Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 47 (2006) 1081–1085
Tetrahedron Letters

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

Sousuke Hara, Kazuishi Makino and Yasumasa Hamada*

Graduate School of Pharmaceutical, Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received 4 November 2005; revised 2 December 2005; accepted 7 December 2005

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]

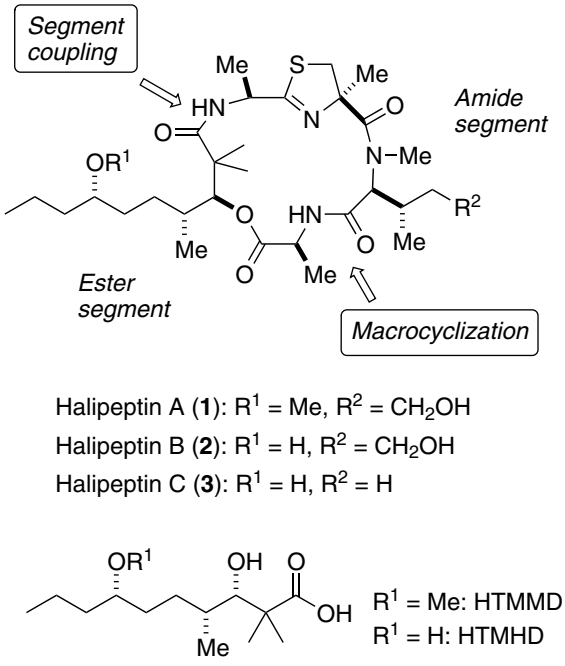
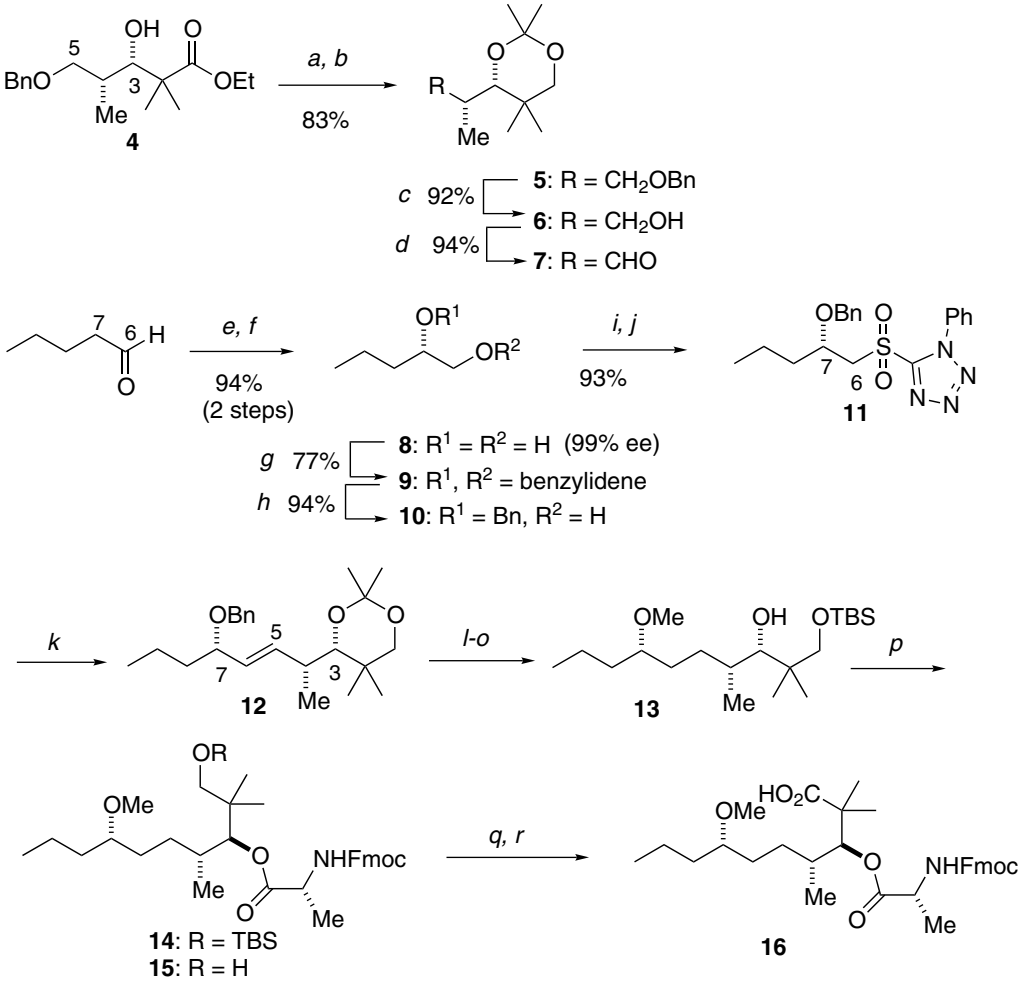


Figure 1.

Keywords: Halipeptin A; Proline-catalyzed asymmetric α-oxidation; Asymmetric aldol reaction; Cyclodepsipeptide; Macrolactamization.
* Corresponding author. Tel./fax: +81 43 290 2987; e-mail: hamada@p.chiba-u.ac.jp

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.026

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

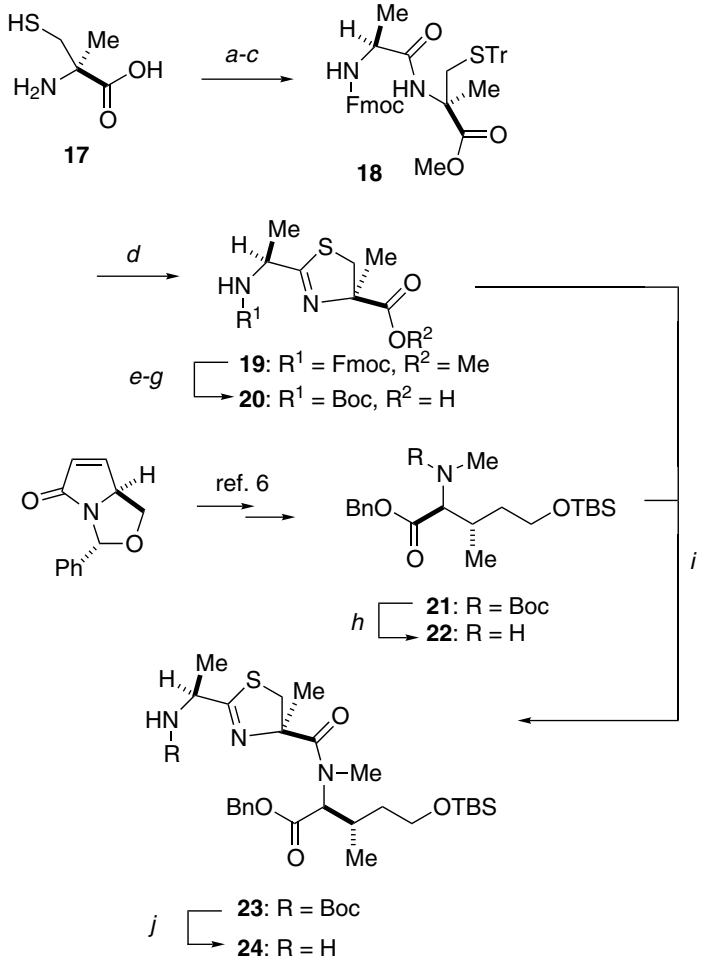


Scheme 1. Synthesis of the ester segment **16**. Reagents and conditions: (a) $LiAlH_4$, Et_2O, 23 °C, 5.5 h; (b) 2,2-dimethoxypropane, TsOH, CH_2Cl_2, 23 °C, 15 h, 83% (two steps); (c) H_2, Raney-Ni, MeOH, 23 °C, 14 h, 92%; (d) DMP, CH_2Cl_2, 23 °C, 4 h, 94%; (e) PhNO, (*R*)-proline, $CHCl_3$, 4 °C, 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.

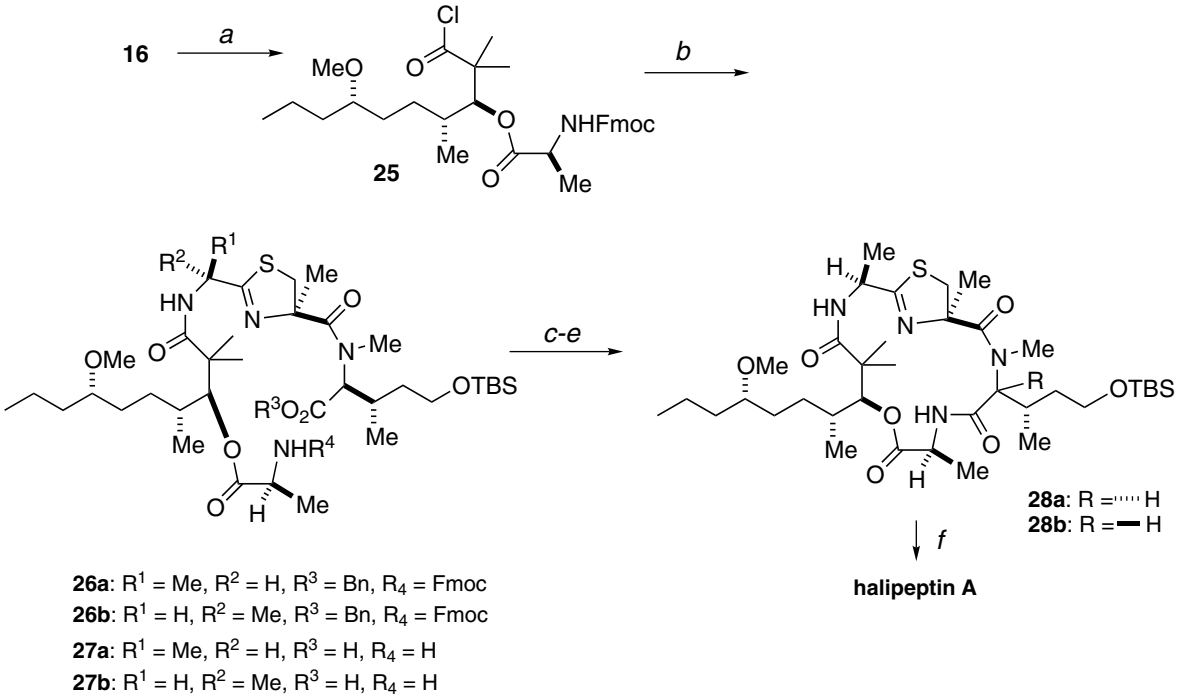
chemical yield remained to be improved. Deprotection of the silyl ether in **14** and oxidation of the resulting **15** with Jones' reagent afforded ester segment **16**.

As depicted in Scheme 2, the amide segment **24** was prepared from the known α-methylcysteine **17**, which was converted to thiazoline **19** in four steps according to the Kelly method[14] for preparation of a thiazoline from cysteine. *S*-Tritylation of **17** with trityl alcohol and borontrifluoride etherate, esterification of the protected amino acid with thionyl chloride and methanol, condensation of the methyl ester with Fmoc-(*S*)-Ala-OH and EDCI/DIEA, and deprotective cyclization of the resulting dipeptide **18** with triphenylphosphine oxide and triflic anhydride afforded thiazoline **19** in 53% yield from **17**. Deprotection of the Fmoc group in **19** was achieved by use of TBAF in THF–DMF and reprotection with Boc_2O followed by saponification with lithium hydroxide provided thiazoline building block **20**. Coupling of **20** with *N*-MeOHIle **22** derived from **21**,[6] which was previously prepared from the bicyclic α,β-unsaturated lactam,[15] was difficult by even using several coupling reagents due to the severe steric congestion. Fortunately, use of BMTB/DIEA[11,16] successfully effected the condensation to give amide **23** in 94% yield. However, the thus-obtained **23** was found to be a mixture of the diastereomers. Careful experiment revealed that the saponification of Boc-(*S*)-(ala)Thz-OMe with lithium hydroxide caused severe epimerization at the α-position of the thiazoline. The mixture was used for further elaboration because the problem could be solved at the later step. Deprotection of the Boc group with TMSOTf and 2,6-lutidine provided amide segment **24**.

Activation of ester segment **16** to acid chloride **25** with oxalyl chloride in methylene chloride followed by coupling with **24** in the presence of DIEA smoothly proceeded to afford a mixture of linear precursor **26a** and epimer **26b** at the α-position of the thiazoline in 89% yield (Scheme 3). Fortunately, protection-free precursor **27a** from the respective deprotection of the Fmoc group and the benzyl ester with diethylamine and Pd black was separable with epimer **27b** by chromatography and was obtained in 40% yield along with 35% yield of **27b**. Macrolactamization of pure **27a** using HATU[11]/DIEA furnished protected halipeptin A (**28a**) in 61% yield together with 29% yield of epimer **28b**, which was generated from racemization at the *N*-MeOHIle residue



Scheme 2. Synthesis of the amide segment **24**. Reagents and conditions: (a) TrOH, $BF_3{\cdot}OEt_2$, AcOH, 80 °C, 0.5 h; (b) $SOCl_2$, MeOH, reflux, 11 h; (c) Fmoc-Ala-OH, EDC, DIEA, CH_2Cl_2, 0–23 °C, 10.5 h, 70% (three steps); (d) $Ph_3P(O)$, Tf_2O, CH_2Cl_2, −18 to −10 °C, 3.5 h, 75%; (e) TBAF, THF–DMF (5:1), 0–23 °C, 5 h; (f) Boc_2O, 23 °C, 2 h, 87% (two steps); (g) LiOH, THF–H_2O (4:1), 0–23 °C, 1.5 h; (h) TMSOTf, 2,6-lutidine, CH_2Cl_2, 90%; (i) BMTB, DIEA, CH_2Cl_2, 0–23 °C, 94% (from **22**); (j) TMSOTf, 2,6-lutidine, CH_2Cl_2, 23 °C, 2 h, 77%.



Scheme 3. Construction of halipeptin A. Reagents and conditions: (a) $(COCl)_2$, CH_2Cl_2, 23 °C, 5 h; (b) **24**, DIEA, CH_2Cl_2, 0–23 °C, 6.5 h, 89% from **15**; (c) Et_2NH–MeCN (1:1), 0–23 °C, 1.5 h, 97%; (d) H_2, Pd-black, MeOH–buffer (10:1), 23 °C, 8 h, 40% and 35% of the epimer; (e) HATU, DIEA, CH_2Cl_2, 23 °C, 24 h, 61% and 29% of the epimer; (f) 4 M HCl–dioxane, ether, 0–23 °C, 4 h, 35% and 50% of the epimer.

during the cyclization. Final deprotection of the TBS group in **28a** was carried out using 4 M HCl–dioxane, which caused again extensive epimerization at the α-position of the thiazoline. Pure halipeptin A (**1**)[17] was obtained after chromatographic purification in 35% yield. Interestingly, when [(*R*)-(ala)Thz]-epimer **27b** was subjected to macrolactamization under the same conditions, the TBS ether of [(*R*)-(ala)Thz]-halipeptin A was obtained in 73% yield without any epimerization at the *N*-MeOHIle residue.

In conclusion, we have succeeded in total synthesis of halipeptin A through stereoselective construction of the HTMMD fragment. Further studies on the synthesis of halipeptins and the relatives for biological evaluation are underway.

Acknowledgements

This work was financially supported in part by Grant-in-Aid for Scientific Research on Priority Areas (17035015) from The Ministry of Education, Culture, Sports, Science, and Technology (MEXT). We are grateful for a JSPS research fellowship for young scientists (to S.H.).

References and notes

1. Randazzo, A.; Bifulco, G.; Giannini, C.; Bucci, M.; Debitus, C.; Cirino, G.; Gomez-Paloma, L. *J. Am. Chem. Soc.* **2001**, *123*, 10870–10876.
2. Monica, C. D.; Randazzo, A.; Bifulco, G.; Cimino, P.; Aquino, M.; Izzo, I.; De Riccardis, F.; Gomez-Paloma, L. *Tetrahedron Lett.* **2002**, *43*, 5707–5710.
3. Snider, B. B.; Duvall, J. R. *Tetrahedron Lett.* **2003**, *44*, 3067–3070.
4. Monica, C. D.; Maulucci, N.; De Riccardis, F.; Izzo, I. *Tetrahedron: Asymmetry* **2003**, *14*, 3371–3378.
5. Izzo, I.; Avallone, E.; Corte, L. D.; Maulucci, N.; De Riccardis, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1181–1186.
6. Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron* **2004**, *60*, 8031–8035.
7. Yu, S.; Pan, X.; Lin, X.; Ma, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 135–138.
8. Nicolaou, K. C.; Kim, D. W.; Schlawe, D.; Lizos, D. E.; de Noronha, R. G.; Longbottom, D. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 4925–4929.
9. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.
10. Kiyooka, S.-I.; Kaneko, Y.; Komura, M.; Matsuo, H.; Nakano, M. *J. Org. Chem.* **1991**, *56*, 2276–2278.
11. Abbreviations: DMP (Dess–Martin periodinane), DEAD (diethyl azodicarboxylate), KHMDS (potassium hexamethylsilazide), EDCI (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride), DMAP (4-(dimethylamino)pyridine), DIEA (*N*,*N*-diisopropylethylamine), BMTB (2-bromo-3-methyl-4-methylthiazolium bromide), HATU (*O*-(7-azabenzotriazol-1yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate).
12. Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365–366.
13. Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833–4836.
14. You, S.-L.; Razavi, H.; Kelly, J. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 83–85.
15. (a) Hamada, Y.; Kawai, A.; Kohno, Y.; Hara, O.; Shioiri, T. *J. Am. Chem. Soc.* **1989**, *111*, 1524–1525; (b) Hamada,

Y.; Hara, O.; Kawai, A.; Kohno, Y.; Shioiri, T. *Tetrahedron* **1991**, *47*, 8635–8652; (c) Okamoto, N.; Hara, O.; Makino, K.; Hamada, Y. *Tetrahedron: Asymmetry* **2001**, *12*, 1353–1358.

16. Wischnat, R.; Rudolph, J.; Kaese, R.; May, A.; Theis, H.; Zuther, U. *Tetrahedron Lett.* **2003**, *44*, 4393–4394.
17. Synthetic halipeptin A: $[\alpha]_D^{24}$ −11.8 (*c* 0.035, $CHCl_3$) (lit. −16.6 (*c* 0.029, $CHCl_3$)); IR ν_{max} 3851, 3451, 2925, 2055, 1749, 1636, 1507, 1455, 1260, 1032, 801, 655 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.81 (3H, d, $J = 7.0$ Hz), 0.91 (3H, t, $J = 7.0$ Hz), 0.98 (3H, d, $J = 6.4$ Hz), 1.13 (3H, s), 1.20 (3H, s), 1.25–1.58 (10H, m), 1.42 (3H, d, $J = 7.3$ Hz), 1.48 (3H, s), 1.51 (3H, d, $J = 7.0$ Hz), 1.91–1.92 (1H, m), 2.51–2.52 (1H, m), 2.82 (3H, s), 3.08–3.10 (1H, m), 3.298 (3H, s), 3.302 (1H, d, $J = 11.9$ Hz), 3.63–3.66 (1H, m), 3.77–3.79 (1H, m), 4.16 (1H, d, $J = 12.2$ Hz), 4.71 (1H, d, $J = 2.8$ Hz), 4.76–4.87 (2H, m), 5.08 (1H, d, $J = 10.4$ Hz), 7.01 (1H, $J = 8.2$ Hz), 7.22 (1H, d, $J = 7.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.3, 14.4, 18.0, 18.4, 18.5, 22.0, 22.3, 23.1, 26.2, 28.2, 30.7, 31.2, 31.9, 34.2, 35.2, 35.7, 44.3, 45.8, 48.6, 49.6, 56.5, 60.9, 64.7, 80.6, 82.6, 83.9, 169.2, 169.6, 172.5, 173.6, 177.3. FAB-HRMS calcd for $C_{31}H_{55}N_4O_7S$ (M+H): 627.3791. Found: 627.3743.