidal properties ( $LC_{50}$  20  $\mu\text{g/mL}$ ). In order to prove the significant antifouling activity and explore the possibility of its application as a novel non-toxic antifouling agent, the author embarked on establishing a practical

total synthesis of dolastatin 16.

Towards the development of a practical total synthesis of dolastatin 16, the development of robust synthetic methods for its two unusual amino acid units dolaphenvaline and dolamethylleuine was essential. Construction of the contiguous stereogenic centers of the unusual amino acid units was achieved using a highly enantio- and diastereoselective asymmetric Mannich reaction. Using these methods, subgram quantities of the Boc-derivatives of dolaphenvaline and dolamethylleuine with overall yields of 26% (5 steps) and 48% (5 steps) were afforded respectively. In Chapter 2 of this thesis, the author describes the concise and scalable syntheses of these unusual amino acid units.

With enough unusual amino acid units in hand, the assembly of the peptide skeleton of dolastatin 16 was tackled next. Because initial attempt toward the total synthesis of dolastatin 16 using a linear approach was found to be inefficient in providing enough material, a highly convergent route was strategized. This route involves the concise and scalable synthesis of two major segments - the northern and southern segment and the efficient assembly of the two segments to construct the macrocyclic framework of dolastatin 16. The developed synthetic schemes provided subgram amounts of the northern and southern segments with overall yields of 56% (7 steps) and 69% (3 steps), respectively. The synthesis of northern segment features the use of an aminoalcohol instead of the corresponding  $\alpha$ -amino acid as a C-terminal amino acid unit to avoid the undesirable formation of diketopiperazine by the dipeptide sequence containing L-proline and *N*-methyl-D-valine. This method was revealed to be a highly useful strategy for peptide chain elongation in the *N*-terminal direction. Furthermore, the current total synthesis allowed the confirmation of the significant antifouling activity of dolastatin 16. In chapter 3 of this thesis, the author describes the details of the synthesis and antifouling activity of dolastatin 16.

In addition to the excellent academic knowledge in the research, her academic records throughout the Ph. D. course are excellent. Based on these evidences, the committee reached to a conclusion that L. O. Casalme deserves to become a Doctor of Environmental Science.