Tetrahedron Letters 56 (2015) 168–171

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthetic study on dolastatin 16: concise and scalable synthesis of two unusual amino acid units

Taiki Umezawa *, Akinori Sato, Yasuto Ameda, Loida O. Casalme, Fuyuhiko Matsuda *

Division of Environmental Materials Science, Graduate School of Environmental Science, Hokkaido University, Sapporo 060-0810, Japan

ARTICLE INFO

Article history:
Received 8 September 2014
Revised 10 November 2014
Accepted 13 November 2014
Available online 20 November 2014

Keywords:
Dolastatin 16
Unusual amino acid
Total synthesis
Mannich reaction
Organocatalyst

ABSTRACT

A convenient and scalable synthesis of two unusual amino acid units found in dolastatin 16, dolaphenvaline, and dolamethylleuine, is described. Dolastatin 16, which was first isolated from the sea hare *Dolabella auricularia* by Pettit, exhibits not only strong inhibition of growth for a variety of human cancer cell lines but also potent antifouling activity against the larvae of the barnacle *Balanus amphitrite*. The key element of the synthesis is an organocatalytic Mannich reaction to construct two contiguous stereocenters in the amino acid units with almost complete enantio- and diastereoselectivity.

Dolastatin 16 (**1**), a macrocyclic depsipeptide, was first isolated by Pettit as a potential antineoplastic metabolite in 1997 from the sea hare *Dolabella auricularia*, collected in Papua New Guinea (Fig. 1).[1] This unique depsipeptide proved to be a strong growth inhibitor for a variety of human cancer cell lines and a candidate for further development. Five years after the original report, the isolation of **1** from a Madagascan cyanobacterium, *Lyngbya majuscula*, was described by Gerwick.[2] With regard to structural features, **1** contains the new and unusual amino acid units dolaphenvaline (**2**) and dolamethylleuine (**3**). Although the stereostructures of **2** and **3** were not assigned in these publications, their absolute configurations were determined to be (2*S*,3*R*) and (2*R*,3*R*), respectively, through X-ray crystallographic analysis of **1** performed by Pettit in 2011.[3]

In 2010, Tan reported that **1** showed a strong antifouling activity (EC_{50} 0.003 μg/mL) against the larvae of the barnacle *Balanus amphitrite*, as well as low toxicity (LC_{50} 20 μg/mL).[4] Biofouling—that is, adverse growth of marine organisms on manmade submerged structures—results in significant economic and environmental problems. Tributyltin (TBT),[5] which inhibits the settlement of larvae, has been widely used all over the world for this purpose since the early 1960s. However, the deleterious effects of TBT on marine ecosystems prompted the International Maritime Organization (IMO) to call in 2008 for a ban on the use of TBT-based antifouling paint on ships.[6] Since marine organisms prevent fouling of their outer surfaces through the use of natural substances with antifouling properties without causing serious environmental problems, natural antifouling products, especially those with good settlement-inhibiting properties but without biocidal properties, have attracted considerable attention.[7] Among these, **1** shows promise as a lead compound for the development of new environmentally friendly antifouling agents due to its potent antifouling activity and low toxicity.[8]

Because of its intriguing and unprecedented structure, **1** is an attractive target for total synthesis. For the total synthesis of **1**, synthetic methods for the optically active amino acid units **2** and **3** must be developed. Syntheses of these unusual amino acid units have been carried out previously. Scheuer synthesized all four stereoisomers of **2** from both enantiomers of *N*-phthaloyl-3,4-dehydrovaline (**4**) during structure elucidation of kulokekahilide-1, a cytotoxic depsipeptide from the cephalaspidean mollusk

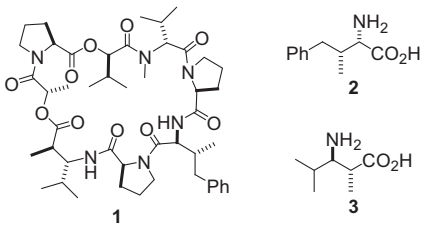
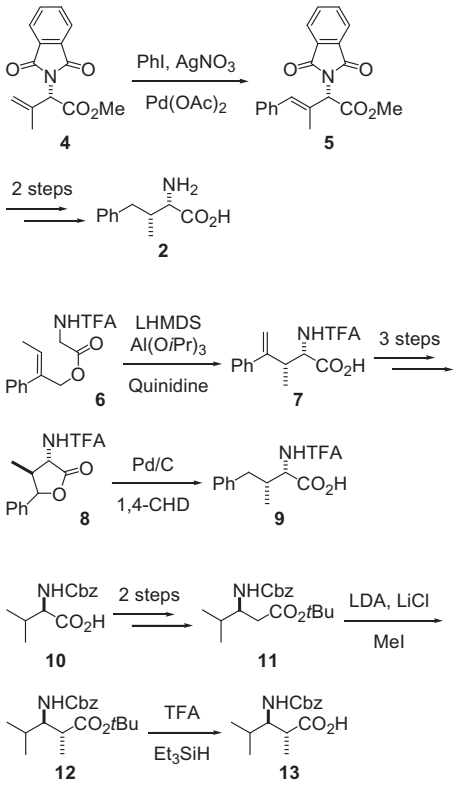


Figure 1. Dolastatin 16 (**1**) and the unusual amino acid units **2** and **3**.

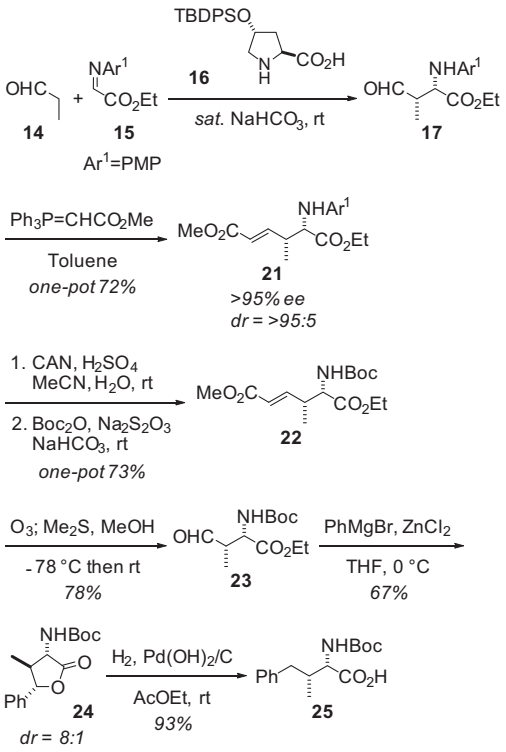
* Corresponding authors. Tel.: +81 11 706 2358; fax: +81 11 706 4517 (T.U.); tel./fax: +81 11 706 4520 (F.M.).

E-mail addresses: umezawa@ees.hokudai.ac.jp (T. Umezawa), fmatsuda@ees.hokudai.ac.jp (F. Matsuda).

http://dx.doi.org/10.1016/j.tetlet.2014.11.054
0040-4039/



Scheme 1. Previous syntheses of **2** and **3**.

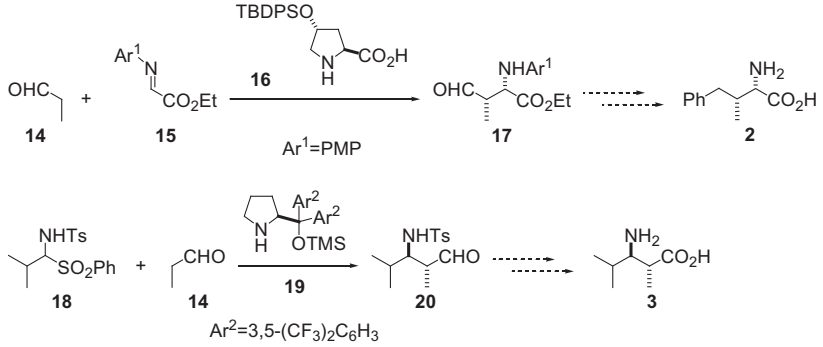


Scheme 3. Stereoselective synthesis of **25**.

Philinopsis speciosa.[9] The synthesis involved a Mizoroki–Heck reaction of **4** with iodobenzene and non-diastereoselective hydrogenation of olefin **5** (Scheme 1). Pettit prepared *N*-TFA-dolaphenvaline (**9**) from allyl ester **6** through asymmetric Claisen rearrangement of **6** to give *syn*-carboxylic acid **7** and hydrogenolysis of lactone **8** derived from **7**.[3] Pettit also achieved a synthesis of *N*-Cbz-dolamethylleuine (**13**) through diastereoselective alkylation[10] of the β-amino acid ester **11** prepared from *N*-Cbz-L-valine (**10**) and cleavage of *t*-butyl ester of *anti*-ester **12**.[3] Although the two amino acid units have been prepared, total synthesis of **1** has not yet been reported.

In conjunction with our program directed toward a practical total synthesis of **1**, we developed a concise and scalable synthetic procedure for the unusual amino acid units **2** and **3** by using highly enantio- and diastereoselective Mannich reactions promoted by chiral organocatalysts.[11,12] This method provides flexible access to a wide variety of congeners of **2** and **3**, such as diastereomers and enantiomers, by simply changing the catalyst or starting material. The synthetic plan for both amino acid units (**2** and **3**) is shown in Scheme 2. We envisioned the derivation of **2** or **3** from *syn*-β-amino aldehyde **17** or *anti*-β-amino aldehyde **20**, which were prepared by Hayashi through enantio- and diastereoselective Mannich reactions with chiral organocatalysts **16** or **19**.[13,14] Herein, we report the asymmetric synthesis of these unusual amino acid units.

First, we synthesized *N*-Boc-dolaphenvaline (**25**) as illustrated in Scheme 3. As reported by Hayashi,[13] a *syn*-Mannich reaction between propanal (**14**) and ethyl α-imino glyoxylate **15** promoted by the chiral organocatalyst **16** afforded *syn*-adduct **17**, which was directly treated with Wittig reagent in a one-pot operation to isolate the *syn*-α,β-unsaturated ester **21** in 72% yield (two steps) with excellent enantio- and diastereoselectivity (>95% ee, dr = >95:5).[15,16] Conversion of the aldehyde into the α,β-unsaturated ester was essential for further transformation because the aldehyde moiety of **17** was labile under the reaction conditions for addition of a phenyl group or removal of the *N*-*p*-methoxyphenyl (*N*-PMP) group. One-pot protecting group manipulation followed by ozonolysis produced aldehyde **23** in 57% yield (three steps). While attempted nucleophilic addition of PhMgBr, PhLi, or $PhCeCl_2$[17] to the aldehyde part of **23** failed, we eventually found that the addition of PhMgBr took place cleanly in the presence of



Scheme 2. Synthetic plan for **2** and **3**.