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Total synthesis of halipeptin A, a potent anti-inflammatory cyclodepsipeptide from a marine sponge

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Abstract—Total synthesis of halipeptin A, a potent anti-inflammatory cyclodepsipeptide, was achieved through proline-catalyzed asymmetric α-oxidation, diastereoselective aldol reaction, silver cyanide-mediated esterification, and macrolactamization.

Halipeptins A (**1**) and B (**2**)[1] are novel 16-membered cyclodepsipeptides isolated from the marine sponge *Haliclona* sp. collected in waters off the Vanuatu Islands by Gomez-Paloma and co-workers in 2001. Halipeptin A is known to show strong anti-inflammatory activity in vivo. In 2002, Gomez-Paloma and co-workers. reported isolation of halipeptin C (**3**) closely related to **1** and **2** from the same sponge, reexamined the original assignments with a novel oxazetidine ring, and corrected the oxazetidine amino acid to thiazoline amino acid in halipeptins A and B (Fig. 1).[2] Snider reported confirmation of the above revision based on synthesis of the oxazetidine amino acid.[3] Halipeptins consist of (*S*)-alanine and three unique components, the thiazoline-amino acid ((ala)Thz), *N*-methyl hydroxyisoleucine (*N*-MeOHIle) (or *N*-MeVal for **3**), and 3-hydroxy-2,2,4-trimethyl-7-methoxy(or hydroxy for **2** and **3**)decanoic acid (HTMMD or HTMHD). The stereostructure at the C3 and C4 of HTMMD and HTMHD remained to be determined except C7, which was confirmed to be *S* by the Mosher method using HTMHD. In addition to their potent biological activities, their intriguing structures led several groups to initiate efforts directed toward the total synthesis.[4–6] The first total synthesis of this unique cyclodepsipeptide, halipeptin A, was accomplished by Ma and co-workers, leading to the structural confirmation of the revised halipeptins.[7] A little later, the Nicolaou group also succeeded in synthesis of halipeptin A and the relatives.[8] These recent reports prompted us to disclose our efforts on the total synthesis of halipeptin A. Our synthesis includes coupling of the ester and amide segments at the HTMMD/(ala)Thz site and final macrocyclization at the *N*-MeOHIle/Ala site. As part of our studies on synthesis of cyclodepsipeptides with biologically interesting activities, we have already demonstrated synthesis of the *N*-MeOHIle derivative.[6]

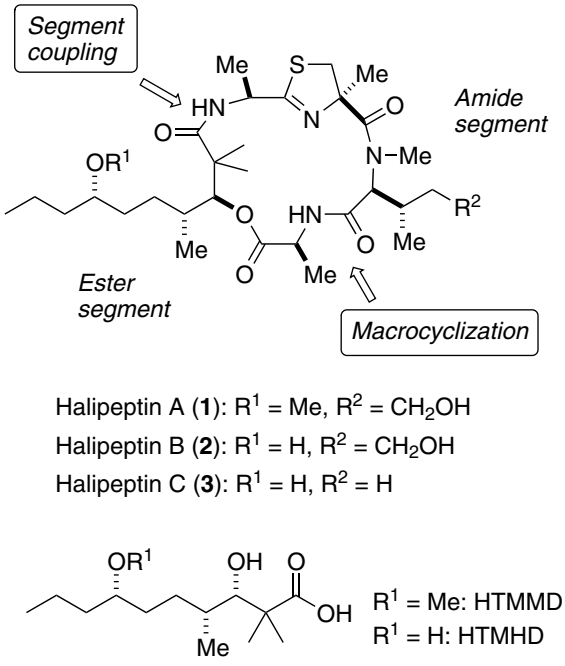

Figure 1.

Keywords: Halipeptin A; Proline-catalyzed asymmetric α-oxidation; Asymmetric aldol reaction; Cyclodepsipeptide; Macrolactamization.
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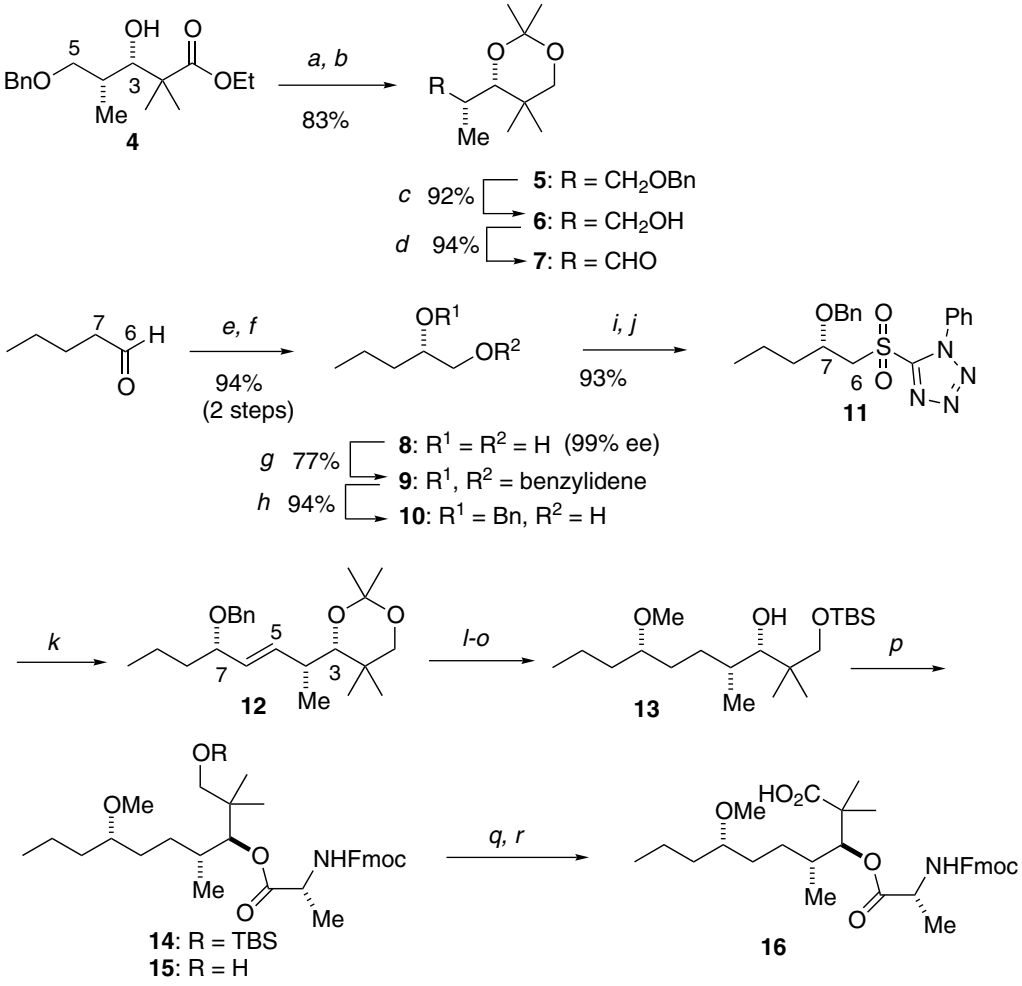
Our study began with convergent synthesis of the ester segment including proline-catalyzed α-oxidation,[9] diastereoselective aldol condensation, and the Julia coupling as the key steps as shown in Scheme 1. Aldol **4** from Kiyooka's chiral oxazaborolidinone-catalyzed asymmetric aldol condensation[10] was converted to acetonide **5** by reduction of **4** and subsequent protection with 2,2-dimethoxypropane and TsOH, which was subjected to deprotection of the benzyl ether and subsequent oxidation of **6** with DMP[11] to give aldehyde **7**. The required sulfone **11** was prepared from (*S*)-pentane-1,2-diol (**8**), which was synthesized from pentanal by introduction of the (*S*)-hydroxy function using proline-catalyzed asymmetric α-oxidation and subsequent reductive removal of the anilino group. Synthesis of benzyl ether **10** by selective protection was carried out by a sequence of benzylidene acetalization with benzaldehyde dimethylacetal and reductive cleavage of the acetal to a benzyl ether with DIBAL-H. Thianation of **10** with *N*-phenyl-5-mercaptotetrazole, DEAD, and triphenylphosphine,[12] and subsequent oxidation with *m*CPBA gave sulfone **11** in excellent yield. The Julia coupling[13] of **7** and **11** was performed by using KHMDS[11] in DME to produce the HTMMD skeleton **12**, which was derivatized to HTMMD building block **13** in four steps by simultaneous hydrogenation of the double bond and the benzyl ether, O-methylation with iodomethane and KHMDS, deprotection of the acetonide, and protection of the primary alcohol with TBSCl. In the Julia coupling, the choice of base was critical for success. Use of lithium hexamethyldisilazide and *n*-butyl lithium, common bases for the Julia coupling, in DME failed to afford the coupling product **12**. Esterification of the HTMMD **13** with Cbz-(*S*)-Ala-OH and EDCI/DMAP[11] provided the ester in 68% yield with slight epimerization of a 3:1 ratio at the alanine residue as the Ma group observed,[7] which was unfortunately inseparable. However, use of Fmoc-(*S*)-Ala-Cl in the presence of silver cyanide in toluene accomplished racemization-free esterification to afford ester **14** in 14% yield but the



Scheme 1. Synthesis of the ester segment **16**. Reagents and conditions: (a) $LiAlH_4$, Et_2O, 23 °C, 5.5 h; (b) 2,2-dimethoxypropane, TsOH, CH_2Cl_2, 23 °C, 15 h, 83% (two steps); (c) H_2, Raney-Ni, MeOH, 23 °C, 14 h, 92%; (d) DMP, CH_2Cl_2, 23 °C, 4 h, 94%; (e) PhNO, (*R*)-proline, $CHCl_3$, 4 °C, 2 h, then $NaBH_4$, EtOH, 5 °C, 35 min, >99% ee; (f) H_2, Pd–C, MeOH, 23 °C, 17 h, 94% (two steps); (g) $PhCH(OMe)_2$, $TsOH{\cdot}H_2O$, PhMe, 23 °C, 17.5 h, 77%; (h) DIBAL-H, CH_2Cl_2, −17 to −10 °C, 1.5 h, 94%; (i) 1-phenyl-5-mercapto-tetrazole, DEAD, Ph_3P, THF, 23 °C, 9.5 h, 94%; (j) *m*CPBA, CH_2Cl_2, 0–23 °C, 16 h, 93%; (k) KHMDS, DME, **7**, −65 to 23 °C, 16 h, 63%; (l) H_2, Raney-Ni, MeOH, 23 °C, 11.5 h, 63%; (m) KHMDS, THF, then MeI, −78 to 23 °C, 5 h, 86%; (n) 6 M HCl–MeOH (4:1), 0–23 °C, 3 h, 100%; (o) TBSCl, imidazole, 0–23 °C, 3 h, 82%; (p) Fmoc-Ala-Cl, AgCN, PhMe, 23 °C, 18 h, 14%; (q) HF–EtOH (1:4), 0 °C, 1 h, 97%; (r) Jones' reagent, acetone, −15 to 0 °C, 3 h.