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Asymmetric Total Syntheses of Marine Cyclic Depsipeptide Halipeptins A–D

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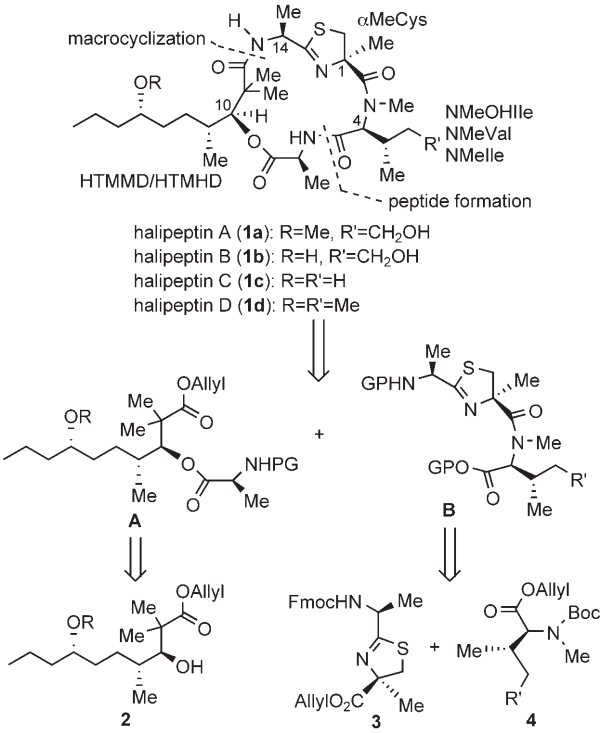
Abstract: Halipeptins A–D (**1a–d**) are a family of natural cyclic depsipeptides isolated from marine sponges. Total syntheses of these four compounds are detailed in this report. The key elements in this synthesis include the elaboration of the polysubstituted decanoic acid parts by two asymmetric aldol reactions, assembly of the *N*-methyl-δ-hydroxyisoleucine residue by using either aza-Claisen rearrangement or methylation of aspartates as the key steps, and macrocyclization at the polysubstituted decanoic acid alanine site.

Keywords: cyclic depsipeptides · macrocyclization · natural products · total synthesis · unnatural amino acids

Introduction

Halipeptins A–D (**1a–d**, Scheme 1) are a family of natural cyclic depsipeptides recently isolated from marine sponges.[1] The structures of **1a** and **b** were initially assigned as the 17-membered cyclic depsipeptides containing an unusual 1,2-oxazetidine based on MS and NMR spectroscopic analysis by Gomez-Paloma and co-workers.[1a] One year later another member of this family, namely halipeptin C (**1c**), was isolated by the same group and was accurately assigned as a thiazoline-containing structure, which led to the revision of the structures for halipeptins A and B from the oxazetidine structures to the thiazoline structures, respectively.[1b] During the same period, Manam and Faulkner discovered halipeptin D from the marine sponge *Leiosella* cf. *arenifibrosa* collected in the northwestern waters off Boracay Island (Philippines).[1c] Structurally, these four compounds all bear two L-alanine residues, one of which is connected to an α-methylcysteine unit through a methylthiazoline ring. One difference in the structure of these compounds comes from their polysubstituted decanoic acid parts as evidenced by 3-hydroxy-2,2,4-trimethyl-7-methoxy decanoic acid (HTMMD) in halipeptins A and D, and 3-hydroxy-2,2,4-trimethyl-7-hydroxy decanoic acid (HTMHD) in halipeptins B and C. Another difference in these structures is in their *N*-methyl amino acid fragments as *N*-methyl-δ-hydroxyisoleu-



Scheme 1. Strategic bond disconnections of halipeptins A–D. PG = protecting group.

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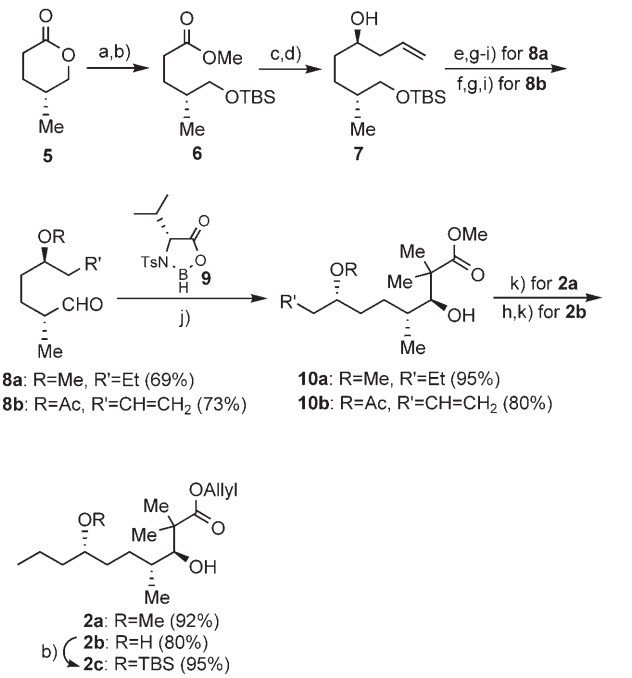
cine (NMeOHIle) was found in halipeptins A and B, *N*-methyl valine (NMeVal) in halipeptin C, and *N*-methyl isoleucine (NMeIle) in halipeptin D. A noteworthy point is that HTMMD, HTMHD, and NMeOHIle residues had never been discovered from other natural resources. Preliminary pharmacological tests revealed that halipeptin A has potent anti-inflammatory activity (60% reduction of carrageenan-induced edema at an intraperitoneal dose of 0.3 mg kg^{-1} in mice),[1a] while the natural halipeptin D exhibited a strong in vitro inhibitory activity against a human colon cancer (HCT-116) cell line ($IC_{50}=7$ nM) and a BMS ODCA (oncology diverse cell panel) of tumor cell lines ($IC_{50}=420$ nM).[1c] The unique structures and important biological characteristics displayed by halipeptins have attracted considerable synthetic attention.[2] The first total synthesis and structural confirmation of halipeptin A was disclosed by our group in early 2005.[2e] Later, Nicolaou and co-workers reported their story for the construction of halipeptins A and D. Interestingly, the synthetic halipeptin D exhibited only weak cytotoxicity against the human colon cancer (HCT-116) cell line ($IC_{50}=32.5$ μM).[2f] The reason behind these controversial results is as yet unclear. Recently, the third total synthesis for halipeptin A was described by the Hamada group.[2g] In this report, we wish to detail our efforts on the assembly of all the members of the halipeptin family.

Retrosynthetic analysis: The strategic bond disconnections of the halipeptins are outlined in Scheme 1. As these molecules are highly methylated, the most critical problem in their 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 Ala1-NMeAA and HTMMD/HTMHD-Ala2 sites. Our plan therefore required the elaboration of ester parts **A** and amide units **B**, and hence the stereoselective synthesis of the building blocks polysubstituted decanoic acids **2**, α-methylthiazoline **3**, and *N*-methyl amino acids **4**. Furthermore, ready racemization at C14 directed by the α-methylthiazoline group would be another critical problem,[3,4] and therefore the protecting groups for all these units should be removable under mild conditions.

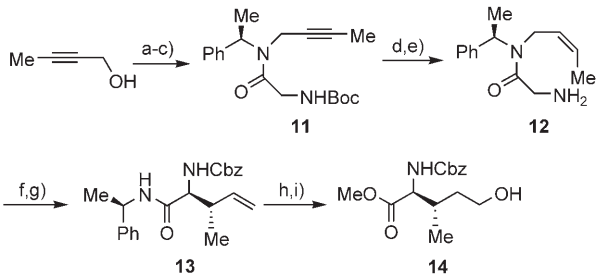
Results and Discussion

Synthesis of the HTMMD and HTMHD units: Our campaign towards halipeptins began from the assembly of polysubstituted decanoic acids units. As depicted in Scheme 2, (*R*)-4-methyl-5-valerolactone **5**, an oxidative degradation product of diosgenin,[5] was chosen as the starting material. Ring opening of **5** with methanolic sodium methoxide followed protection of the hydroxy group as the silyl ether afforded **6**. Reduction of ester **6** with DIBAL-H gave an aldehyde,[6] which was subjected to asymmetric allylboration based on the procedure by Brown and Racherla[7] to deliver homoallyl alcohol **7**. Methylation of **7** with NaH/MeI followed by cleavage of the silyl ether with TBAF yielded an alcohol. Hydrogenation of the terminal C=C double bond and subsequent Swern oxidation of the primary alcohol produced aldehyde **8a** in 69% yield. Meanwhile, protection of alcohol **7** with an acyl group, removal of TBS group, and Swern oxidation gave aldehyde **8b** in a yield of 73% for three steps. At this stage we planned to build the requisite β-hydroxy-α,α-dimethylester part by an enantioselective chiral-borane-mediated Mukaiyama-aldol reaction.[8] Accordingly, treatment of the aldehydes **8a** and **b** with 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene in the presence of borane **9** at −78 °C produced methyl esters **10a** and **b**, respectively, as single isomers. Assembly of the HTMMD unit **2a** from **10a** was accomplished by hydrolysis with LiOH and subsequent esterification with allyl bromide. In a parallel procedure, hydrogenation of **10b** followed by switching of the methyl ester to an allyl ester produced the HTMHD fragment **2b**, which was protected with TBSCl to give silyl ether **2c**.



Scheme 2. Synthesis of the HTMMD and the HTMHD unit. a) NaOMe, MeOH, 0 °C→RT, 82%; b) TBSCl, imidazole, DMF, 98%; c) DIBAL-H, ether, −90 °C; d) [D]B-allyldiisopinocampheylborane, then H_2O_2, NaOH, 90% yield for 2 steps; e) NaH, MeI, DMF, RT; f) Ac_2O, TEA, DMAP, CH_2Cl_2, RT; g) TBAF, THF; h) Pt/C, H_2, EtOAc; i) Swern oxidation; j) 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene, borane **9**, CH_2Cl_2, −78 °C; k) aq. LiOH, THF, MeOH, then allyl bromide, K_2CO_3, DMSO, RT. TBS = *tert*-butyldimethylsilyl; DIBAL = diisobutylaluminun hydride; TBAF = tetrabutylammonium fluoride; DMAP = 4-dimethylaminopyridine.

Syntheses of *N*-methyl amino acid units: NMeOHIle residue is the most complex unit of the three *N*-methyl amino acids in the halipeptins. Our initial approach to this residue is outlined in Scheme 3. The route was based on an asymmetric aza-Claisen rearrangement developed by Tsunoda et al.[9]

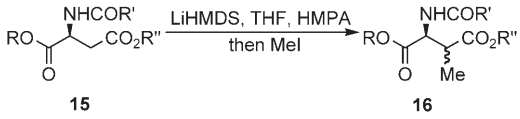


Scheme 3. First-generation synthesis of the NMeOHIle unit. a) MsCl, Et_3N, −20°C→RT; b) (*R*)-α-methylbenzylamine, 65% (2 steps); c) *N*-Boc-Gly, EDCI, HOBT, iPr_2NEt, 0°C→RT, 96%; d) Lindlar catalyst, H_2, ether, RT 91%; e) TFA, CH_2Cl_2, 96%; f) LiHMDS, THF, −78°C→RT; g) CbzCl, Et_3N, DMAP, CH_2Cl_2, RT, 52% yield for 2 steps; h) HCl (5 N), MeOH, reflux, then CH_2N_2, ether, 76%; i) BH_3·THF; then H_2O_2, pH 7 buffer, 72%; EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; HOBT = 1-hydroxy-1*H*-benzotriazole; TFA = trifluoroacetic acid; HMDS = hexamethyldisilazide.

Although in their report only diastereoselective rearrangement of N-substituted *N*-(*E*)-2-butenylpropanamides to *syn* products was mentioned,[9] according to the related studies[10] we envisaged that if (*Z*)-olefin **12** was used, the desired *anti* product 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**. Partial hydrogenation of **11** with Lindlar catalyst and subsequent deprotection with trifluoroacetic acid delivered the (*Z*)-olefin **12**. Exposure of **12** to LiHMDS afforded the aza-Claisen rearrangement products,[9] which were masked with Cbz to give a mixture of diastereomers. ^{1}H NMR spectroscopic analysis revealed that the ratio of 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 to alcohol **14** through a hydroboration/oxidation operation.

Although the above protocol could provide the desired intermediate **14**, the moderate diastereoselectivity in the asymmetric aza-Claisen rearrangement step prompted us to develop an alternative synthetic route. Consequently methylation of aspartates was considered because its product could be easily converted into **14** through a carbon chain elongation.

Literature survey indicated that diastereoselectivity for the alkylation of aspartates relies highly on the bulkiness of the alkylation agents. When allyl halides, benzyl bromide, and *tert*-butyl bromoacetate were employed, moderate to excellent diastereoselectivity was observed.[11] However, only 3:1 to 1:1 diastereoselectivity has been recorded for methylation except, for Chamberlin's report.[12] As Chamberlin's products were not satisfactory for our synthetic purpose,[12d] we decided to study the methylation with protected aspartates by using Hanessian's reaction conditions (Scheme 4).[11b] Accordingly, methylation of *N*-Cbz-Asp(OTMSE)-OMe **15a** was conducted in mixed THF and



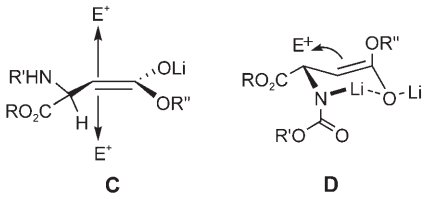
Scheme 4.

HMPA by using LiHMDS as the base. Unfortunately, poor diastereoselectivity was obtained as a 3:2 diastereomeric mixture was detected by ^{1}H NMR spectroscopy (Table 1, entry 1). This ratio was much lower than that observed in Hanessian's allylation reaction, which showed the importance of steric hindrance in the alkylation agents. Considering that in Chamberlin's studies bulkier N-protecting groups were favored for *anti* selectivity,[12d] we next checked N-Boc protected aspartate **15b**, but surprisingly found that the selectivity was still poor (entry 2). However, when α-*tert*-butyl ester **15c** was employed, the ratio for *anti* and *syn* isomers reached 3.5:1 (entry 3). Encouraged by this result, further optimization was undertaken by tuning the other protecting groups in aspartates. We were pleased to find that excellent diastereoselectivity could be achieved by reducing the size of the β-ester moiety (entries 4 and 5). Taken together, we concluded that in the methylation reaction larger α- and smaller β-esters in aspartates are favored for *anti* selectivity. This rule might be extended to the other alkylation reactions of aspartates. The model proposed by Chamberlin and co-workers could not rationalize the present selectivity because, as indicated in model **C** for our substrates, there is not a big difference in steric hindrance between either side of the enolate.[12d] However, transition-state **D** based on an ordered Zimmerman–Traxler-type model could be used to explain our results.[13,11c] The stereochemical outcome of the alkylation reaction is due to 1,2-asymmetric induction of dianionic aspartates. Obviously, this transition state benefited from increased hindrance of R and decreased hindrance of R′ and R″.

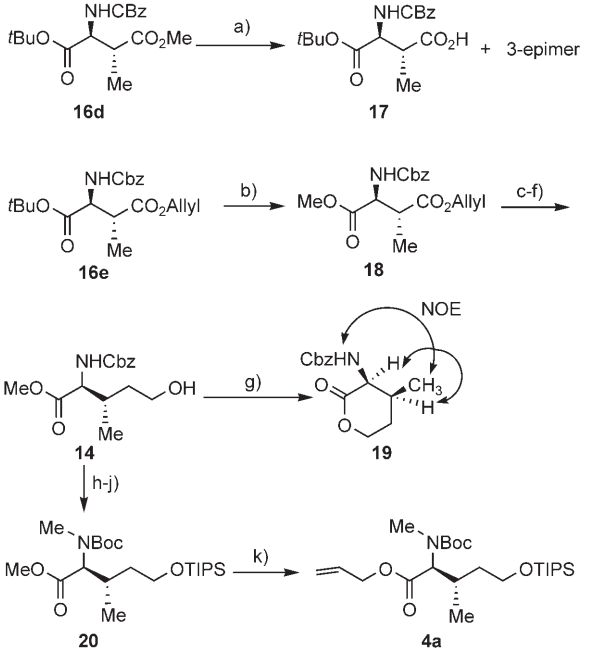
Table 1. Methylation of aspartates.

Entry	Substrate	R	R′	R″	Product	Yield [%][a]	*anti*/*syn*[b]
1	**15a**	Me	Bn	TMSE	**16a**	81	1.5:1
2	**15b**	Me	*t*Bu	Bn	**16b**	74	2.3:1
3	**15c**	*t*Bu	Bn	TMSE	**16c**	77	3.5:1
4	**15d**	*t*Bu	Bn	Me	**16d**	94	>20:1
5	**15e**	*t*Bu	Bn	allyl	**16e**	91	>20:1

[a] Isolated yield. [b] Determined by ^{1}H NMR spectroscopy.



After our success in the highly diastereoselective methylation of aspartates, we next attempted to convert the alkylation products into the desired NMeOHIle unit **4a** (Scheme 5). Initially, methyl ester **16d** was chosen for this



Scheme 5. Second-generation synthesis of the NMeOHIle unit. a) aq. LiOH, MeOH, THF; b) TFA, CH_2Cl_2, then CH_2N_2, Et_2O, RT, 95%; c) $[Pd(PPh_3)_4]$, NMA, CH_2Cl_2, RT; d) $ClCOiBu$, NMM, THF, −20°C then CH_2N_2, Et_2O, −20°C→RT; e) $AgNO_3$, H_2O, THF; f) $ClCO_2Et$, NMM, THF, 0°C then $NaBH_4$, MeOH, 0°C→RT 35% yield for 4 steps; g) $TsOH{\cdot}H_2O$, PhH, reflux, 75%; h) TIPSCl, imidazole, DMAP, CH_2Cl_2, RT, 89%; i) Pd/C, Boc_2O, H_2, MeOH, RT; j) Ag_2O, MeI, DMF, 50°C, 94% yield for 2 steps; k) aq. LiOH, THF, MeOH, then allyl bromide, K_2CO_3, DMSO, RT, 92%. NMA = *N*-methylaniline; NMM = *N*-methylmorpholine; TIPS = triisopropylsilyl.

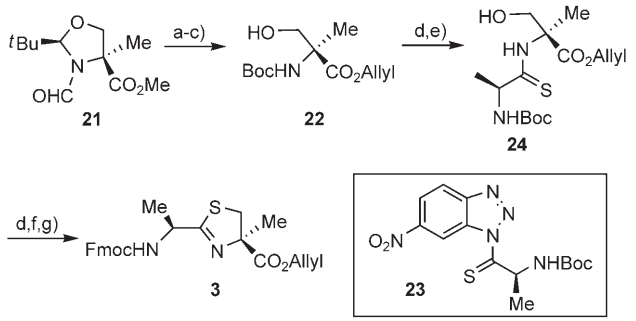
purpose. Unfortunately, hydrolysis of **16d** with aqueous LiOH in methanol gave a mixture of the acid **17** and its 3-epimer in a ratio of 5:1, indicating that partial racemization had occurred at the C3 position of **16d**. This observation prompted us to employ compound **16e** which contains an easily removable allyl ester for further transformations. As a result, treatment of **16e** with TFA followed by esterification of the resulting acid with diazomethane afforded methyl ester **18**. After removing the allyl-protecting group with $[Pd(PPh_3)_4]$/NMA from **18**, the free acid was extended by one carbon by the Arndt–Eistert reaction.[14] Reacting this product with ethyl chloroformate and subsequent $NaBH_4$ reduction produced the alcohol **14**.[15] The stereochemistry of the methyl group in **14** was further confirmed by NOE effects observed in its cyclization product **19**. Next, protection of **14** with TIPSCl yielded silyl ether, which was subjected to hydrogenolysis in the presence of di-*tert*-butyl carbonate, and then methylation with iodomethane, to deliver ester **20** in 84% yield. Finally, the methyl ester of **20** was saponified and the resultant acid was reacted with allyl bromide to furnish the desired NMeOHIle unit **4a**.

The preparation of the other two *N*-methyl amino acid residues is outlined in Scheme 6. Boc-protected L-valine and

Scheme 6. Syntheses of NMeVal and NMeIle units. a) Boc_2O, Na_2CO_3, H_2O, RT; b) NaH, MeI, THF, 0°C→RT; c) allyl bromide, K_2CO_3, DMSO, RT.

L-isoleucine were exposed to iodomethane and NaH,[16] followed by esterification with allyl bromide to provide **4c** and **d**, respectively.

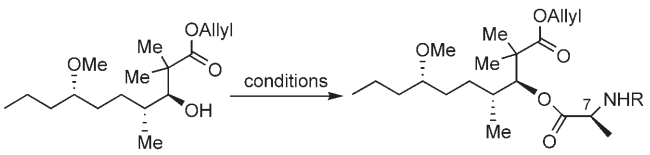
Synthesis of the α-methylthiazoline unit: As depicted in Scheme 7, (*S*)-*N*-Boc-α-methylserine allyl ester **22** was pre-



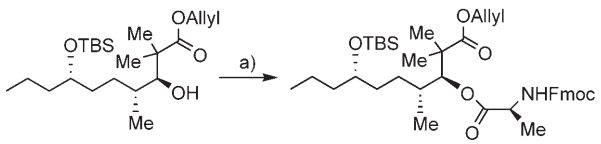
Scheme 7. Synthesis of α-methylthiazoline unit. a) AcCl, MeOH, reflux; b) Boc_2O, Na_2CO_3, THF, H_2O, RT, 80% yield for 2 steps; c) aq. LiOH, THF, MeOH, then allyl bromide, K_2CO_3, DMSO, RT, 94%; d) TFA, CH_2Cl_2; e) **23**, Et_3N, CH_2Cl_2, 0°C→RT, 50% yield for 2 steps; f) FmocOSu, Na_2CO_3, dioxane, H_2O, 80%; g) DAST, CH_2Cl_2, −78°C, 89%. Fmoc = 9-fluorenylmethoxycarbonyl; DAST = (diethylamino)sulphur trifluoride.

pared from known compound **21**[17] in three steps. After cleavage of the Boc-protecting group in **22**, the liberated amine was condensed with known thioacylating agent **23**[18] to produce the thioamide **24** in 50% yield. Ring closure of **24** was accomplished with DAST at −78°C to produce trisubstituted thiazoline **3**,[19] after switching the protecting group of the amine from Boc to Fmoc.

Connection of the alcohol 2 with L-alanine derivatives: Following our synthetic plan, the next task was esterification of **2** with suitable L-alanine derivatives (Scheme 8). The esterification was found to be very sluggish, mainly because of the steric hindrance resulting from high methylation near the secondary hydroxy group. This fact resulted in racemization of L-alanine-derived activated esters. For example, the



Scheme 8.



Scheme 9. Synthesis of the ester **26**. a) *N*-Fmoc-Ala-Cl (5.0 equiv), DMAP (0.5 equiv), *i*Pr_2NEt (5.5 equiv), CH_2Cl_2, −15 °C, 37 % yield, 62 % starting material was recovered.

coupling reaction of **2a** with *N*-Boc-Ala in the presence of DMAP (5 equiv) and EDCI (5 equiv) was completed in 24 h; however, a 1:1 mixture of **25b** and its epimer were detected (Table 2, entry 1). Attempts to minimize racemization

Table 2. Esterification of alcohol **2a**.

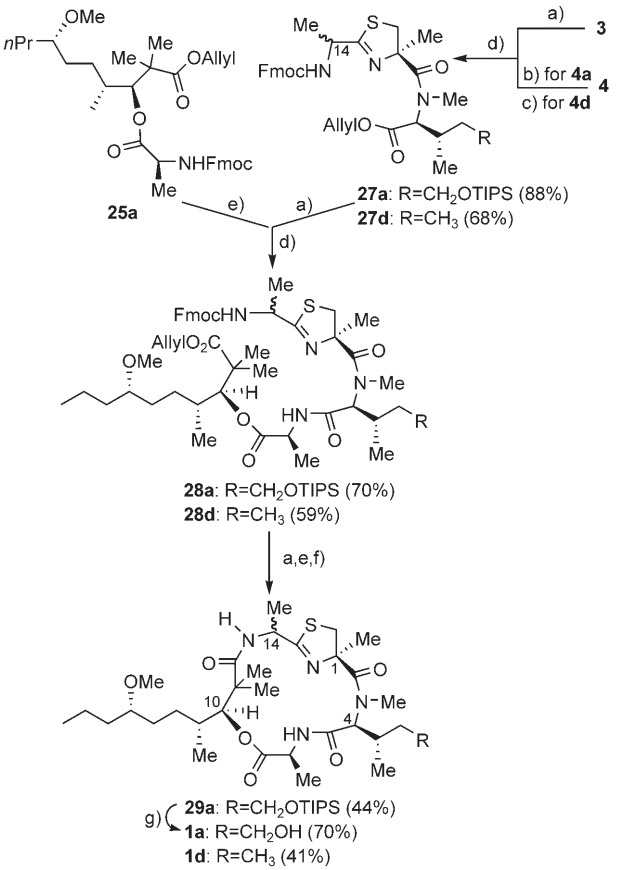
Entry	Conditions	Product	Yield [%]
1	*N*-Boc-Ala (3 equiv), EDCI (5 equiv), DMAP (5 equiv), CH_2Cl_2, RT	**25b**	95[a]
2	*N*-Boc-Ala (3 equiv), EDCI (3 equiv), DMAP (1 equiv), CH_2Cl_2, RT	–	
3	*N*-Tr-Ala (3 equiv), EDCI (5 equiv), DMAP (5 equiv), CH_2Cl_2, RT	–	
4	*N*-Boc-Ala-ONp (1.5 equiv), HOBt (1.5 equiv), NMM, DMF, RT	–	
5	*N*-Boc-Ala (2 equiv), 2,4,6-trichlorobenzoyl chloride (2 equiv), DMAP (2 equiv), *i*Pr_2NEt (2.5 equiv), PhH, reflux	–	
6	*N*-Fmoc-Ala-Cl (5 equiv), DMAP (0.5 equiv), *i*Pr_2NEt (5.5 equiv), CH_2Cl_2, −15 °C	**25a**	86[b]

[a] Racemization occurred at C7. [b] 10 % of **2a** was recovered. Tr = trityl; Np = *p*-nitrophenol.

by reducing the amounts of DMAP and EDCI and by using trityl-protected L-alanine[20] failed to give any coupling products (entries 2 and 3). Similar results were observed when Yamaguchi's mixed anhydride method[21] and the *p*-nitrophenol[22] activated ester procedure were employed (entries 4 and 5). Other activated esters, such as succinimide[23] and imidazolyl[24] ester, did not work either (data not shown). At this stage we moved our attention to more reactive acyl chlorides. After some experimentation, we were gratified to find that the coupling reaction of **2a** with *N*-Fmoc-Ala-Cl[25] in the presence of DMAP (0.5 equiv) at −15 °C worked well to afford **25a** without racemization in 85 % yield (entry 6). However, the reaction conditions were quite critical, as racemization at C7 was still observed when this reaction was conducted at 0 °C or when one equivalent of DMAP was used, and poor conversion was noticed when the amount of DMAP was reduced to 0.05 equivalents (data not shown).

By using the above optimized conditions, esterification of HTMHD unit **2c** was explored next (Scheme 9). It was found that in this case the desired product **26** was isolated in only 37 % yield, while the starting material was recovered in 62 % yield. The poor conversion might result from the additional steric hindrance contributed by the silyl ether moiety in **2c**.

Assembly of halipeptins A–D: With all required fragments **3**, **4**, **25a**, and **26** in hand, we started to elaborate the target molecules by connecting them with each other. The syntheses of halipeptins A (**1a**) and D (**1d**) are outlined in Scheme 10. Removal of the allyl-protecting group from **3** by palladium chemistry[26] gave an acid, which was coupled with the amines liberated from **4a** and **d** by using BEP[27] as an



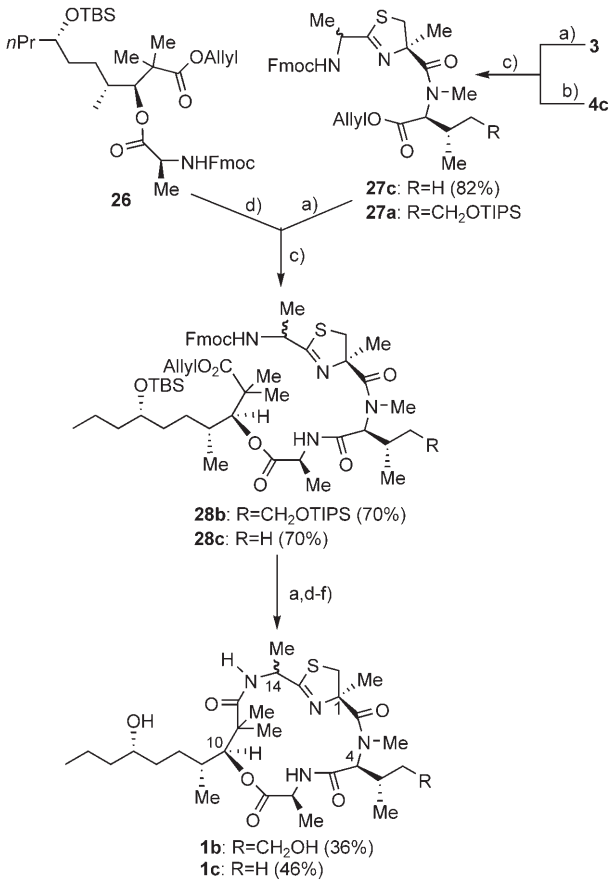
Scheme 10. Completion of syntheses of halipeptins A and D. a) [Pd(PPh_3)$_4$], NMA, CH_2Cl_2, RT; b) $AlCl_3$, CH_2Cl_2, 0 °C→RT; c) TFA, CH_2Cl_2; d) BEP, *i*Pr_2NEt, CH_2Cl_2, 0 °C→RT; e) CH_3CN, Et_2NH; f) HATU, *i*Pr_2NEt, DMF, CH_2Cl_2, 0 °C→RT; g) TBAF, THF, 70 %. BEP = 2-bromo-1-ethyl-pyridinium tetrafluoroborate; HATU = *N*-[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl-methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide.

activating agent to deliver the amide parts **27a** and **d**, respectively. Surprisingly, two isomers in a ratio of 3:1 were determined by ^{1}H NMR in each coupling product, indicating that partial racemization at C14 still occurred even under the above mild conditions.

Deprotection of **27a** and **d** gave free acids, which were respectively coupled with the amine liberated from **25a** assisted by BEP to afford the precedents of macrocyclization **28a** and **d**. Sequential deprotection of **28d** ([Pd(PPh$_3$)$_4$]; then Et$_2$NH) followed by HATU-mediated[28] macrocyclization furnished halipeptin D (**1d**) and its C14 epimer which could be separated by preparative TLC. Similarly, a mixture of TIPS-protected halipeptin A **29a** and its C14 epimer were obtained from **28a**. Upon treatment with TBAF, we were pleased to find that **1a** was isolated as a single product. In this case the undesired isomer might be transformed into more thermodynamically stable halipeptin A. A similar phenomenon has been observed by the groups of Wipf[3b] and Pattenden[3c] during the syntheses of thiazoline-containing cyclopeptides.

The elaborations of halipeptins B and C are illustrated in Scheme 11. Deallylation of **3** with Pd^0 followed by coupling with a liberated amine from **4c** produced amide **27c**. After cleavage of the allyl ester in **27a** or **c**, condensation with a liberated amine from **26** was carried out to afford **28b** or **c**. Treatment of **28b** or **c** with [Pd(PPh$_3$)$_4$]/NMA and diethylamine subsequently provided the corresponding cyclization precursor, which was exposed on HATU/*i*Pr$_2$NEt in a diluted mixture of CH$_2$Cl$_2$ and DMF to yield halipeptins B or C protected as the silyl ethers. Removal of the silyl-protecting group in these two products with aqueous HF delivered halipeptins B (**1b**) and halipeptin C (**1c**) and their C14 epimers, respectively. The ratio for two isomers in these two products was about 1:1. Interestingly, halipeptin C (**1c**) and its epimer could be separated by preparative TLC, while halipeptin B (**1b**) and its epimer were inseparable. Fortunately, the ratio for halipeptin B could be enriched to 6:1 after treatment of the diastereomer mixture with TBAF in THF.

As expected, all analytical data of each synthetic halipeptin were identical with those of the corresponding natural source compounds. Thus, the total syntheses of all the members of the halipeptin family were achieved. The present protocols would permit assembling halipeptin analogues in great diversity, which will be of benefit for their structure-activity relationship studies, as well as for exploring their possible anti-inflammatory mechanism.



Scheme 11. Completion of syntheses of halipeptins B and C. a) [Pd(PPh$_3$)$_4$], NMA, CH$_2$Cl$_2$, RT; b) TFA, CH$_2$Cl$_2$; c) BEP, *i*Pr$_2$NEt, CH$_2$Cl$_2$, 0 °C→RT; d) CH$_3$CN, Et$_2$NH; e) HATU, *i*Pr$_2$NEt, DMF, CH$_2$Cl$_2$, 0 °C→RT; f) aq. HF, CH$_3$CN, RT.

Experimental Section

General procedure: All the reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise indicated. Optical rotations were measured by using a Perkin–Elmer 241MC polarimeter in the solvent indicated. IR spectra were recorded on an AVATAR-360 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a MERCURY300, Bruker DRX-400, and Bruker AV-500 spectrometers with TMS as the internal standard. HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers. Flash-column chromatography was carried out on silica gel (300–400 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated.

Compound 6: Metal Na (1.23 g, 53.4 mmol) was added to dry MeOH (150 mL) at 0 °C. After the sodium had disappeared, a solution of lactone **5** (5.67 g, 49.7 mmol) in MeOH (10 mL) was added and the mixture was stirred at room temperature for 36 h. After this time, the reaction was quenched with saturated NH$_4$Cl solution (500 mL) and the product was extracted with EtOAc (4×200 mL), washed with brine, and dried over anhydrous Na$_2$SO$_4$. The extract was concentrated to give the crude alcohol (5.98 g, 82 %) as a colorless oil.

TBSCl (9.55 g, 61.4 mmol) was added in portions to a solution of the above alcohol and imidazole (5.55 g, 81.6 mmol) in DMF (60 mL). The mixture was stirred at room temperature for 12 h before being diluted with EtOAc (100 mL) and hexane (500 mL). The solution was washed with water and brine, dried (Na$_2$SO$_4$), and filtered. The solvent was removed in vacuo and the residue was chromatographed on silica gel (hexanes/EtOAc 50:1) to give silyl ether **6** (10.37 g, 98 %) as a colorless oil. $[\alpha]_D^{25}=+4.1$ ($c=1.05$ in CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$): $\delta=3.66$ (s, 1H), 3.42 (d, $J=2.1$ Hz, 1H), 3.41 (d, $J=2.1$ Hz, 1H), 2.43–2.25 (m, 2H), 1.81–1.70 (m, 1H), 1.66–1.52 (m, 1H), 1.50–1.37 (m, 1H), 0.88 (s, 9H), 0.87 (d, $J=3.0$ Hz, 3H), 0.01 ppm (s, 6H); EIMS: m/z: 245 $[M-CH_3]^+$, 203 $[M-C_4H_9]^+$.

Compound 7: To a stirred solution of the silyl ether **6** (4.67 g, 17.9 mmol) in dry ether (45 mL) at −90 °C was added DIBAL-H (1.0 M solution in toluene, 19 mL, 19.0 mmol) over 1 h. Stirring of the reaction mixture was continued at −90 °C for 30 min, and then the reaction mixture was

quenched with MeOH (1 mL). This mixture was subsequently poured into a saturated solution of Rochelle salts (150 mL). The resulting mixture was stirred until the solution became clear and was then extracted with ether (3×100 mL). The combined organic phase was washed with brine, dried (Na_2SO_4), and concentrated to give the crude aldehyde (4.08 g) as a colorless oil.

A solution of the crude aldehyde (4.08 g) in dry ether (10 mL) was added dropwise to a freshly prepared solution of (+)-Ipc_2BAll (18.5 mmol) in dry ether (45 mL) at −78 °C. After the reaction mixture had been stirred at −78 °C for 2 h and room temperature for 3 h, it was treated with NaOH (3 N, 12 mL) and H_2O_2 (30 %, 5 mL), and was then refluxed for 2 h. The resulting mixture was extracted with ether (2×100 mL), dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc 25:1 to 15:1) gave homoallyl alcohol **7** (4.41 g, 90 % for 2 steps) as a colorless oil. $[\alpha]_D^{25}=+6.3$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.88$–5.79 (m, 1H), 5.20–5.11 (m, 2H), 3.67–3.59 (m, 1H), 3.48–3.37 (m, 2H), 2.35–2.27 (m, 1H), 2.21–2.10 (m, 1H), 1.76 (s, 1H), 1.66–1.36 (m, 4H), 1.31–1.02 (m, 1H), 0.89–0.87 (m, 12H), 0.04 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=134.9$, 118.0, 70.9, 68.3, 41.9, 35.7, 34.1, 29.1, 25.9, 18.3, 16.7, −5.4 ppm; IR (film): $\tilde{\nu}=3370$, 2957, 2931, 2859, 1642, 1473, 1256, 1097, 914, 837, 776 cm^{-1}; ESIMS: m/z: 273.3 $[M+H]^+$; elemental analysis calcd for $C_{15}H_{32}O_2Si$: C 66.11, H 11.84; found: C 65.93, H 11.82.

Compound 8a: NaH (60 % in mineral oil, 882 mg, 22.1 mmol) was added to a stirred solution of alcohol **7** (1.48 g, 5.4 mmol) in dry DMF (20 mmol). The suspension was stirred at room temperature for 1 h and was then treated with MeI (2.0 mL, 32.0 mmol). The mixture was stirred for 24 h before quenched with saturated NH_4Cl solution (100 mL). The product was extracted with a solution of EtOAc (30 mL) and hexane (150 mL), washed with water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc 75:1) gave the methyl ether (1.40 g, 91 %) as a colorless oil. $[\alpha]_D^{27}=+5.1$ ($c=1.8$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.87$–5.75 (m, 1H), 5.10–5.02 (m, 2H), 3.46–3.31 (m, 2H), 3.30 (s, 3H), 3.21–3.16 (m, 1H), 2.35–2.23 (m, 2H), 1.60–1.37 (m, 4H), 1.16–1.01 (m, 1H), 0.88–0.85 (m, 12H), 0.03 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=134.9$, 116.8, 80.7, 68.2, 56.5, 37.7, 35.9, 30.7, 28.6, 25.9, 18.3, 16.7, −5.4 ppm; IR (film): $\tilde{\nu}=2957$, 2931, 2858, 1745, 1642, 1472, 1362, 1097, 913, 837, 776, 667 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{16}H_{34}O_2SiNa$: 309.2220; found: 309.2227 $[M+Na]^+$.

TBAF (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added to a stirred solution of the above methyl ether (0.58 g, 2.0 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature until the substrate had been completely consumed. The solvent was removed and the residue was directly loaded onto a silica-gel column (hexanes/EtOAc 5:1) to afford the product (0.304 g, 90 %) as a colorless oil. $[\alpha]_D^{27}=+20.8$ ($c=2.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.83$–5.69 (m, 1H), 5.07–5.00 (m, 2H), 3.46–3.35 (m, 2H), 3.33 (s, 3H), 3.21–3.13 (m, 1H), 2.40 (s, 1H), 2.29–2.20 (m, 2H), 1.60–1.34 (m, 4H), 1.26–1.17 (m, 1H), 0.87 ppm (d, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=134.7$, 116.8, 80.6, 67.8, 56.4, 37.6, 35.7, 30.4, 28.4, 16.4 ppm; IR (film): $\tilde{\nu}=3402$, 2934, 1642, 1459, 1195, 1095, 1044, 993, 914, 734 cm^{-1}; HRMS (EI): m/z: calcd for $C_{10}H_{20}O_2$: 172.1463; found: 172.1432 $[M]^+$.

Pt/C (5 %, 233 mg) was added to a solution of the above alcohol (2.25 g, 13.0 mmol) in EtOAc (25 mL) and the reaction mixture was stirred under H_2 (1 atm) for 3 h. After this time, the catalyst was filtered off and the filtrate was concentrated to give the alcohol (2.26 g, 99 %) as a colorless oil. $[\alpha]_D^{29}=+5.2$ ($c=0.70$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 3.53–3.40 (m, 2H), 3.31 (s, 3H), 3.15–3.10 (m, 1H), 1.71 (s, 1H), 1.66–1.55 (m, 1H), 1.54–1.29 (m, 6H), 1.27–1.13 (m, 2H), 0.93–0.86 ppm (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=81.0$, 68.1, 56.4, 35.8, 35.6, 30.6, 28.5, 18.5, 16.5, 14.2 ppm; IR (film): $\tilde{\nu}=3398$, 2959, 2874, 1730, 1459, 1378, 1194, 1096, 1041, 940, 818 cm^{-1}; HRMS (EI): m/z: calcd for $C_9H_{19}O_2$: 159.1385; found: 159.1398 $[M-CH_3]^+$.

A solution of DMSO (3.7 mL, 52.1 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of $(COCl)_2$ (2.2 mL, 25.6 mmol) in CH_2Cl_2 (60 mL) at −78 °C. After 20 min, a solution of the above alcohol (2.26 g, 12.9 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The mixture was stirred for another 15 min at −78 °C, and then TEA (11 mL, 79 mmol) was added. The reaction mixture was stirred at −78 °C for 15 min and at 0 °C for 30 min, before being quenched with phosphate buffer (pH 7, 100 mL), extracted with CH_2Cl_2 (100 mL × 2), washed with brine, and dried over Na_2SO_4. Concentration to remove the solvent and flash chromatography (hexanes/EtOAc 10:1) gave aldehyde **8a** (1.88 g, 85 %) as a colorless oil. $[\alpha]_D^{26}=-9.8$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=9.61$ (d, $J=1.8$ Hz, 1H), 3.31 (s, 3H), 3.16–3.12 (m, 1H), 2.36–2.31 (m, 1H), 1.73–1.67 (m, 1H), 1.52–1.26 (m, 7H), 1.10 (d, $J=6.9$ Hz, 3H), 0.93–0.85 ppm (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.0$, 80.4, 56.4, 46.3, 35.5, 30.7, 26.1, 18.4, 14.2, 13.4 ppm; IR (film): $\tilde{\nu}=2960$, 2934, 2875, 1729, 1709, 1460, 1378, 1316, 1297, 1095 cm^{-1}; HRMS (ESI-TOF): m/z: calcd for $C_{10}H_{20}O_2Na$: 195.1355; found: 195.1371 $[M+Na]^+$.

Compound 10a: BH_3·THF (1.0 M solution in THF, 11 mL) was added dropwise to a stirred solution of *N*-Ts-(*R*)-Val (3.09 g, 11.0 mmol) in CH_2Cl_2 (110 mL) at room temperature. The reaction mixture was stirred for 30 min at this temperature and was then cooled to −78 °C and a solution of the aldehyde **8a** (1.88 g, 10.9 mmol) in CH_2Cl_2 (5 mL) and 1-(trimethylsiloxy)-1-methoxy-2-methyl-1-propene (2.28 g, 13.2 mmol) in CH_2Cl_2 (5 mL) were added subsequently. Stirring was continued for 3 h at the same temperature and the reaction mixture was quenched with phosphate buffer (pH 7, 100 mL), extracted with CH_2Cl_2 (2×100 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 15:1) gave methyl eater **10a** (2.85 g, 95 %) as a colorless oil. $[\alpha]_D^{26}=-10.9$ ($c=2.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=3.65$ (s, 3H), 3.42 (br s, 1H), 3.26 (s, 3H), 3.08–3.04 (m, 2H), 1.60–1.56 (m, 1H), 1.44–1.25 (m, 7H), 1.24 (s, 3H), 1.19–1.17 (m, 1H), 1.11 (s, 3H), 0.85 (t, $J=7.0$ Hz, 3H), 0.71 ppm (d, $J=6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.5$, 80.9, 79.9, 56.3, 51.8, 45.8, 35.7, 34.6, 31.5, 31.2, 24.5, 21.9, 18.4, 14.2, 13.2 ppm; IR (film): $\tilde{\nu}=3477$, 2959, 1731, 1461, 1263, 1193, 1141, 1096, 991 cm^{-1}; ESIMS: m/z: 275.2 $[M+Na]^+$.

Compound 2a: LiOH·H_2O (189 mg, 4.50 mmol) was added to a stirred solution of **10a** (604 mg, 2.20 mmol) in THF/H_2O/MeOH (10 mL, 3:1:1). After the reaction mixture had been stirred at room temperature for 12 h, it was acidified with HCl (5 %), extracted with EtOAc (3×30 mL), washed with brine, and dried over Na_2SO_4. After concentration, the residue was dissolved in DMSO (20 mL) and K_2CO_3 (920 mg, 6.66 mmol) and allylic bromide (0.38 mL, 4.49 mmol) were successively added. The resulting reaction mixture was stirred at room temperature for 12 h and was then poured into water (100 mL), extracted with EtOAc (50 mL × 3), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 15:1) gave **2a** (611 mg, 92 % for 2 steps) as a colorless oil. $[\alpha]_D^{18}=-12.7$ ($c=1.14$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.97$–5.86 (m, 1H), 5.36–5.22 (m, 2H), 4.59–4.56 (m, 2H), 3.45 (dd, $J=2.3$, 9.2 Hz, 1H), 3.34 (s, 3H), 3.12–3.06 (m, 2H), 1.65–1.62 (m, 1H), 1.51–1.27 (m, 8H), 1.30 (s, 3H), 1.17 (s, 3H), 0.94–0.86 (m, 3H), 0.75 ppm (d, $J=6.9$ Hz, 3H); IR (film): $\tilde{\nu}=3477$, 2960, 2935, 1730, 1650, 1460, 1390, 1257, 1137, 1097, 987, 932, 823, 770 cm^{-1}; ESIMS: m/z: 301.3 $[M+H]^+$; elemental analysis calcd for $C_{17}H_{32}O_4$: C 67.96, H 10.74; found: C 67.84, H 10.65.

Compound 8b: Ac_2O (0.73 mL, 7.74 mmol) and Et_3N (1.4 mL, 10.1 mmol) were added successively to a stirred solution of the alcohol **7** (1.06 g, 3.89 mmol) and DMAP (48 mg, 0.39 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 5 h and was then poured into Et_2O (50 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 50:1) gave the ester (1.09 g, 89 %) as a colorless oil. $[\alpha]_D^{24}=+12.0$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.82$–5.68 (m, 1H), 5.11–5.04 (m, 2H), 4.93–4.85 (m, 1H), 3.44–3.35 (m, 2H), 2.33–2.25 (m, 2H), 2.03 (s, 3H), 1.62–1.38 (m, 4H), 1.08–0.98 (m, 1H), 0.88 (s, 9H), 0.85 (d, $J=$ 6.9 Hz, 3H), 0.03 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.7$, 133.8, 117.6, 73.6, 68.1, 38.6, 35.6, 31.0, 28.7, 25.9, 21.2, 18.3, 16.7, −5.4 ppm; IR (film): $\tilde{\nu}=3081$, 2957, 1742, 1644, 1473, 1373, 1241, 1097, 1025, 917, 837, 776, 667 cm^{-1}; ESIMS: m/z: 315.3 $[M+H]^+$, 337.3 $[M+Na]^+$; elemental analysis calcd for $C_{17}H_{34}O_3Si$: C 64.92, H 10.90; found: C 65.30, 10.92.

To a stirred solution of the above ester (1.04 g, 3.32 mmol) in THF (25 mL) was added TABF (1.0 M solution in THF, 5.0 mL). After stirring

at room temperature for 3 h, the reaction mixture was concentrated and purified by flash chromatography (hexanes/EtOAc 3:1) to give the alcohol (579 mg, 87%) as a colorless oil.

A solution of DMSO (0.89 mL, 12.5 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a stirred solution of $(COCl)_2$ (0.54 mL, 6.29 mmol) in CH_2Cl_2 (30 mL) at −78 °C. After 20 min, a solution of the above alcohol (624 mg, 3.12 mmol) in CH_2Cl_2 (1 mL) was added dropwise. The mixture was stirred for 15 min at −78 °C, and then TEA (2.6 mL, 18.7 mmol) was added. After the resulting reaction mixture had been stirred at −78 °C for 15 min and at 0 °C for 30 min, the reaction mixture was quenched with phosphate buffer (pH 7, 50 mL), extracted with CH_2Cl_2 (2×50 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 10:1) gave aldehyde **8b** (587 mg, 95%) as a colorless oil. $[\alpha]_D^{27} = +9.6$ ($c = 1.4$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.60$ (s, 1H), 5.80–5.66 (m, 1H), 5.10–5.05 (m, 2H), 4.91 (p, $J = 6.0$ Hz, 1H), 2.37–2.29 (m, 3H), 2.02 (s, 3H), 1.77–1.65 (m, 1H), 1.65–1.54 (m, 2H), 1.44–1.33 (m, 1H), 1.09 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 204.5$, 170.7, 133.3, 117.9, 72.9, 46.0, 38.5, 30.8, 26.0, 21.1, 13.3 ppm; IR (film): $\tilde{\nu} = 3081$, 2978, 1739, 1709, 1644, 1375, 1241, 1025, 920 cm^{-1}; HRMS (MALDI-TOF): m/z: calcd for $C_{11}H_{18}O_3Na$: 221.1148; found: 221.1156 $[M+Na]^+$.

Compound 10b: Prepared from **8b** by the same method as that described for the preparation of **10a** (80%). $[\alpha]_D^{24} = +0.11$ ($c = 0.65$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.82$–5.58 (m, 1H), 5.10–5.03 (m, 2H), 4.93–4.85 (m, 1H), 3.68 (s, 3H), 3.43–3.40 (m, 1H), 3.14 (brs, 1H), 2.34–2.25 (m, 2H), 2.02 (s, 3H), 1.70–1.60 (m, 1H), 1.60–1.50 (m, 2H), 1.50–1.20 (m, 2H), 1.28 (s, 3H), 1.15 (s, 3H), 0.73 ppm (d, $J = 3.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.7$, 170.7, 133.7, 117.6, 80.1, 73.4, 52.0, 45.7, 38.5, 34.4, 31.4, 31.2, 24.9, 22.0, 21.2, 13.1 ppm; IR (film): $\tilde{\nu} = 3500$, 2952, 1737, 1644, 1436, 1375, 1244, 1193, 1141, 1024, 993, 919 cm^{-1}; ESIMS: m/z: 301.2 $[M+H]^+$, 323.4 $[M+Na]^+$.

Compound 2b: Pt/C (10%, 71 mg) was added to a solution of methyl ester **10b** (725 mg, 2.41 mmol) in EtOAc (20 mL). The reaction mixture was stirred under H_2 (1 atm) for 2 h and then the catalyst was filtered off and the resulting filtrate was concentrated to give the crude product as a colorless oil.

$LiOH{\cdot}H_2O$ (502 mg, 12.0 mmol) was added to a stirred solution of the above crude product in THF (9 mL), H_2O (3 mL) and MeOH (3 mL). After the mixture had been stirred at room temperature for 12 h, it was quenched with solid $KHSO_4$ (3.38 g, 24.8 mmol). The residue produced was filtered off, concentrated, and then dissolved in DMSO (20 mL). K_2CO_3 (974 mg, 7.05 mmol) and allyl bromide (0.40 mL, 4.73 mmol) were added successively to this residue and the resulting mixture was stirred at room temperature for 12 h. After this time, the reaction mixture was poured into water (100 mL), extracted with EtOAc (3×50 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexane/EtOAc 5:1) gave **2b** (552 mg, 80%) as a colorless oil. $[\alpha]_D^{24} = -10.7$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.99$–5.86 (m, 1H), 5.38–5.24 (m, 2H), 4.61–4.58 (m, 2H), 3.62–3.58 (m, 1H), 3.58–3.45 (m, 1H), 3.12 (brs, 1H), 1.70–1.62 (m, 1H), 1.60–1.38 (m, 8H), 1.32 (s, 3H), 1.19 (s, 3H), 0.94–0.91 (m, 3H), 0.77 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.9$, 131.7, 118.6, 79.9, 71.8, 65.4, 45.9, 39.6, 35.1, 34.6, 31.9, 24.7, 22.0, 18.8, 14.1, 13.4 ppm; IR (film): $\tilde{\nu} = 3428$, 2960, 2935, 1717, 1650, 1458, 1393, 1258, 1139, 987, 932, 846, 771 cm^{-1}; HRMS (MALDI-TOF): m/z: calcd for $C_{16}H_{30}O_4Na$: 309.2036; found: 309.2044 $[M+Na]^+$.

Compound 2c: The alcohol **2b** (528 mg, 1.84 mmol), TBSCl (431 mg, 2.86 mmol), and imidazole (250 mg, 3.67 mmol) were dissolved in DMF (6 mL). After the reaction mixture had been stirred at room temperature for 1.5 h, it was poured into a solution of EtOAc (10 mL) and hexane (50 mL), washed with water and brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 10:1) gave silyl ether **2c** (700 mg, 95%) as a colorless oil. $[\alpha]_D^{24} = -6.6$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.96$–5.85 (m, 1H), 5.36–5.23 (m, 2H), 4.58 (d, $J = 4.8$ Hz, 2H), 3.65–3.55 (m, 1H), 3.52–3.40 (m, 1H), 3.00 (d, $J = 9.9$ Hz, 1H), 1.68–1.60 (m, 1H), 1.48–1.25 (m, 8H), 1.30 (s, 3H), 1.17 (m, 3H), 0.90–0.80 (m, 12H), 0.75 (d, $J = 6.3$ Hz, 3H), 0.02 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 177.8$, 131.8, 118.5, 80.2, 72.3, 65.4, 46.1, 39.4, 35.0, 34.8, 31.7, 25.9, 25.0, 21.7, 18.5, 18.1, 14.3, 13.4, −4.4 ppm; IR (film): $\nu_{max} = 3499$, 2959, 2933, 1732, 1650, 1473, 1390, 1255, 1136, 1079, 1040, 987, 938, 836, 774, 663 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{44}O_4Si$: C 65.95, H 11.07; found: C 65.89, H 10.75; HRMS (MALDI-TOF): m/z: calcd for $C_{22}H_{44}SiO_4Na$: 423.2901; found: 423.2921 $[M+Na]^+$.

Compound 11: TEA (8.3 mmol) and MsCl (4.2 mmol) were successively added to a stirred solution of 2-butyn-1-ol (3.50 g, 50 mmol) in CH_2Cl_2 (50 mL) at −40 °C. The reaction mixture was stirred at room temperature for 2 h, diluted with CH_2Cl_2 (50 mL), washed with saturated NH_4Cl solution and brine, and dried over Na_2SO_4. After concentration, the residue was dissolved in (*R*)-(+)-1-phenylethylamine (11.4 mL, 90 mmol) and stirred at room temperature overnight. Concentration and flash chromatography (hexanes/EtOAc 2:1) gave the alkyne (5.60 g, 65% for 2 steps) as a colorless oil.

DIPEA (2.9 mL, 16.6 mmol) was added to a stirred solution of the above oil (1.31 g, 7.56 mmol), *N*-Boc-Gly (1.54 g, 8.80 mmol), HOBt (1.35 g, 9.97 mmol), and EDCI (1.84 g, 9.60 mmol) at 0 °C. After the reaction mixture had been stirred at room temperature for 15 h, it was diluted with CH_2Cl_2 (100 mL), washed with water and brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 5:1) gave **11** (2.39 g, 96%) as a colorless oil. $[\alpha]_D^{25} = +98.1$ ($c = 1.20$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–7.25 (m, 5H), 5.99 (q, $J = 3.6$ Hz, 1H), 5.60 (brs, 1H), 4.16–4.12 (m, 2H), 3.76–3.54 (m, 2H), 1.83 (s, 3H), 1.61 (d, $J = 6.9$ Hz, 3H), 1.48 ppm (s, 9H); ESIMS: m/z: 331.2 $[M+H]^+$, 353.2 $[M+Na]^+$.

Compound 12: Lindlar catalyst (120 mg) was added to a solution of **11** (2.40 g, 7.3 mmol) in Et_2O (70 mL). The reaction mixture was stirred at room temperature under H_2 (1 atm) for 10 h. The catalyst was filtered off, and the filtrate was concentrated to give the crude olefin (2.2 g, 91%) as a colorless oil.

A solution of the above olefin (1.89 g, 5.68 mmol) in CH_2Cl_2 (40 mL) and TFA (10 mL) was stirred for 1 h at 0 °C. After this time the solvent was removed in vacuo and the residue was dissolved in water (100 mL) and TEA (2 mL) and extracted with EtOAc (3×100 mL). The combined organic phase was washed with water and brine and dried over Na_2SO_4. Concentration and flash chromatography (EtOAc/MeOH 5:1) gave **12** (1.27 g, 96%) as a colorless oil. $[\alpha]_D^{25} = +118.2$ ($c = 0.96$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.37$–7.26 (m, 5H), 6.08 (q, $J = 6.9$ Hz, 1H), 5.50–5.42 (m, 1H), 5.08–4.98 (m, 1H), 3.72–3.38 (m, 4H), 1.56–1.51 ppm (m, 6H).

Compound 13: LiHMDS (2.4 mL of 1 M solution in THF, 2.4 mmol) was added dropwise to a solution of **12** (0.46 g, 2 mmol) in THF (10 mL) at −78 °C. After the reaction mixture had been stirred at −78 °C for 30 min and then at room temperature for 15 h, it was quenched with saturated NH_4Cl solution (50 mL), extracted with EtOAc (3×30 mL), washed with brine, and dried over Na_2SO_4. After concentration, the residue was dissolved in CH_2Cl_2 (5 mL) and TEA (0.28 mL, 2 mmol), DMAP (12 mg, 0.1 mmol), and CbzCl (0.17 mL, 1.2 mmol) were added. The resulting mixture was stirred at room temperature for 10 h and was then diluted with CH_2Cl_2 (20 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc) gave a pair of diastereomers of **13** (3:1, the majority is the desired product). Pure **13** (0.28 g, 52% for 2 steps) was obtained by recrystallization (hexanes/EtOAc) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.38$–7.26 (m, 10H), 6.07 (d, $J = 6.9$ Hz, 1H), 5.77–5.69 (m, 1H), 5.41 (d, $J = 7.8$ Hz, 1H), 5.13–5.06 (m, 4H), 4.14–4.04 (m, 1H), 1.47–1.38 (m, 4H), 0.98 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.8$, 156.4, 143.0, 138.6, 136.2, 128.5, 128.2, 127.9, 127.4, 126.2, 116.8, 67.1, 59.0, 48.9, 40.0, 21.7, 15.7 ppm; ESIMS: m/z: 367.2 $[M+H]^+$, 389.2 $[M+Na]^+$.

Compound 14: HCl (6 M, 8 mL) was added to a stirred solution of **13** (0.37 g, 1 mmol) in MeOH (2 mL). After refluxing for 10 h, the reaction mixture was diluted with water (20 mL) and EtOAc (20 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (20 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. After concentration, the residue was dissolved in ether (10 mL) and a solution of CH_2N_2 in ether was added dropwise until the solution turned yellow. After the reaction mixture had been stirred for a further 2 h, it was concentrated and flash chromatographed (hexanes/

EtOAc 9:1) to give the methyl ester (0.2 g, 76% for 2 steps) as a colorless oil.

BH_3·THF was added dropwise (9.0 mL of a 1 M solution in THF, 9.0 mmol) to a stirred solution of 2-methyl-2-butene (0.95 mL, 9 mmol) in dry THF (9 mL) at 0 °C. An hour later, a solution of the above methyl ester (2.27 g, 8.2 mmol) in THF (4 mL) was added. After the reaction mixture had been stirred at room temperature for 1 h, it was quenched with MeOH (1 mL) at 0 °C and then buffer (pH 7, 10 mL) and H_2O_2 (30%, 10 mL) were added. This mixture was stirred at room temperature for 14 h and was then poured into brine (150 mL) and extracted with ether (3×100 mL). The combined organic phase was washed with saturated $Na_2S_2O_3$ solution, water and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc 2:1) gave **14** (1.91 g, 72%) as a colorless oil. $[\alpha]_D^{25}=+6.9$ ($c=1.5$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.34$ (s, 5H), 5.69 (d, $J=7.5$ Hz, 1H), 5.11 (s, 2H), 4.38 (dd, $J=8.7$, 4.5 Hz, 1H), 3.74 (s, 3H), 3.69–3.66 (m, 2H), 2.23–2.15 (m, 1H), 1.70–1.63 (m, 1H), 1.50–1.43 (m, 1H), 0.95 ppm (d, $J=6.6$ Hz, 3H); ESIMS: m/z: 296.1 $[M+H]^+$, 318.2 $[M+Na]^+$.

Compound 16e: A solution of **15e** (prepared according to ref. [29], 6.72 g, 18.6 mmol) in dry THF (80 mL) was added dropwise to a stirring solution of LiHMDS (39.0 mL of a 1 M solution in THF 39.0 mmol) and HMPA (20 mL). After about 45 min, freshly distilled MeI (3.5 mL, 56.2 mmol, neat) was added and the reaction mixture was stirred at −78 °C for 3 h. After this time, the mixture was quenched with HCl (10%) at −78 °C, extracted with EtOAc (150 mL ×3), and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 15:1) provided compound **16e** (6.64 g, 95%). $[\alpha]_D^{21}=-6.2$ ($c=1.2$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.38$–7.30 (m, 5H), 5.96–5.83 (m, 1H), 5.66 (d, $J=8.7$ Hz, 1H), 5.36–5.17 (m, 2H), 5.14 (s, 2H), 4.64–4.50 (m, 3H), 3.27–3.20 (m, 1H), 1.33 (s, 9H), 1.23 ppm (d, $J=7.5$ Hz, 3H); IR (film): $\tilde{\nu}=3433$, 2981, 1736, 1650, 1502, 1456, 1370, 1219, 1157, 1089, 1060, 985, 931, 846, 750, 698 cm^{-1}; ESIMS: m/z: 378.2 $[M+H]^+$, 400.2 $[M+Na]^+$.

Compound 18: TFA (20 mL) was added to a solution of **16e** (3.14 g, 8.36 mmol) in CH_2Cl_2 (60 mL). After the reaction mixture had been stirred for 3 h at room temperature, the solvent was removed. A solution of CH_2N_2 in Et_2O was added to a stirring solution of the residue in Et_2O (100 mL) until the solution turned yellow. When the yellow color had disappeared, the solvent was removed and the residue was purified by silica-gel column chromatography (hexanes/EtOAc 15:1) to give compound **18** (2.68 g, 95%). $[\alpha]_D^{21}=+2.1$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.38$–7.30 (m, 5H), 5.94–5.83 (m, 1H), 5.70 (d, $J=9.3$ Hz, 1H), 5.34–5.22 (m, 2H), 5.14 (s, 2H), 4.61–4.55 (m, 3H), 3.71 (s, 3H), 3.36–3.29 (m, 1H), 1.25 ppm (d, $J=7.8$ Hz, 3H); IR (film): $\tilde{\nu}=3359$, 2954, 1734, 1649, 1508, 1457, 1438, 1388, 1214, 1089, 1062, 1002, 930, 775, 738, 699 cm^{-1}; HRMS: (MALDI-TOF): m/z: calcd for $C_{17}H_{21}NO_6Na$: 358.1261; found: 358.1276 $[M+Na]^+$.

Compound 19: $[Pd(PPh_3)_4]$ (537 mg, 0.46 mmol) and NMA (6.1 mL, 56.2 mmol) were added successively to a solution of **18** (9.53, 28.4 mmol) in CH_2Cl_2 (200 mL). After the mixture had been stirred for 1 h, it was concentrated and chromatographed (hexanes/EtOAc 5:1 to EtOAc/MeOH 10:1) to give the crude acid.

NMM (3.5 mL, 31.8 mmol) and $ClCO_2iBu$ (4.1 mL, 31.2 mmol) were successively added to a solution of the above acid in THF (170 mL) at −20 °C. After the solution had been stirred for 15 min, CH_2N_2 (400 mL of 0.4 M in Et_2O) was added. The mixture was warmed to room temperature over 10 h and was then quenched with H_2O (400 mL). The mixture was extracted with Et_2O (3×150 mL), dried over Na_2SO_4, and concentrated. $AgNO_3$ (5.43 g, 40.0 mmol) was added to a solution of the residue in THF (100 mL) and H_2O (10 mL). After the reaction mixture had been stirred at room temperature for 10 h, it was concentrated and partitioned between EtOAc and H_2O. The aqueous phase was extracted with EtOAc (2×100 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 5:1 to EtOAc) gave the crude acid.

NMM (2.0 mL, 18.1 mmol) and $ClCO_2Et$ (1.7 mL, 17.7 mmol) were successively added to a solution of the above acid in THF (150 mL) at 0 °C. After the solution had been stirred for 15 min, $NaBH_4$ (1.81 g, 47.6 mmol) was added, followed by the slow addition of MeOH (150 mL). This mixture was stirred for 1 h, and then the reaction was quenched by using HCl (10%, 100 mL). The organic solvent was removed and the residue was partitioned between H_2O and EtOAc. The aqueous phase was extracted with EtOAc (2×100 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 4:1 to 2:1) gave alcohol **14**.

TsOH·H_2O (58 mg) and 4 Å MS (582 mg) were added to a solution of **14** (588 mg, 1.99 mmol) in PhH (10 mL). After refluxing for 12 h, the mixture was filtered off. Concentration and flash chromatography (hexanes/EtOAc 4:1) gave **19** (401 mg, 77%) as a white solid. $[\alpha]_D^{19}=+0.47$ ($c=0.82$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.38$–7.27 (m, 5H), 5.71 (d, $J=5.7$ Hz, 1H), 5.12 (s, 2H), 4.62 (t, $J=6.5$ Hz, 1H), 4.38–4.33 (m, 2H), 2.84–2.79 (m, 1H), 2.33–2.25 (m, 1H), 1.78–1.65 (m, 1H), 0.93 ppm (d, $J=7.1$ Hz, 3H); IR (film): $\tilde{\nu}=3291$, 3068, 2960, 1735, 1685, 1547, 1488, 1455, 1418, 1375, 1340, 1305, 1289, 1248, 1157, 1086, 1044, 987, 943, 905, 861, 759, 708, 593 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{17}NO_4$: C 63.87, H 6.51, N 5.32; found: C 63.87, H 6.51, N 5.29; ESIMS: m/z: 264.1 $[M+H]^+$, 286.1 $[M+Na]^+$.

Compound 20: Alcohol **14** (447 mg, 1.51 mmol), DMAP (19 mg, 0.16 mmol), imidazole (159 mg, 2.34 mmol), and TIPSCl (0.40 mL, 1.87 mmol) were dissolved in CH_2Cl_2 (5 mL). The resulting mixture was stirred at room temperature for 12 h and was then partitioned between water (100 mL) and EtOAc (100 mL). The organic phase was washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc 100:1 to 20:1) gave the silyl ether (605 mg, 89%) as a colorless oil. $[\alpha]_D^{18}=+0.43$ ($c=0.99$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.35$–7.26 (m, 5H), 5.64 (d, $J=6.0$ Hz, 1H), 5.10 (s, 2H), 4.30 (dd, $J=4.7$, 8.9 Hz, 1H), 3.78–3.64 (m, 2H), 3.69 (s, 3H), 2.30–2.27 (m, 1H), 1.67–1.59 (m, 1H), 1.41–1.30 (m, 1H), 1.04 (s, 18H), 1.03 (s, 3H), 0.99 ppm (d, $J=6.9$ Hz, 3H); IR (film): $\tilde{\nu}=3354$, 2945, 2867, 1729, 1523, 1463, 1385, 1340, 1209, 1104, 1072, 1013, 884, 738, 682, 659 cm^{-1}; ESIMS: m/z: 452.4 $[M+H]^+$, 474.4 $[M+Na]^+$, 490.4 $[M+K]^+$; elemental analysis calcd (%) for $C_{24}H_{41}NO_5Si$: C 63.82, H 9.15, N 3.10; found: C 63.94, H 8.92, N 3.18.

Boc_2O (180 mg, 0.82 mmol) and Pd/C (10%, 28 mg) were successively added to a stirred solution of the above silyl ether (245 mg, 0.54 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature under H_2 (1 atm) for 2 h. After filtration and concentration, the residue was dissolved in DMF (2.5 mL) and Ag_2O (346 mg, 1.99 mmol) and MeI (125 μL, 2.01 mmol) were added. This mixture was stirred at 50 °C overnight and was then poured into a solution of hexane (50 mL) and EtOAc (50 mL), washed with water and brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 50:1) gave **20** (218 mg, 94% for 2 steps) as a colorless oil. $[\alpha]_D^{18}=+1.13$ ($c=0.95$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=4.54$, 4.22 (due to the rotamers, each a d, $J=10.7$ Hz, 1H), 3.78–3.69 (m, 5H), 2.85, 2.83 (due to the rotamers, each a s, 3H), 2.23–2.25 (m, 1H), 1.71–1.62 (m, 1H), 1.45 (s, 9H), 1.26–1.14 (m, 1H), 1.13–1.05 (m, 21H), 0.93 ppm (d, $J=6.3$ Hz, 3H); IR (film): $\tilde{\nu}=2945$, 2868, 1745, 1701, 1463, 1392, 1367, 1315, 1254, 1152, 1104, 997, 883, 738, 682, 659 cm^{-1}; ESIMS: m/z: 454.3 $[M+Na]^+$, 470.4 $[M+K]^+$; elemental analysis calcd (%) for $C_{22}H_{45}NO_5Si$: C 61.21, H 10.51, N 3.24; found: C 61.20, H 10.32, N 3.34.

Compound 4a: Prepared from **20** by the same method as for the preparation of **2a** (92%). $[\alpha]_D^{18}=+0.50$ ($c=1.4$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.97$–5.85 (m, 1H), 5.35–5.20 (m, 2H), 4.63–4.59 (m, 2H), 4.60, 4.26 (due to the rotamers, both a d, $J=10.5$ Hz, 1H), 3.78–3.68 (m, 2H), 2.84, 2.87 (due to the rotamers, each a s, 3H), 2.34–2.22 (m, 1H), 1.76–1.67 (m, 1H), 1.46 (s, 9H), 1.27–1.15 (m, 1H), 1.12–1.01 (m, 21H), 0.96 (d, $J=6.6$ Hz, 3H); ESIMS: m/z: 480.4 $[M+Na]^+$, 496.3 ppm $[M+K]^+$; elemental analysis calcd (%) for $C_{24}H_{47}NO_5Si$: C 62.98, H 10.35, N 3.06; found: C 62.75, H 10.25, N 3.17.

Compound 4c: Na_2CO_3 (5.17 g, 48.6 mmol) and Boc_2O (7.95 g, 36.5 mmol) were added to a solution of L-valine (2.85 g, 24.3 mmol) in H_2O (40 mL) and THF (5 mL) at 0 °C. After the reaction mixture had been stirred at room temperature for 12 h, it was neutralized with HCl (10%) until pH 2 had been reached. The mixture was then extracted

with EtOAc (50 mL ×3), washed with brine, and dried over Na_2SO_4. Concentration gave the crude *N*-Boc-valine (5.29 g, 100%).

NaH (60% in mineral oil, 4.91 g, 122.7 mmol) was added in ortions to a solution of *N*-Boc-valine (5.29 g, 24.3 mmol) and MeI (12.1 mL, 184 mmol) in THF (100 mL) at 0°C. After the reaction mixture had been stirred at room temperature for 36 h, it was poured into saturated NH_4Cl solution (500 mL), extracted with EtOAc (3×150 mL) and dried over Na_2SO_4. Concentration gave *N*-methyl-*N*-Boc-valine (5.16 g, 92%).

K_2CO_3 (6.17 g, 44.7 mmol) and allyl bromide (2.8 mL, 33.1 mmol) were added to a solution of *N*-methyl-*N*-Boc-valine (5.16 g, 22.3 mmol) in DMSO (80 mL). After the mixture had been stirred at room temperature for 12 h, it was partitioned between EtOAc (150 mL) and brine (150 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (2×100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography gave **4c** (5.52 g, 91%) as a colorless oil. $[\alpha]_D^{24}=-85.1$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.97$–5.84 (m, 1H), 5.34–5.20 (m, 2H), 4.62–4.60 (m, 2H), 4.47, 4.12 (due to the rotamers, both a d, $J=10.5$ Hz, 1H), 2.85, 2.81 (due to the rotamers, both a s, 3H), 2.21–2.17 (m, 1H), 1.45 (s, 9H), 0.97 (d, $J=6.3$ Hz, 3H), 0.89 ppm (d, $J=6.3$ Hz, 3H); IR (film): $\tilde{\nu}=2971$, 2935, 1741, 1700, 1473, 1392, 1368, 1330, 1313, 1147, 993, 879, 773 cm^{-1}; ESIMS: *m*/*z*: 294.2 $[M+Na]^+$, 272.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{14}H_{25}NO_4$: C 61.97, H 9.29, N 5.16; found: C 62.24, H 9.45, N 5.14.

Compound 4d: Prepared from L-isoleucine by the same method as for the preparation of **4c** (76% for 3 steps). $[\alpha]_D^{21}=-74.7$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.97$–5.84 (m, 1H), 5.34–5.20 (m, 2H), 4.62–4.60 (m, 2H), 4.55, 4.26 (due to the rotamers, both a d, $J=11.1$ Hz, 1H), 2.81, 2.78 (due to the rotamers, both a s, 3H), 2.04–1.95 (m, 1H), 1.45 (m, 10H), 1.13–1.01 (m, 1H), 0.92 (d, $J=6.0$ Hz, 3H), 0.87 (d, $J=7.2$ Hz, 3H); IR (film): $\tilde{\nu}=3089$, 2971, 2936, 2880, 1741, 1701, 1650, 1480, 1456, 1393, 1367, 1313, 1255, 1183, 1145, 1047, 990, 931, 871, 773 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{27}NO_4$: C 63.13, H 9.54, N 4.91; found: C 63.15, H 9.72, N 4.97; ESIMS: *m*/*z*: 286.1 $[M+H]^+$.

Compound 22: AcCl (20 mL) was added to a solution of **21** (prepared according to the literature,[17] 1.05 g, 4.59 mmol) in MeOH (40 mL) at 0°C. After the mixture had been refluxed for 10 h, the solvent was removed. The residue was dissolved in THF (25 mL) and H_2O (5 mL). Na_2CO_3 (1.24 g, 1.17 mmol) and Boc_2O (1.60 g, 7.34 mmol) were added and the resulting mixture was stirred for 10 h and then another portion of Boc_2O (0.80 g, 3.67 mmol) was added. After another 10 h, the solvent was removed. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL). The aqueous phase was extracted with EtOAc (2×50 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Concentration and flash chromatography gave the methyl ester (857 mg, 80%) as a colorless oil.

$LiOH\cdot H_2O$ (409 mg, 9.75 mmol) was added to a stirred solution of the above ester (1.12 g, 4.80 mmol) in THF/H_2O/MeOH (20 mL, 3:1:1). After the mixture had been stirred at 0°C for 1 h, the reaction mixture was quenched with $KHSO_4$ (2.63 g). The solvent was removed in vacuo, and the resulting residue was diluted with EtOAc (150 mL), filtered, and dried over Na_2SO_4. The solvent was removed, the residue was dissolved in DMSO (20 mL), and K_2CO_3 (1.99 g, 14.4 mmol) and allylic bromide (0.82 mL, 9.70 mmol) were successively added. This mixture was stirred at room temperature for 12 h, before being poured into water (100 mL), extracted with EtOAc (100 mL ×3), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 3:1) gave **22** (1.09 g, 88% for 2 steps) as a colorless oil. $[\alpha]_D^{19}=-11.0$ ($c=1.04$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.97$–5.86 (m, 1H), 5.38–5.22 (m, 3H), 4.68- 4.64 (m, 2H), 3.99 (d, $J=10.1$ Hz, 1H), 3.79 (d, $J=10.1$ Hz, 1H), 3.31 (br s, 1H), 1.48 (s, 3H), 1.41 ppm (s, 9H); IR (film): $\tilde{\nu}=3412$, 2981, 2941, 1718, 1650, 1502, 1456, 1393, 1369, 1299, 1552, 1171, 1129, 1058, 987, 933, 783 cm^{-1}; EIMS: *m*/*z*: 228 $[M-31]^+$, 204 $[M-55]^+$; elemental analysis calcd (%) for $C_{12}H_{21}NO_5$: C 55.58, H 8.16, N 5.40; found: C 55.45, H 8.32, N 5.35.

Compound 24: A solution of the allyl ester **22** (0.58 g, 2.24 mmol) in CH_2Cl_2 (15 mL) was treated with TFA (5 mL). The resulting mixture was stirred at room temperature for 2 h, and then the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL) at 0°C and TEA (0.63 mL, 4.5 mmol) was added. Ten minutes later, a solution of **23** (790 mg, 2.24 mmol) in CH_2Cl_2 was added. The reaction mixture was left at room temperature for 12 h, and a further portion of **23** (393 mg, 1.12 mmol) was added. After another 12 h, concentration and flash chromatography (hexanes/EtOAc 6:1 to 3:1) gave **24** (391 mg, 50% for 2 steps) as light yellow foam. $[\alpha]_D^{27}=-41.0$ ($c=1.03$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.49$ (s, 1H), 6.00–5.82 (m, 1H), 5.36–5.15 (m, 3H), 4.66 (d, $J=4.2$ Hz, 2H), 4.43 (d, $J=11.4$ Hz, 1H), 4.39–4.30 (m, 1H), 4.09 (d, $J=10.8$ Hz, 1H), 2.90 (br s, 1H), 1.71 (s, 3H), 1.42 ppm (m, 12H); IR (film): $\tilde{\nu}=3315$, 2982, 2935, 1695, 1510, 1450, 1369, 1282, 1251, 1166, 1053, 987, 935, 859, 734 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{15}H_{26}N_2O_5SNa$: 369.1455; found: 369.1454 $[M+Na]^+$.

Compound 3: A solution of **24** (0.391 g, 1.13 mmol) in CH_2Cl_2 (6 mL) was treated with TFA (2 mL) and the mixture was stirred at room temperature for 2 h. After this time, the solvent was removed in vacuo and the residue was dissolved in dioxane (5 mL) and water (5 mL). Na_2CO_3 (304 mg, 2.87 mmol) and FmocOSu (474 mg, 1.26 mmol) were added successively to the mixture and it was then stirred at room temperature overnight. The reaction mixture was diluted with water (50 mL), extracted with EtOAc (3×30 mL), washed with brine, and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 4:1 to 2:1) gave *N*-Fmoc thioamide (396 mg, 75% for 2 steps) as a colorless foam. $[\alpha]_D^{27}=-19.4$ ($c=1.12$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.49$ (s, 1H), 7.76 (d, $J=7.2$ Hz, 2H), 7.61–7.57 (m, 2H), 7.43–7.34 (m, 2H), 7.31–7.27 (m, 2H), 5.94–5.84 (m, 1H), 5.57 (d, $J=6.6$ Hz, 1H), 5.35–5.22 (m, 2H), 4.66 (d, $J=5.7$ Hz, 2H), 4.50–4.31 (m, 4H), 4.20 (t, $J=7.1$ Hz, 1H), 3.97 (d, $J=10.8$ Hz, 1H), 2.89 (br s, 1H), 1.72 (s, 3H), 1.47 ppm (m, 3H); IR (film): $\tilde{\nu}=3309$, 2985, 2947, 1706, 1514, 1450, 1370, 1248, 1230, 1128, 1053, 987, 937, 760, 741, 621 cm^{-1}; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{25}H_{28}N_2O_5SNa$: 491.1611; found: 491.1622 $[M+Na]^+$.

A solution of the above thioamide (0.518 g, 1.11 mmol) in CH_2Cl_2 (10 mL) at −78°C was treated with DAST (0.22 mL, 1.67 mmol). After the mixture had been stirred at −78°C for 30 min, it was quenched with K_2CO_3 (307 mg), poured into brine, extracted with CH_2Cl_2 (3×50 mL) and dried over Na_2SO_4. Concentration and flash chromatography (hexanes/EtOAc 4:1) gave **3** (0.447 g, 89%) as a colorless foam. $[\alpha]_D^{27}=-6.2$ ($c=0.53$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.82$–7.76 (m, 2H), 7.64–7.59 (m, 2H), 7.43–7.38 (m, 2H), 7.34–7.29 (m, 2H), 6.01–5.88 (m, 1H), 5.61 (d, $J=7.8$ Hz, 1H), 5.38–5.25 (m, 2H), 4.70 (d, $J=5.1$ Hz, 2H), 4.69–4.60 (m, 1H), 4.46–4.33 (m, 2H), 4.24 (t, $J=6.9$ Hz, 1H), 3.81 (d, $J=11.1$ Hz, 1H), 3.21 (d, $J=11.4$ Hz, 1H), 1.57 (s, 3H), 1.47 ppm (d, $J=6.9$ Hz, 3H); IR (KBr): $\tilde{\nu}=3188$, 3004, 2916, 1729, 1712, 1621, 1539, 1479, 1451, 1385, 1293, 1251, 1166, 1112, 1066, 1028, 980, 934, 749, 663, 574 cm^{-1}; ESIMS: *m*/*z*: 451.3 $[M+H]^+$, 473.2 $[M+Na]^+$, 489.3 $[M+K]^+$; elemental analysis calcd (%) for $C_{25}H_{26}N_2O_4S$: C 66.64, H 5.82, N 6.22; found: C 66.47, H 5.42, N 6.20.

Compound 25a: DIPEA (112 μL, 0.64 mmol) was added dropwise to a stirred solution of **2a** (35 mg, 0.12 mmol), *N*-Fmoc-Ala-Cl (193 mg, 0.59 mmol), and DMAP (7.5 mg, 61 μmol) in CH_2Cl_2 (2 mL) at −15°C. After the mixture had been stirred at −15°C for 5 h, it was poured into water (20 mL) and extracted with CH_2Cl_2 (2×20 mL). The combined organic phase was washed with HCl (5%) and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexanes/EtOAc 25:1 to 15:1) gave **25a** (60 mg, 86%) as a colorless oil and **2a** (3.5 mg). $[\alpha]_D^{25}=+1.6$ ($c=0.98$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=7.8$ Hz, 2H), 7.60 (d, $J=7.5$ Hz, 2H), 7.40 (t, $J=7.2$ Hz, 2H), 7.30 (t, $J=7.2$ Hz, 2H), 5.95–5.84 (m, 1H), 5.41–5.18 (m, 4H), 4.55 (d, $J=5.4$ Hz, 2H), 4.44–4.37 (m, 3H), 4.22 (t, $J=6.8$ Hz, 1H), 3.25 (s, 3H), 3.04- 3.08 (m, 1H). 1.78–1.66 (m, 1H), 1.45 (d, $J=7.2$ Hz, 3H), 1.42–1.25 (m, 8H), 1.21 (s, 6H), 0.91–0.82 ppm (m, 6H); IR (film): $\tilde{\nu}=3341$, 2957, 2937, 1731, 1527, 1452, 1391, 1337, 1252, 1209, 1182, 1145, 1078, 964, 759, 741, 622 cm^{-1}; elemental analysis calcd (%) for $C_{35}H_{47}NO_7$: C 70.80, H 7.98, N 2.36; found: C 70.77, H 8.00, N 2.17; HRMS (ESI-TOF): *m*/*z*: calcd for $C_{35}H_{47}NO_7Na$: 616.3244; found: 616.3224 $[M+Na]^+$.

Compound 26: Prepared from **2c** by the same method as that described for the preparation of **25a** (37%, 60%, **2c** was recovered). $[\alpha]_D^{23}=+1.7$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.75$ (d, $J=7.2$ Hz,

2H), 7.58 (d, $J=7.5$ Hz, 2H), 7.38 (t, $J=7.2$ Hz, 2H), 7.29 (t, $J=7.5$ Hz, 2H), 5.93–5.83 (m, 1H), 5.40 (d, $J=7.2$ Hz, 1H), 5.34–5.16 (m, 3H), 4.54 (d, $J=5.4$ Hz, 2H), 4.42–4.35 (m, 3H), 4.21 (t, $J=6.9$ Hz, 1H), 3.60–3.50 (m, 1H), 1.78–1.65 (m, 1H), 1.43 (d, $J=6.9$ Hz, 3H), 1.43–1.30 (m, 8H), 1.19 (s, 6H), 0.92–0.78 (m, 15H), 0.00 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=175.2$, 143.8, 141.3, 132.0, 127.7, 127.1, 125.1, 120.0, 118.5, 80.9, 72.2, 67.0, 65.5, 49.8, 47.2, 46.9, 39.3, 34.9, 34.7, 31.7, 25.9, 22.6, 21.3, 18.9, 18.5, 18.1, 15.2, 14.3, −4.37, −4.45 ppm; IR (film): $\tilde{\nu}=3348$, 2957, 2934, 2858, 1733, 1651, 1526, 1452, 1338, 1255, 1209, 1143, 1076, 1039, 1006, 964, 836, 775, 759, 740, 622 cm^{-1}; elemental analysis calcd (%) for $C_{40}H_{59}NO_7Si$: C 69.23, H 8.57, N 2.02; found: C 69.32, H 8.45, N 2.07; HRMS (MALDI-TOF): m/z: calcd for $C_{40}H_{59}NO_7SiNa$: 716.3950; found: 716.3938 $[M+Na]^+$.

Compound 27a: $AlCl_3$ (25 mg, 0.19 mmol) was added in portions to a stirred solution of **4a** (57 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C. The suspension was vigorously stirred at room temperature for 2 h and was then neutralized with saturated $NaHCO_3$ solution, extracted with EtOAc (3×10 mL), and dried over Na_2SO_4. Concentration and flash chromatography (hexane/EtOAc 4:1) gave the free amine.

$[Pd(PPh_3)_4]$ (25 mg, 22 μmol) and NMA (55 μL, 0.51 mmol) were added to a solution of **3** (76 mg, 0.17 mmol) in CH_2Cl_2 (2 mL). After the mixture had been stirred at room temperature for 30 min, it was diluted with CH_2Cl_2, washed with 5% HCl and brine, and dried over Na_2SO_4. Concentration gave the crude carboxyl acid.

DIPEA (120 μL, 0.69 mmol) was added to a stirred solution of BEP (103 mg, 0.38 mmol) and the above amine and acid in CH_2Cl_2 (2 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Flash chromatography (hexane/EtOAc 6:1) gave a pair of epimers of **27a** (67 mg, 71% for 2 steps) as a colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=7.5$ Hz, 2H), 7.59 (d, $J=6.9$ Hz, 2H), 7.43–7.38 (m, 2H), 7.33–7.27 (m, 2H), 5.95–5.80 (m, 1H), 5.51–5.21 (m, 3H), 4.97–4.897 (m, 1H), 4.65–4.50 (m, 3H), 4.48–4.37 (m, 2H), 4.25–4.05 (m, 2H), 3.81–3.63 (m, 2H), 3.37–2.89 (m, 4H), 2.46–2.34 (m, 1H), 1.80–1.73 (m, 1H), 1.57–1.52 (m, 3H), 1.47–1.39 (m, 3H), 1.27–1.22 (m, 1H), 1.11–0.92 ppm (m, 24H); HRMS (ESI-TOF): m/z: calcd for $C_{41}H_{59}N_3O_6SSiNa$: 772.3786; found: 772.3755 $[M+Na]^+$.

Compound 28a: A solution of **25a** (46 mg, 77 μmol) in CH_3CN (1 mL) and Et_2NH (0.5 mL) was stirred for 30 min. Concentration and flash chromatography (hexane/EtOAc 10:1 to 1:1) gave the free amine.

$[Pd(PPh_3)_4]$ (10 mg, 8.7 μmol) and NMA (19 μL, 0.17 mmol) were added to a solution of **27a** (43 mg, 0.057 mmol) in CH_2Cl_2 (1 mL). After the reaction mixture had been stirred at room temperature for 30 min, flash chromatography (hexane/EtOAc 5:1 to EtOAc/MeOH 50:1) gave the crude carboxyl acid.

DIPEA (50 μL, 0.29 mmol) was added to a stirred solution of BEP (42 mg, 0.15 mmol) and the above amine and acid in CH_2Cl_2 (1 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight. Flash chromatography (hexane/EtOAc 4:1) gave a pair of diastereomers of **28a** (43 mg, 71% for 2 steps) as a colorless foam. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.76$ (d, $J=6.6$ Hz, 2H), 7.60 (d, $J=6.6$ Hz, 2H), 7.42–7.36 (m, 2H), 7.33–7.28 (m, 2H), 6.80–6.61 (m, 1H), 5.95–5.82 (m, 1H), 5.36–5.09 (m, 3H), 4.74–4.42 (m, 5H), 4.40–3.94 (m, 3H), 3.74–3.62 (m, 3H), 3.37–2.87 (m, 3H), 2.51–2.41 (m, 1H), 2.07–1.59 (m, 14H), 1.54–1.38 (m, 13H), 1.04 (s, 21), 0.98–0.71 ppm (m, 9H); ESIMS: m/z: 1063.7 $[M+H]^+$, 1085.8 $[M+Na]^+$.

Halipeptin A (1a): $[Pd(PPh_3)_4]$ (3.5 mg, 3.0 μmol) and NMA (8 μL, 74 μmol) were added to a solution of **28a** (20 mg, 19 μmol) in CH_2Cl_2 (1 mL), and the reaction mixture was stirred at room temperature for 30 min. Flash chromatography (hexanes/EtOAc 5:1 to EtOAc/MeOH 100:1) gave the crude carboxyl acid. A solution of the acid in CH_3CN (0.35 mL) and Et_2NH (0.35 mL) was stirred for 30 min. Concentration gave the amino acid. DIPEA (21 μL, 0.12 mmol) was added to a stirred solution of the amino acid and HATU (23 mg, 0.060 mmol) in CH_2Cl_2 (8 mL) and DMF (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 d, after which time, the solvent was removed and the residue was purified by flash chromatography (hexanes/EtOAc 6:1 to 3:1) to give a pair of diastereomers **29**a (6.7 mg, 45% for 3 steps) as a colorless foam.

A solution of **29a** (2.6 mg, 3.3 μmol) in THF (0.5 mL) was treated with TBAF (6 μL of a 1 M solution in THF, 6 μmol). The mixture was stirred at room temperature for 48 h. Concentration and preparative TLC (EtOAc) gave halipeptin A (**1a**) (1.4 mg, 70%). $[\alpha]_D^{27}=-13.6$ ($c=0.20$ in $CHCl_3$), (lit.[1a] $[\alpha]_D=-16.6$ ($c=2.9$ in $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.21$ (d, $J=7.9$ Hz, 1H), 7.01 (d, $J=8.2$ Hz, 1H), 5.08 (d, $J=10.2$ Hz, 1H), 4.82 (q, $J=7.1$ Hz, 1H), 4.78 (q, $J=7.4$ Hz, 1H), 4.71 (d, $J=2.4$ Hz, 1H), 4.16 (d, $J=12.1$ Hz, 1H), 3.75–3.80 (m, 1H), 3.70–3.64 (m, 1H), 3.29 (d, $J=11.9$ Hz, 1H), 3.30 (s, 3H), 3.12–3.06 (m, 1H), 2.82 (s, 3H), 2.54–2.49 (m, 1H), 1.93–1.88 (m, 1H), 1.51 (d, $J=6.9$ Hz, 3H), 1.48 (s, 3H), 1.42 (d, $J=7.2$ Hz, 3H), 1.39–1.28 (m, 10H), 1.20 (s, 3H), 1.13 (s, 3H), 1.00 (d, $J=6.9$ Hz, 3H), 0.87–0.93 (m, 3H), 0.81 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=174.4$, 173.6, 172.5, 169.7, 169.2, 84.0, 82.6, 80.6, 64.7, 60.8, 56.5, 49.6, 48.6, 45.8, 44.3, 35.8, 35.3, 34.3, 32.0, 31.3, 30.7, 28.2, 26.2, 23.1, 22.4, 22.1, 18.5, 18.4, 18.1, 14.5, 14.3 ppm; HRMS (ESI-TOF): m/z: calcd for $C_{31}H_{54}N_4O_7SNa$: 649.3605; found: 649.3620 $[M+Na]^+$.

Halipeptin D (1d) and *epi*-halipeptin D (*epi*-1d): Halipeptins **1d** and ***epi*-1d** were prepared from **3**, **4d**, and **25a** by the same method as that described for the preparation of **29a**, and were separated by preparative TLC (CH_2Cl_2/acetone 20:1).

*Halipeptin D (**1d**)*: Yield: 8% for 7 steps; $[\alpha]_D^{23}=-29.1$ ($c=0.3$ in $CHCl_3$), (lit.[1c] $[\alpha]_D^{25}=-26.0$ ($c=2.9$ in $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.22$ (d, $J=7.8$ Hz, 1H), 7.01 (d, $J=8.4$ Hz, 1H), 5.01 (d, $J=10.4$ Hz, 1H), 4.84 (q, $J=7.2$ Hz, 1H), 4.79 (q, $J=7.0$ Hz, 1H), 4.71 (d, $J=2.4$ Hz, 1H), 4.15 (d, $J=12.0$ Hz, 1H), 3.31 (d, $J=12.0$ Hz, 1H), 3.31 (s, 3H), 3.12–3.05 (m, 1H), 2.80 (s, 3H), 2.25–2.18 (m, 1H), 1.95–1.87 (m, 1H), 1.51 (d, $J=7.0$ Hz, 3H), 1.50–1.30 (m, 10H), 1.46 (s, 3H), 1.41 (d, $J=7.2$, 3H), 1.22 (s, 3H), 1.14 (s, 3H), 1.00–0.85 (m, 9H), 0.81 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=177.3$, 173.6, 172.6, 169.6,169.4, 84.0, 82.7, 80.6, 65.1, 56.5, 49.5, 48.6, 45.8, 44.4, 35.7, 34.3, 33.6, 32.0, 31.3, 30.7, 26.2, 25.1, 23.2, 22.3, 22.0, 18.5, 18.1, 17.7, 14.4, 14.3, 12.6 ppm; HRMS (MALDI-TOF): m/z: calcd for $C_{31}H_{55}N_4O_6S$: 611.3867; found: 611.3841 $[M+H]^+$.

*epi-Halipeptin D (epi-**1d**)*: Yield: 8% for 6 steps; $[\alpha]_D^{23}=-17.5$ ($c=0.45$ in $CHCl_3$) (lit.[2e] $[\alpha]_D^{32}=-13.8$ ($c=0.45$ in $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.80$ (d, $J=5.2$ Hz, 1H), 6.60 (d, $J=9.0$ Hz, 1H), 5.32 (d, $J=10.2$ Hz, 1H), 4.86 (q, $J=7.3$ Hz, 1H), 4.77 (q, $J=6.3$ Hz, 1H), 4.74 (s, 1H), 4.03 (d, $J=12.1$ Hz, 1H), 3.34 (d, $J=12.1$ Hz, 1H), 3.29 (s, 3H), 3.10–3.08 (m, 1H), 2.81 (s, 3H), 2.23–2.10 (m, 1H), 2.15–2.00 (m, 1H), 1.47 (d, $J=6.7$ Hz, 3H), 1.45–1.25 (m, 10H), 1.45 (s, 3H), 1.35 (d, $J=7.1$, 3H), 1.25 (s, 3H), 1.13 (s, 3H), 1.02 (d, $J=6.4$ Hz, 3H), 1.00 (t, $J=7.2$ Hz, 3H), 0.91 (t, $J=7.1$ Hz, 3H), 0.68 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=176.9$, 173.6, 172.8, 170.4, 169.4, 84.9, 82.3, 80.6, 64.9, 56.5, 49.2, 49.1, 45.2, 43.4, 35.7, 33.5, 33.0, 32.4, 31.2, 30.7, 25.6, 24.4, 23.3, 22.9, 21.5, 19.6, 18.5, 17.5, 14.3, 14.1, 12.5 ppm; HRMS (MALDI-TOF): m/z: calcd for $C_{31}H_{55}N_4O_6S$: 611.3867; found: 611.3841 $[M+H]^+$.

Compound 28b: Prepared from **26** and **27a** by the same method as for the preparation of **28a**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.74$ (d, $J=7.2$ Hz, 2H), 7.67 (d, $J=6.9$ Hz, 1H), 7.56 (d, $J=6.6$ Hz, 2H), 7.40–7.36 (m, 2H), 7.30–7.24 (m, 2H), 6.70 (d, $J=8.1$ Hz, 1H), 5.91–5.80 (m, 1H), 5.37–5.15 (m, 3H), 4.62–4.52 (m, 4H), 4.45–3.99 (m, 4H), 3.69–3.48 (m, 3H), 3.34–2.85 (m, 4H), 2.69–2.37 (m, 1H), 2.10–1.95 (m, 1H), 1.56–1.17 (m, 23H), 1.10–0.60 (m, 39H), 0.04–0.00 ppm (m, 6H); HRMS (MALDI-TOF): m/z: calcd for $C_{63}H_{102}N_4O_{10}SSi_2Na$: 1185.6747; found: 1185.6763 $[M+Na]^+$.

Halipeptin B (1b) and *epi*-halipeptin B (*epi*-1b): The halipeptin B silyl derivative was prepared from **28b** by the same method as that described for the preparation of **29a** (33% for 4 steps).

HF (40%, 0.05 mL) was added to a solution of the above silyl ether (25 mg, 0.028 mmol) in CH_3CN (1 mL). After the mixture had been stirred for 2 h, it was partitioned between H_2O (10 mL) and EtOAc (10 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL). The combined organic phase was washed with brine and dried over Na_2SO_4. Preparative TLC (EtOAc/MeOH 20:1) gave a pair of diastereomers **1b** and ***epi*-1b** (13 mg, 76%) in a ratio of about 1:1.

TBAF (30 μL, 30 μmol) and hexylOTBS (3.3 mg, 15 μmol) were added to a solution of **1b**/*epi*-**1b** (9 mg, 15 μmol). After the mixture had been stirred at room temperature for 48 h, it was purified by preparative TLC to give a pair of diastereomers, **1b** and *epi*-**1b** (4.5 mg, 50%), in the ratio of about 6:1. $[\alpha]_D^{23}=-22.7$ ($c=0.95$ in $CHCl_3$) (lit.[1a] $[\alpha]_D=-22.7$ ($c=0.2$ in $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$): major: $\delta=7.21$ (d, $J=7.2$ Hz, 1H), 7.02 (d, $J=8.4$ Hz, 1H), 5.08 (d, $J=10.2$ Hz, 1H), 4.87–4.80 (m, 1H), 4.78–4.73 (m, 1H), 4.72 (d, $J=2.7$ Hz, 1H), 4.16 (d, $J=12.0$ Hz, 1H), 3.85–3.75 (m, 1H), 3.75–3.62 (m, 1H), 3.62–3.50 (m, 1H), 3.30 (d, $J=11.4$ Hz, 1H), 2.82 (s, 3H), 2.60–2.43 (m, 1H), 2.00–1.90 (m, 1H), 1.55–1.30 (m, 10H), 1.51 (d, J=7.5 Hz, 3H), 1.48 (s, 3H), 1.42 (d, $J=6.9$ Hz, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 0.98 (d, $J=6.0$ Hz, 3H), 0.92 (t, $J=6.9$ Hz, 3H), 0.81 ppm (d, $J=6.9$ Hz, 3H); minor: $\delta=6.82$ (d, $J=5.7$ Hz, 1H), 6.60 (d, $J=9.3$ Hz, 1H), 5.39 (d, $J=9.9$ Hz, 1H), 4.87–4.73 (m, 3H), 4.05 (d, $J=12.0$ Hz, 1H), 3.85–3.75 (m, 1H), 3.75–3.62 (m, 1H), 3.62–3.50 (m, 1H), 3.34 (d, $J=11.7$ Hz, 1H), 2.83 (s, 3H), 2.40–2.30 (m, 1H), 2.18–2.08 (m, 1H), 1.55–1.30 (m, 10H), 1.51 (d, $J=7.5$ Hz, 3H), 1.50 (s, 3H), 1.38 (d, $J=5.4$ Hz, 3H), 1.21 (s, 3H), 1.13 (s, 3H), 1.06 (d, $J=5.7$ Hz, 3H), 0.92 (t, $J=6.9$ Hz, 3H), 0.68 ppm (d, $J=6.9$ Hz, 3H); HRMS (MALDI-TOF): m/z: calcd for $C_{30}H_{52}N_4O_7SNa$: 635.3449; found: 635.3467 $[M+Na]^+$.

Compound 27c: Prepared from **3** and **4c** by the same method as described for the preparation of **27a** (82%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 7.76 (d, $J=7.5$ Hz, 2H), 7.67 (d, $J=7.5$ Hz, 1H), 7.58 (d, $J=7.8$ Hz, 2H), 7.41 (d, $J=7.5$ Hz, 2H), 7.31 (d, $J=6.6$ Hz, 2H), 5.90–5.84 (m, 1H), 5.43–5.21 (m, 2H), 4.80–4.54 (m, 3H), 4.42–4.20 (m, 2H), 4.25–4.21 (m, 2H), 3.33–2.98 (m, 4H), 2.29–2.23 (m, 1H), 1.53 (d, $J=7.5$ Hz, 3H), 1.01–0.78 ppm (m, 6H); ESIMS: m/z: 564.5 $[M+H]^+$, 586.4 $[M+Na]^+$.

Compound 28c: Prepared from **27c** and **26** by the same method as described for the preparation of **28a** (70%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.71$ (d, $J=6.6$ Hz, 2H), 7.70–7.65 (m, 1H), 7.56 (d, $J=6.9$ Hz, 2H), 7.40–7.30 (m, 2H), 7.28–7.18 (m, 2H), 6.70–6.64 (m, 1H), 5.92–5.78 (m, 1H), 5.36–5.14 (m, 3H), 4.81–4.45 (m, 4H), 4.43–3.96 (m, 4H), 3.56–3.50 (m, 2H), 3.26–2.81 (m, 3H), 2.50–2.23 (m, 1H), 1.75–1.60 (m, 2H), 1.50–1.10 (m, 23H), 1.10–0.60 (m, 21H), 0.00 ppm (s, 6H); HRMS (MALDI-TOF): m/z: calcd for $C_{53}H_{80}N_4O_9SSiNa$: 999.5308; found: 999.5313 $[M+Na]^+$.

Halipeptin C (1c) and *epi*-halipeptin C (*epi*-1c): Halipeptins **1c** and *epi*-**1c** were prepared from **28a** by the same method as that described for the preparation of **1b**/*epi*-**1b**, which were separated by preparative TLC (CH_2Cl_2/MeOH 25:1).

*Halipeptin C (**1c**)*: Yield: 23% for 4 steps; $[\alpha]_D^{23}-33.4$ ($c=0.30$ in $CHCl_3$), (lit.[1b] $[\alpha]_D=-30$ ($c=0.3$ in $CHCl_3$)); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=$ 7.23 (d, $J=7.8$ Hz, 1H), 6.97 (d, $J=8.0$ Hz, 1H), 4.99 (d, $J=10.3$ Hz, 1H), 4.83 (q, $J=7.4$ Hz, 1H), 4.74 (q, $J=7.3$ Hz, 1H), 4.71 (d, $J=2.6$ Hz, 1H), 4.16 (d, $J=12.1$ Hz, 1H), 3.60–3.50 (m, 1H), 3.31 (d, $J=12.0$ Hz, 1H), 2.81 (s, 3H), 2.60–2.51 (m, 1H), 1.98–1.93 (m, 1H), 1.51 (d, $J=$ 6.8 Hz, 3H), 1.50 (s, 3H), 1.45–1.25 (m, 8H), 1.41 (d, $J=7.2$ Hz, 3H), 1.20 (s, 3H), 1.16 (s, 3H), 0.98 (d, $J=6.4$ Hz, 3H), 0.93 (d, $J=7.1$ Hz, 3H), 0.91 (t, $J=7.0$ Hz, 3H), 0.80 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=177.2$, 173.6, 172.6, 169.8, 169.5, 84.0, 82.6, 71.5, 65.2, 49.7, 48.6, 45.8, 44.4, 39.8, 34.9, 34.1, 32.2, 30.9, 26.5, 26.2, 23.3, 22.4, 22.0, 21.1, 18.8, 18.4, 17.9, 14.4, 14.1 ppm; HRMS (MALDI-TOF): m/z: calcd for $C_{29}H_{51}N_4O_6S$: 583.3524; found: 583.3544 $[M+H]^+$.

*epi-Halipeptin C (epi-**1c**)*: Yield: 23% for 4 steps; $[\alpha]_D^{23}=-19.2$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=6.82$ (d, $J=5.4$ Hz, 1H), 6.55 (d, $J=8.9$ Hz, 1H), 5.28 (d, $J=10.2$ Hz, 1H), 4.82 (q, $J=8.0$ Hz, 1H), 4.77 (q, $J=6.3$ Hz, 1H), 4.73 (d, $J=1.2$ Hz, 1H), 4.04 (d, $J=12.1$ Hz, 1H), 3.55–3.50 (m, 1H), 3.35 (d, $J=12.1$ Hz, 1H), 2.82 (s, 3H), 2.61–2.52 (m, 1H), 2.15–2.08 (m, 1H), 1.49 (s, 3H), 1.48 (d, $J=8.6$ Hz, 3H), 1.37 (d, $J=7.2$ Hz, 3H), 1.50–1.25 (m, 8H), 1.24 (s, 3H), 1.12 (s, 3H), 1.07 (d, $J=6.4$ Hz, 3H), 0.99 (d, $J=7.1$ Hz, 3H), 0.92 (t, $J=6.4$ Hz, 3H), 0.69 ppm (d, $J=6.8$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=176.8$, 173.6, 172.9, 170.5, 169.5, 84.8, 82.3, 71.4, 65.1, 49.2, 49.1, 45.2, 43.5, 39.7, 35.0, 32.9, 32.5, 30.8, 26.5, 24.4, 23.5, 22.9, 21.5, 21.0, 19.4, 18.85, 18.83, 14.2, 14.1 ppm; HRMS (MALDI-TOF): m/z: calcd for $C_{29}H_{51}N_4O_6S$: 583.3524; found: 583.3544 $[M+H]^+$.

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