Natural Products Synthesis

Total Synthesis of Halipeptin A: A Potent Antiinflammatory Cyclic Depsipeptide**

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The halipeptins A (**1**) and B (**2**) are two cyclic depsipeptides that were isolated from the sponge *Haliclona* species by Gomez-Paloma and co-workers.[1,2] Initially, their structures were misassigned as the 17-membered cyclic depsipeptides containing an unusual oxazetidine.[1] One year later the same group reported the revised structures of these two compounds

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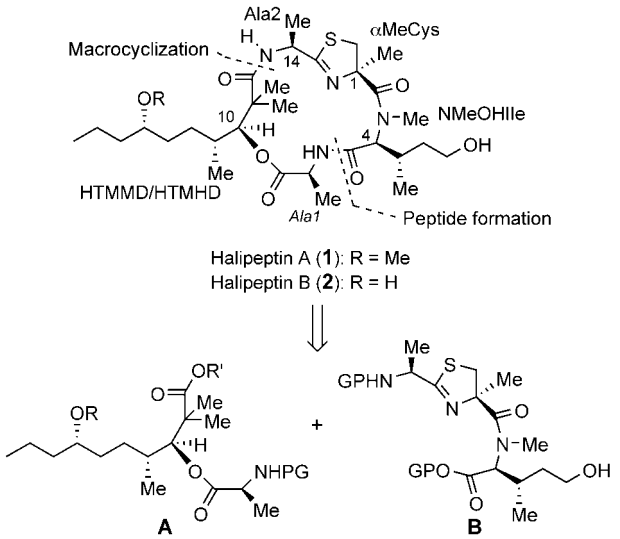
[**] The authors are grateful to the Chinese Academy of Sciences (grant KGCX2-SW-209), the National Natural Science Foundation of China (grant 20321202), and the Science and Technology Commission of Shanghai Municipality (grants 02JC14032 & 03XD14001) for financial support.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 DOI: 10.1002/ange.200461239

as those shown in Scheme 1 which bear two L-alanine residues, an α-methylcysteine unit connected to one of the L-alanine residues through a methylthiazoline ring, and two new residues that had not been discovered from natural

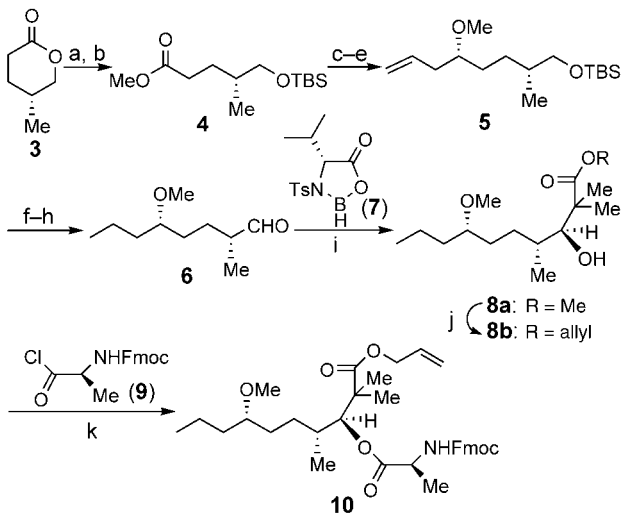


Scheme 1. Structures and retrosynthetic analysis of halipeptins A (**1**) and B (**2**). PG = protecting group.

sources:[2] 3-hydroxy-2,2,4-trimethyl-7-methoxy (or hydroxy) decanoic acid (HTMMD or HTMHD) and *N*-methyl-δ-hydroxyisoleucine (NMeOHIle). Preliminary pharmacological tests revealed that halipeptin A has potent antiinflammatory activity (60% reduction of carrageenan-induced edema at an intraperitoneal dose of 0.3 mg kg^{-1} in mice).[1] The unique structures and important biological characteristics of halipeptins A and B have attracted considerable synthetic attention.[3] As part of the continuing efforts to synthesize of cyclic peptides,[4] we report herein the first total synthesis of halipeptin A and the confirmation of its stereochemistry.

Our retrosynthetic analysis of halipeptin A is outlined in Scheme 1. As this molecule is highly methylated, the most critical problem in its assembly is the connection of the sterically hindered units with other amino acid residues. We envisaged that two less hindered positions could be reserved for late-stage connections, namely the Ala1–NMeOHIle and HTMMD–Ala2 sites. Our plan therefore required the assembly of an ester part **A** and an amide unit **B**, and hence the stereoselective synthesis of the HTMMD, NMeOHIle, and methylthiazoline residues. Because the configurations of C7 of the HTMHD and Cα of the two alanine residues were all established as *S*, the ring system of halipeptin A might have a 1*R*,4*S*,7*S*,10*S*,14*S* configuration, and hence the residues with the corresponding stereochemistry were considered as primary targets. Furthermore, ready racemization at C14 directed by the methylthiazoline group would be another critical problem,[5,6] and therefore the protecting groups for the above two units should be removable under mild conditions.

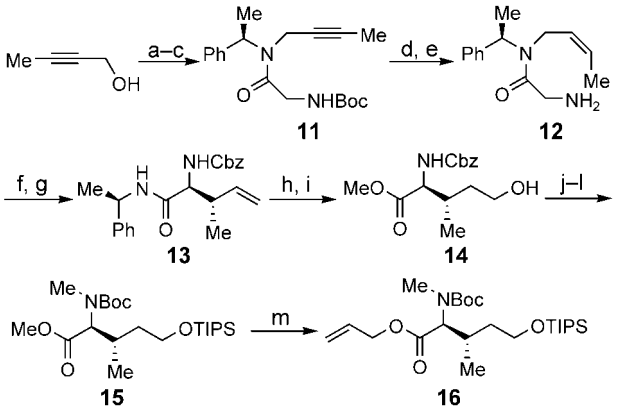
As depicted in Scheme 2, our assembly of the HTMMD unit started from (*R*)-4-methyl-5-valerolactone (**3**), an oxidative degradation product of diosgenin.[7] Ring opening of **3** with methanolic sodium methoxide followed by protection of the hydroxy group as a silyl ether provided **4**. After the ester **4** was reduced to an aldehyde with DIBAL-H, the chain was extended through an asymmetric allylboration based on the procedure of Brown and Racherla[8] to deliver a homoallylic alcohol, which was treated with NaH/MeI to produce ether **5**. Cleavage of silyl ether **5** with TBAF, hydrogenation of the terminal C-C double bond, and Swern oxidation afforded aldehyde **6**. At this stage we planned to build the β-hydroxy-α,α-dimethyl ester part in the HTMMD by an enantioselective chiral borane-mediated aldol reaction.[9] Accordingly, treatment of a mixture of the aldehyde **6** and 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene with the borane **7** at −78 °C produced methyl ester **8a** in 95% yield as a single isomer, which was transformed into allyl ester **8b** through hydrolysis and subsequent alkylation. Esterification of the alcohol **8b** with an *N*-protected L-alanine group proved to be challenging. The method of Yamaguchi and co-workers[10] and other activated ester procedures were unsuccessful. However, we found that coupling of **8b** with acyl chloride **9**[11] at −15 °C in the presence of DMAP (0.5 equiv) gave our desired product **10** in good yield. Notably, both the amount of DMAP used and the reaction temperature are critical, as extensive racemization occurred at Cα of the L-alanine residue when this reaction was conducted at 0 °C in the presence of 0.5 equivalents of DMAP or at −15 °C in the presence of 1 equivalent of DMAP, and low conversion was attained when



Scheme 2. a) NaOMe, MeOH, 0 °C→RT, 82%; b) TBSCl, imidazole, DMF, 98%; c) DIBAL-H, diethyl ether, −100→−90 °C; d) D-B-allyldiisopinocampheylborane; then H_2O_2, NaOH, 90% over three steps; e) NaH, MeI, DMF, room temperature, 91%; f) TBAF, THF, room temperature, 90%; g) Pt/C, H_2, EtOAc, room temperature, 99%; h) Swern oxidation, 85%; i) **7**, 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene, −78 °C, 95%; j) aqueous LiOH, THF, MeOH; then allyl bromide, K_2CO_3, DMSO, 92%; k) **9**, DMAP (0.5 equiv), iPr_2NEt, CH_2Cl_2, −15 °C, 95% yield based on 90% conversion of **8b**. TBS = *tert*-butyldimethylsilyl, DMF = *N*,*N*-dimethylformamide, DIBAL-H = diisobutylaluminum hydride, DMSO = dimethyl sulfoxide, TBAF = tetrabutylammonium fluoride, DMAP = 4-dimethylaminopyridine.

the coupling was carried out at 0 °C in the presence of 0.2 equivalents of DMAP.

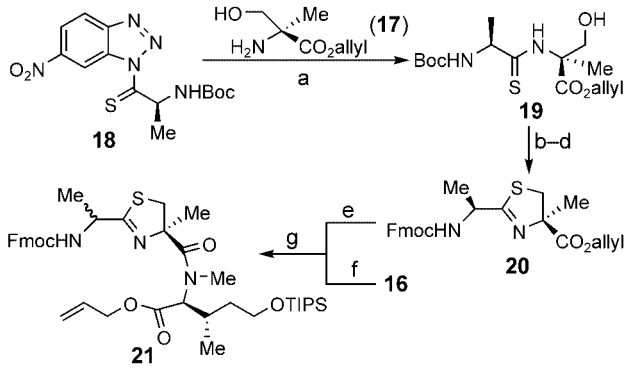
The construction of the NMeOHIle unit relied on an asymmetric aza-Claisen rearrangement developed by Tsunoda et al.[12] Although in their report only diastereoselective rearrangement of *N*-substituted *N*-(*E*)-2-butenylpropanamides to *syn* products was mentioned, based on related studies[13] we reasoned that if olefin (*Z*)-**12** was used, the desired *anti* compound would be the major product. To this end, mesylation of 2-butyn-1-ol followed by introduction of the chiral auxiliary (*R*)-α-methylbenzylamine and subsequent condensation with *N*-Boc-Gly yielded amide **11** (Scheme 3).



Scheme 3. a) MsCl, Et_3N, 82%; b) (*R*)-α-methylbenzylamine, 80%; c) $BocNHCH_2CO_2H$, EDCI, HOBT, *i*Pr_2NEt, 96%; d) Lindlar catalyst, H_2, diethyl ether, 91%; e) CF_3CO_2H, CH_2Cl_2, 96%; f) LiHMDS, THF; g) benzyl chloroformate, Et_3N, 52% over two steps; h) HCl (5 M), MeOH, reflux; then CH_2N_2, diethyl ether, 76%; i) BH_3·THF complex; then H_2O_2, pH 7 buffer, 72%; j) TIPSCl, imidazole, DMAP, 89%; k) Pd/C, H_2, $(Boc)_2O$, MeOH; l) Ag_2O, MeI, DMF, 50 °C, 94% over two steps; m) aqueous LiOH, THF, MeOH; then allyl bromide, K_2CO_3, DMSO, 92%. Ms = methanesulfonyl, Boc = *tert*-butoxycarbonyl, EDCI = ethyl dimethylaminopropyl carbodiimide chloride; HOBT = 1-hydroxy-1*H*-benzotriazole, HMDS = hexamethyldisilazide, TIPS = triisopropylsilyl.

Hydrogenation of **11** with Lindlar catalyst and subsequent deprotection with trifluoroacetic acid delivered the **12**. Exposure of **12** to LiHMDS afforded the aza-Claisen rearrangement products,[12] which were masked with Cbz to give a mixture of diastereomers. ^{1}H NMR spectroscopic analysis revealed that the ratio of the major isomer **13** to other isomers was about 3:1, and pure **13** was isolated in 52% overall yield by recrystallization. Next, removal of the chiral auxiliary from **13** followed by treatment with CH_2N_2 provided a methyl ester, which was then elaborated into the alcohol **14** through a hydroboration–oxidation reaction. After the hydroxy group of **14** was masked as a silyl ether and the *N*-protecting group was changed, methylation was carried out to give **15**. Finally, the methyl ester of **15** was saponified and the resulting acid was treated with allyl bromide to furnish **16**. Notably, Izzo and co-workers recently reported a method to elaborate the NMeOHIle unit through a similar strategy.[3c]

In a parallel procedure, treatment of (*S*)-α-methylserine allyl ester (**17**) with the thioacylating agent **18**[14] produced the thioamide **19**. The Boc protecting group was exchanged for a Fmoc group, and subsequent exposure to DAST[15] afforded the methylthiazoline **20** (Scheme 4). Removal of the allyl protecting group from **20** by a Pd^0-catalyzed reaction[16] gave

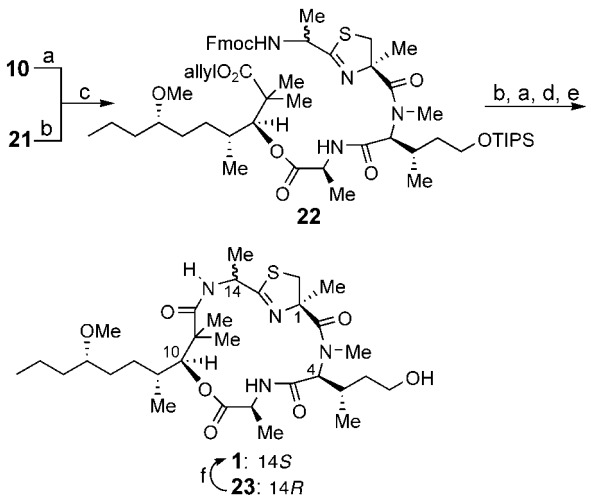


Scheme 4. a) Et_3N, CH_2Cl_2, 50%; b) CF_3CO_2H, CH_2Cl_2; c) FmocOSu, Na_2CO_3, dioxane, H_2O, 75% for two steps; d) DAST, CH_2Cl_2, −78 °C, 89%; e) $[Pd(PPh_3)_4]$, *N*-methylaniline, CH_2Cl, room temperature; f) $AlCl_3$, CH_2Cl_2; g) BEP, *i*Pr_2NEt, CH_2Cl_2, 71% from **16**. Fmoc = 9-fluorenylmethyloxycarbonyl, Su = succinimide; DAST = (diethylamino)sulfur trifluoride; BEP = 2-bromo-1-ethyl pyridinium tetrafluoroborate.

the corresponding acid, which was coupled with the amine liberated from **16**[17] in the presence of BEP[18] as an activating agent to deliver the dipeptide part **21**. Partial racemization at Cα of the L-alanine residue still occurred, even under the very mild conditions, and two isomers (3:1) were determined by ^{1}H NMR spectroscopy. Clearly, installation of the methylthiazoline ring at the ultimate stage of this total synthesis might avoid the racemization problem.[5] Toward this goal, we attempted to link the NMeOHIle residue to various *N*-substituted (*S*)-α-methylserines, but failed to obtain any coupling products as a result of steric hindrance.

The final steps of the synthesis of halipeptin A are described in Scheme 5. Deprotection of **10** with diethylamine and of **21** through palladium-mediated reactions liberated the amine and acid, respectively, which were coupled to afford **22**. Sequential deprotection of **22** provided an amino acid, which was subjected to macrocyclization. To our delight, this transformation worked well in the presence of HATU[19] as the coupling agent and delivered **1** (27% yield from **22**) and its 14-epimer **23** (5% yield from **22**) after cleavage of the silyl ether with TBAF. The 5:1 ratio for **1** to **23** indicated that isomerization at C14 occurred after cyclization because the ratio for two isomers in **21** was only 3:1. Indeed, partial conversion of **23** into **1** (≈2.4:1) was seen by exposure **23** to TBAF in THF. A similar phenomenon was observed by the groups of Wipf[5b] and Pattenden.[5c] The analytical data of **1** were identical with those reported and thus confirmed the stereochemistry of halipeptin A proposed by Gomez-Paloma and co-workers.

Today, the vast majority of antiinflammatory drugs are cyclooxygenase (COX) enzyme inhibitors and lead to several side effects. The unique structures of the halipeptins imply that their mechanism of action is different to that of current drugs, thus making them ideal leads for the discovery of novel



Scheme 5. a) Et_2NH, MeCN; b) $[Pd(PPh_3)_4]$, *N*-methylaniline, CH_2Cl_2, room temperature; c) BEP, iPr_2NEt, CH_2Cl_2, 71% from **21**. d) HATU, iPr_2NEt, DMF/CH_2Cl_2 (1:4); e) TBAF, THF; 27% (for **1**) and 5% (for **23**) overall yield from **22**; f) TBAF, THF, 2.4:1 ratio for **1** and **23** determined by HPLC. HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-ylmethylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide.

antiinflammatory agents.[20] The total synthesis and structure confirmation of halipeptin A presented herein should represent a significant step in this campaign. Further structure–activity relationship studies are actively being pursued in this laboratory and will be reported in due course.

Received: July 8, 2004

Keywords: amino acids · macrocyclization · natural products · peptides · total synthesis

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