Synthesis of Four Lysine-Linked Cereulide Analogues Showing Ionophoric Activity Towards Potassium Cations as Lead Compounds for Emetic Toxin-Detection by Immunoassays

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Abstract: An improved total synthesis of the emetic toxin cereulide and the preparation of four lysine-linked cereulide analogues is described. The cereulide analogues are prepared by replacing one of the amino acid residues in cereulide with lysine. The cereulide analogues demonstrate ionophoric activity towards alkali metal ions and inorganic ammonium ions, and are currently being used to develop an enzyme-linked immunosorbent assay for cereulide.

Key words: cereulide, *Bacillus cereus*, peptide synthesis, ionophore, L-*O*-lysine

The bacterium *Bacillus cereus* can cause two types of food poisoning, emetic and diarrheal. The emetic-type syndrome is caused by an emetic toxin and the diarrheal-type condition is triggered by enterotoxins.[1] The *Bacillus cereus* group of bacteria consists of six related members (*B. anthracis, B. cereus, B. mycoides, B. pseudomycoides, B. thuringiensis and B. weihenstephanensis*). These species are closely related and should be classified within the same species, except for *B. anthracis* which causes anthrax. *Bacillus thuringiensis* is widely used for its insecticidal properties, however, it has also been associated with foodborne disease.[1] Cereulide (**1**) is a known emetic toxin produced through an unusual non-ribosomal peptide synthesis (NRPS) by *Bacillus cereus*. It was first isolated in 1994 by Isobe et al. and its structure elucidated as that shown in Figure 1.[2,3] The configurations of the stereogenic centers of cereulide were confirmed by chemical degradation and the full structure was assigned on the basis of NMR spectroscopy and molecular mechanics calculations. Cereulide (**1**) is a 36-membered cyclic depsipeptide containing 12 stereogenic centers and a *cyclo* [-D-*O*-Leu-D-Ala-L-*O*-Val-L-Val-]$_3$ peptide sequence (Figure 1).[3]

The ionophore properties of cereulide with alkali metal ions (Li^+, Na^+, K^+, Rb^+, Cs^+), hydrogen ions and also with inorganic and organic ammonium ions have been reported. The potassium ion was found to be a highly selective guest in complexation with cereulide.[3,4] This selective binding may be associated with the activity of **1** in forming vacuoles, which is apparent from mitochondrial swelling in HEp-2 cells.[2,5] The emetic effect of cereulide in *Suncus murinus* has been reported.[5] Food contaminated with cereulide can lead to heavy nausea, vomiting, and episodes of abdominal pain.[6] It is therefore clear that the presence of cereulide in food and animal feeds is potentially hazardous to the health of both humans and animals. Furthermore, cereulide contamination affects the economic values of crops and reduces the efficiency of animal production, resulting in higher costs incurred by all sectors from production to consumption. Cereulide con-

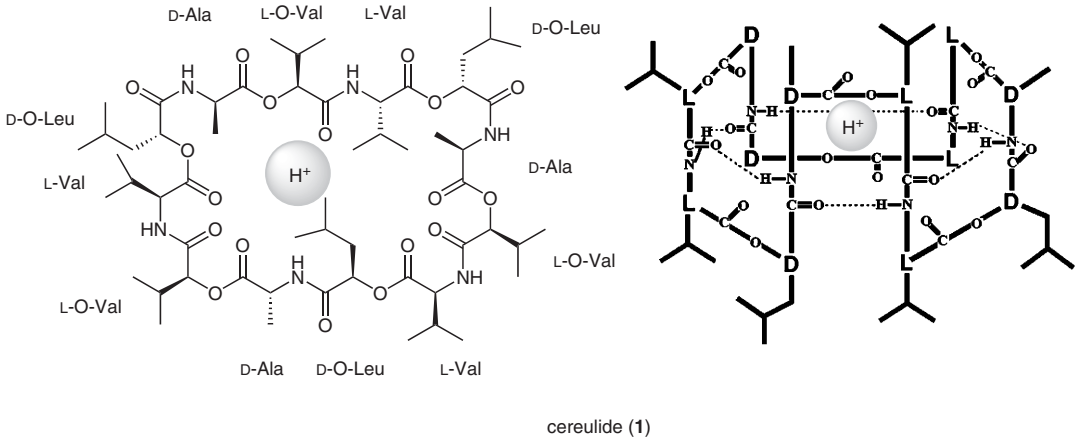

Figure 1 The 2D (left) and 3D (right) structure of cereulide (**1**)

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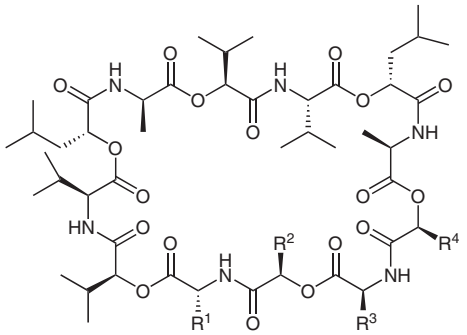
tamination is most frequently found in milk, pasta and cooked rice. Contamination can occur during transportation and storage under conditions where molds can grow. Moreover, this toxin is stable to acidic and basic conditions, heat and proteolytic enzymes, and is very difficult to destroy once formed.[7] Thus, it is important to prevent mold from growing through careful agricultural storage and manufacturing practices, with appropriate monitoring for possible contamination. Additionally, suitable analytical methods for detection and quantification are essential for effective food and/or feed safety control. The current standard methods for detection of cereulide are oral challenge in mammals, microscopic assessment of vacuole formation in HEp-2 cells,[8] high-performance liquid chromatography (HPLC),[9] nano-HPLC-ESI-Q-TOF-MS,[10] liquid chromatography–mass spectrometry (LC–MS)[11] and polymerase chain reaction (PCR) assays for the detection of emetic *Bacillus cereus*.[12] However, these methods require extensive sample preparation and make use of expensive instrumentation.

Enzyme-linked immunosorbent assay (ELISA) is a biochemical technique used largely in immunology to detect the presence of an antibody or an antigen in samples,[13] and has been used as a diagnostic tool in medicine and plant pathology, as well as for quality control checks in various industries. Modification of proteins, DNA and other biopolymers by labeling with reporter molecules is a very powerful research tool in immunology, histochemistry and cell biology.[14] The objective of this study was to synthesize lysine-linked cereulide analogues for the preparation of protein conjugates with biotin to develop a quick and effective ELISA test for cereulide analysis.

Cereulide (**1**) was synthesized in 1995 by Isobe et al. in 14 steps and 2% overall yield using the commercially available components L-*O*-Val, L-Val, L-*O*-Leu and D-Ala.[15a] Synthetic **1** exhibited the same emetic toxin, ionophoric and pathogenic activities as naturally occurring cereulide.[15b] We herein report on the improvement of the total synthesis of cereulide (**1**) and the preparation of four lysine-linked cereulide analogues **2**–**5**. The four cereulide analogues, namely cereulide DAK1 (**2**), cereulide DOLK1 (**3**), cereulide LVK1 (**4**) and cereulide LOVK1 (**5**), which have a lysine-linked side-chain were synthesized by replacing one of the original amino acid residues in cereulide with lysine (Figure 2). For example, cereulide DAK1 (**2**) is a lysine-linked cereulide analogue where one D-alanine residue is replaced by a D-lysine residue.

The synthesis of cereulide (**1**) was started from D-alanine benzyl ester hydrochloride (**7**), itself prepared from D-alanine (**6**) using thionyl chloride and benzyl alcohol. Dipeptide **9** was obtained in excellent yield by coupling compound **7** with L-*O*-leucine (**8**) using *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDCI) and *N*-hydroxybenzotriazole (HOBt) in the presence of *N*,*N*-diisopropylethylamine (DIPEA). These coupling conditions were also utilized for the preparation of dipeptide **12** from L-*O*-valine (**10**) and L-valine benzyl ester (**11**). The hydroxy group in **12** was protected as the *tert*-butyldimethylsilyl ether to afford dipeptide **13** and subsequent cleavage of the benzyl group gave acid **14**. Next, dipeptides **9** and **14** were coupled under Mitsunobu conditions to yield tetrapeptide **15** in quantitative yield with inversion of configuration. Removal of the *tert*-butyldimethylsilyl group in **15** with hydrofluoric acid/pyridine gave tetrapeptide **16** in 95% yield whereas hydrogenation of **15** afforded tetrapeptide **17** in an excellent 99% yield (Scheme 1).



1 cereulide; R^1 = Me, R^2 = *i*-Bu, R^3 = R^4 = *i*-Pr
2 cereulide DAK1; R^1 = $(CH_2)_4NH_3^+$, R^2 = *i*-Bu, R^3 = R^4 = *i*-Pr
3 cereulide DOLK1; R^1 = Me, R^2 = $(CH_2)_4NH_3^+$, R^3 = R^4 = *i*-Pr
4 cereulide LVK1; R^1 = Me, R^2 = *i*-Bu, R^3 = $(CH_2)_4NH_3^+$; R^4 = *i*-Pr
5 cereulide LOVK1 ; R^1 = Me, R^2 = *i*-Bu, R^3 = *i*-Pr; R^4 = $(CH_2)_4NH_3^+$

Figure 2 The structures of cereulide (**1**) and lysine-linked cereulide analogues **2**–**5**

Head-to-tail coupling of tetrapeptides **16** and **17** using inexpensive, commercially available *p*-toluyl chloride in the presence of triethylamine and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) gave octapeptide **18** in 83% yield without any racemization as was evident by NMR analysis.[16] Yamaguchi esterification using the more sterically hindered 2,4,6-trichlorobenzoic anhydride gave only a 44% yield of the desired octapeptide **18**.[15b] Desilylation of **18** with hydrofluoric acid/pyridine gave octapeptide **19** in 92% yield which was then coupled with carboxylic tetrapeptide **17** under identical conditions to those used for the synthesis of octapeptide **18**, to provide dodecapeptide **20** in 68% yield. Removal of the *tert*-butyldimethylsilyl and benzyl protecting groups gave dodecapeptide **22** in excellent yield. Macrolactonization of compound **22** was carried out successfully under high-dilution conditions (1.5 mM) using *m*-nitrobenzoic anhydride (MNBAN)[17] to give cereulide (**1**) in 73% yield (Scheme 2). Only a trace amount of polymerization product was observed. Cereulide was obtained in 23% overall yield in 14 steps via this approach.

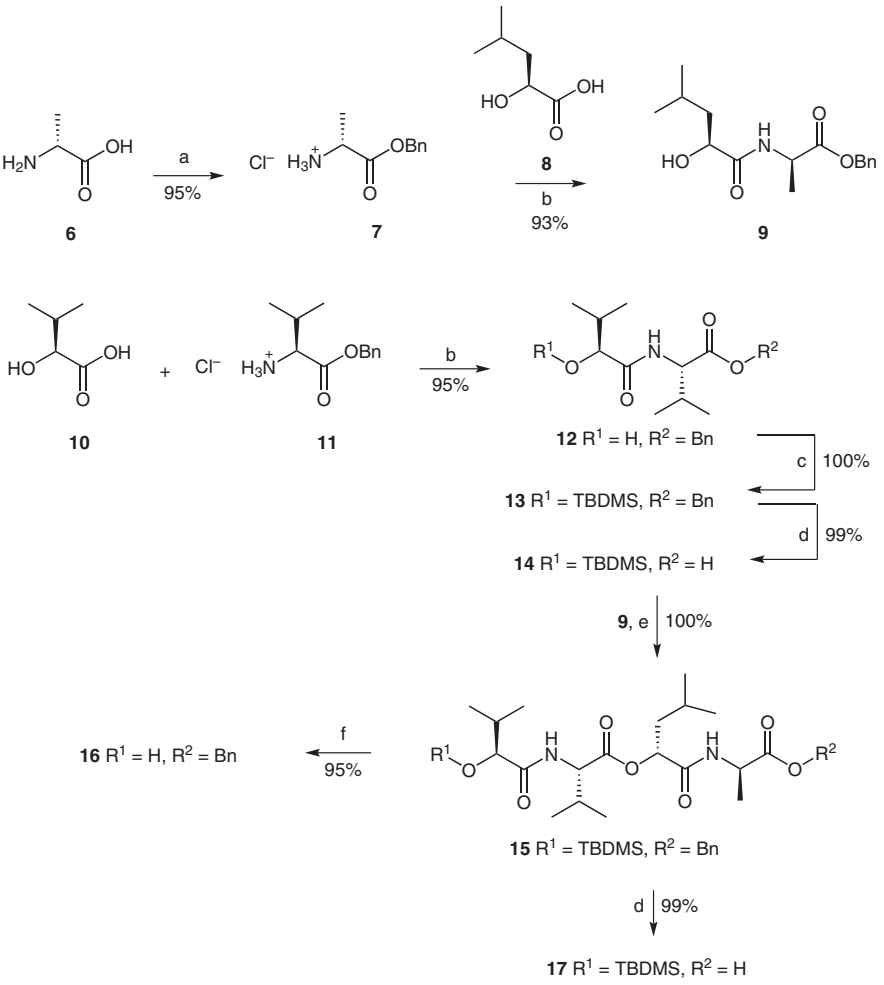
This efficient synthetic strategy, albeit with minor modifications, was utilized for the synthesis of lysine-linked cereulide analogues **2**–**5**. At this stage it was necessary to prepare the precursor L-*O*-lysine(Boc)-OH (**26**). Initially, L-*O*-lysine (**25**) containing an unprotected side-chain was synthesized in two steps starting from L-lysine (**23**). Treatment of **23** with sulfuric acid (10% aqueous solution) followed by sodium nitrite in sulfuric acid (10% aqueous solution)[18] gave L-*O*-lysine (**25**). Protection of the amino

group with di-*tert*-butyl dicarbonate afforded L-*O*-lysine(Boc)-OH (**26**) in 38% yield over the three steps (Scheme 3).[19]

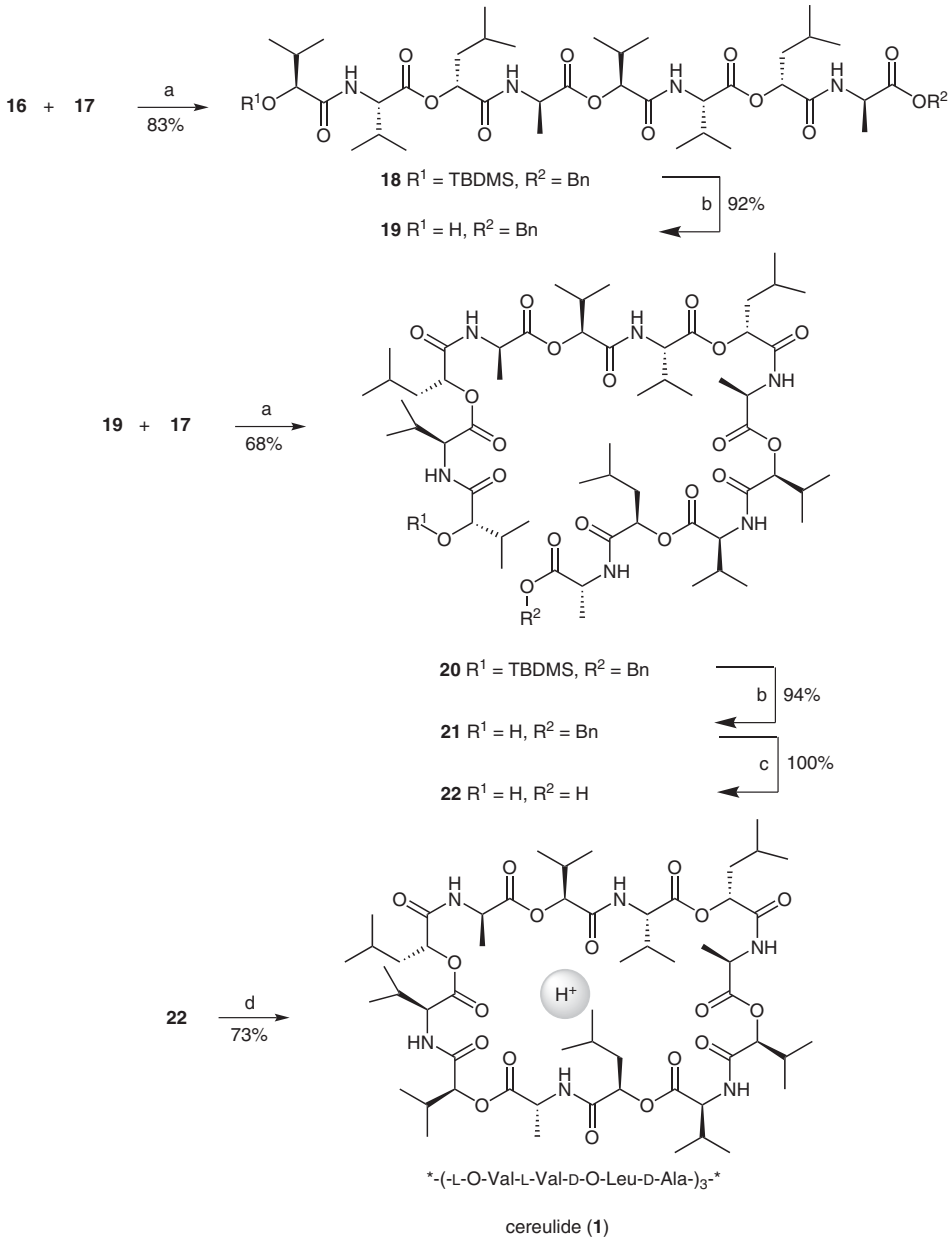
The synthesis of cereulide DAK1 (**2**) is shown in Scheme 4. Fmoc-D-lysine(Boc) benzyl ester (**28**) was prepared in 98% yield from Fmoc-D-lysine(Boc)-OH (**27**) by protection of the carboxyl group using benzyl alcohol in the presence of diisopropyl azodicarboxylate (DIAD) and triphenylphosphine in tetrahydrofuran. Removal of the Fmoc group using diethylamine and coupling of the resulting amine with L-*O*-leucine employing 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) and *N*-hydroxybenzotriazole in the presence of *N*,*N*-diisopropylethylamine gave dipeptide **29**.[20] Dipeptides **29** and **14** were condensed under Mitsunobu conditions to yield tetrapeptide **30** with inversion of configuration. Debenzylation of **30** afforded tetrapeptide **31** which was then coupled with octapeptide **19** (under the same conditions utilized for the synthesis of dodecapeptide **20**) to provide dodecapeptide **32** in 61% yield without racemization as was evident from NMR analysis. The silyl and benzyl protecting groups were removed to give dodecapeptide **34**. Macrolactonization of compound **34** under under high-dilution conditions yielded cereulide DAK1-*N*-Boc (**35**) in 73% yield. Finally, removal of the Boc group using trifluoroacetic acid–dichloromethane (1:1) proceeded smoothly to furnish cereulide DAK1 (**2**) in quantitative yield. Cereulide DAK1 (**2**) was obtained in 12% overall yield over 20 steps.

The synthesis of cereulide DOLK1 **3** is outlined in Scheme 5. Dipeptide **36** was prepared by coupling D-alanine benzyl ester hydrochloride (**7**) with L-*O*-lysine(Boc) (**26**) under the same conditions as reported for the synthesis of compound **9**. Dipeptides **36** and **14** were coupled under Mitsunobu conditions to yield tetrapeptide **37** with inversion of configuration. Debenzylation gave tetrapeptide **38** which was coupled with octapeptide **19** (under the same conditions used for the synthesis of dodecapeptide **20**) to afford dodecapeptide **39** in 74% yield without racemization as was evident from NMR analysis. Cereulide DOLK1 (**3**) was successfully obtained from dodecapeptide **39** using the same conditions described for the synthesis of DAK1 from dodecapeptide **32**. Cereulide DOLK1 (**3**) was obtained in 11% overall yield in 18 steps.

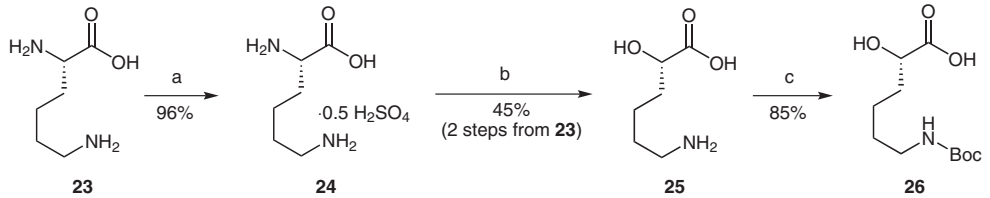
The synthesis of cereulide LVK1 (**4**) was carried out as shown in Scheme 6. Fmoc-L-lysine(Boc)-OH (**43**) was



Scheme 1 Synthesis of tetrapeptides **16** and **17**. *Reagents and conditions*: (a) $SOCl_2$, BnOH, r.t.; (b) EDCI, HOBt, DIPEA, THF, 0 °C to r.t.; (c) TBDMSCl, imidazole, DMF, 50 °C; (d) H_2, 10% Pd/C, THF, r.t.; (e) DIAD, Ph_3P, THF, –15 °C to r.t.; (f) 70% HF/py, THF, r.t.



Scheme 2 Synthesis of cereulide (**1**). *Reagents and conditions*: (a) *p*-toluyl chloride, Et_3N, DMAP, toluene, r.t.; (b) 70% HF/py, THF, r.t.; (c) H_2, 10% Pd/C, THF, r.t.; (d) MNBAN, DMAP, CH_2Cl_2, (*c* 1.5 mM), r.t.

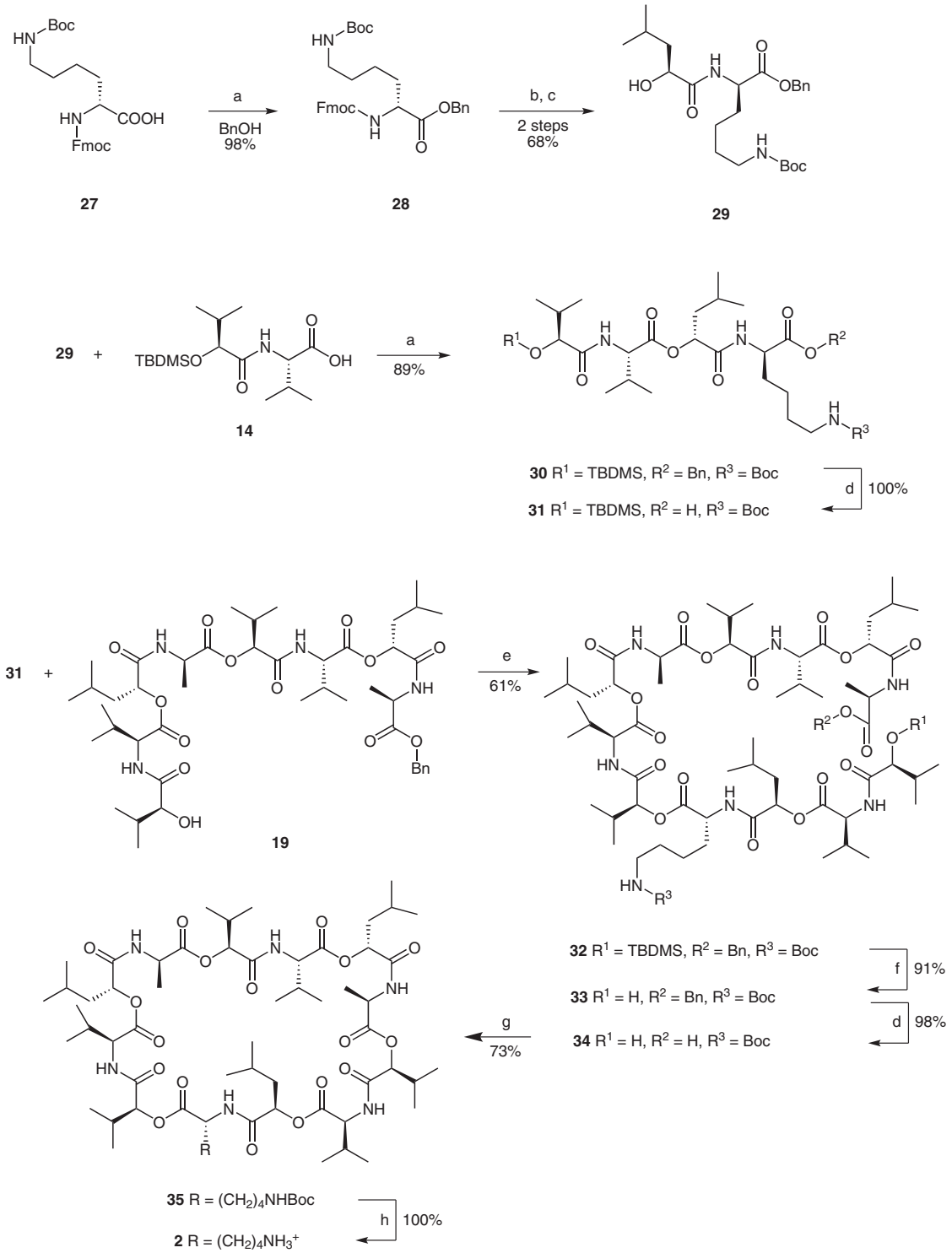


Scheme 3 Synthesis of L-*O*-lysine(Boc)-OH (**26**). *Reagents and conditions*: (a) 10% H_2SO_4, r.t.; (b) $NaNO_2$, 10% H_2SO_4, 45–50 °C; (c) 1 M NaOH; 1,4-dioxane, $(Boc)_2O$, 0 °C.

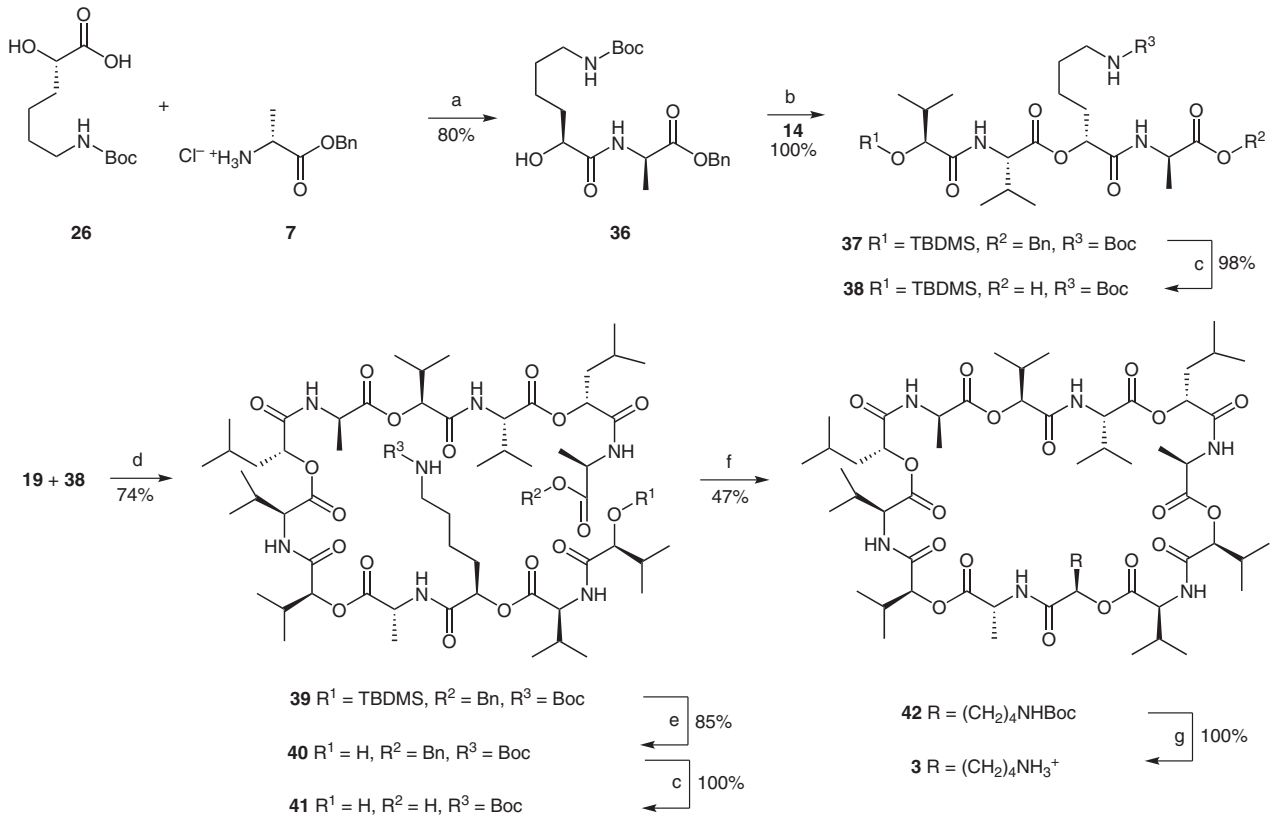
coupled with dipeptide **9** using the Mitsunobu reaction to provide tripeptide **44** with inversion of configuration. Removal of the Fmoc group, followed by coupling with L-*O*-valine (**10**) using 2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate and *N*-hydroxybenzotriazole in the presence of *N*,*N*-diisopropylethylamine provided tetrapeptide **46**. Octapeptide **47**, obtained by debenzylation of **18**, was coupled with tetrapeptide **46** (under the same conditions utilized for the synthesis of dodecapeptide **20**) to afford dodecapeptide **48** in 65% yield without racemization as was evident from NMR analysis. The preparation of cereulide LVK1 (**4**)

was completed from dodecapeptide **48** following the same procedure as described for the synthesis of DAK1 (**2**) from dodecapeptide **32**. Cereulide LVK1 (**3**) was obtained in 7% overall yield in 18 steps.

The preparation of cereulide LOVK1 (**5**) is described in Scheme 7. Dipeptide **52** was obtained by coupling L-valine benzyl ester hydrochloride (**11**) with L-*O*-lysine(Boc) (**26**) using *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide and *N*-hydroxybenzotriazole in the presence of *N*,*N*-diisopropylethylamine. Protection of the hydroxy group in dipeptide **52** as the *tert*-butyldimethylsilyl ether, followed by debenzylation, furnished dipeptide **54** which



Scheme 4 Synthesis of cereulide DAK1 (**2**). *Reagents and conditions*: (a) DIAD, Ph_3P, THF, –15 °C to r.t.; (b) Et_2NH, MeCN, –10 °C; (c) **8**, HATU, HOBt, DIPEA, THF, –10 °C to r.t.; (d) H_2, 10% Pd/C, THF, r.t.; (e) *p*-toluyl chloride, Et_3N, DMAP, toluene, r.t.; (f) 70% HF/py, THF, r.t.; (g) MNBAN, DMAP, CH_2Cl_2, (*c* 1.5 mM), r.t.; (h) TFA–CH_2Cl_2 (1:1), 0 °C.



Scheme 5 Synthesis of cereulide DOLK1 (**3**). *Reagents and conditions*: (a) EDCI, HOBt, DIPEA, THF, 0 °C to r.t.; (b) DIAD, Ph_3P, THF, –15 °C to r.t.; (c) H_2, 10% Pd/C, THF, r.t.; (d) *p*-toluyl chloride, Et_3N, DMAP, toluene, r.t.; (e) 70% HF/py, THF, r.t.; (f) MNBAN, DMAP, CH_2Cl_2, (*c* 1.5 mM), r.t.; (g) TFA–CH_2Cl_2 (1:1), 0 °C.

was coupled with dipeptide **9** under Mitsunobu conditions to provide tetrapeptide **55** with inversion of configuration. After debenzylation, the resulting tetrapeptide **56** was converted to cereulide LOK1 (**5**) using the same procedure as described for the conversion of tetrapeptide **38** into cereulide DOLK1 (**3**). Cereulide LOVK1 (**5**) was obtained in 14% overall yield over 20 steps.

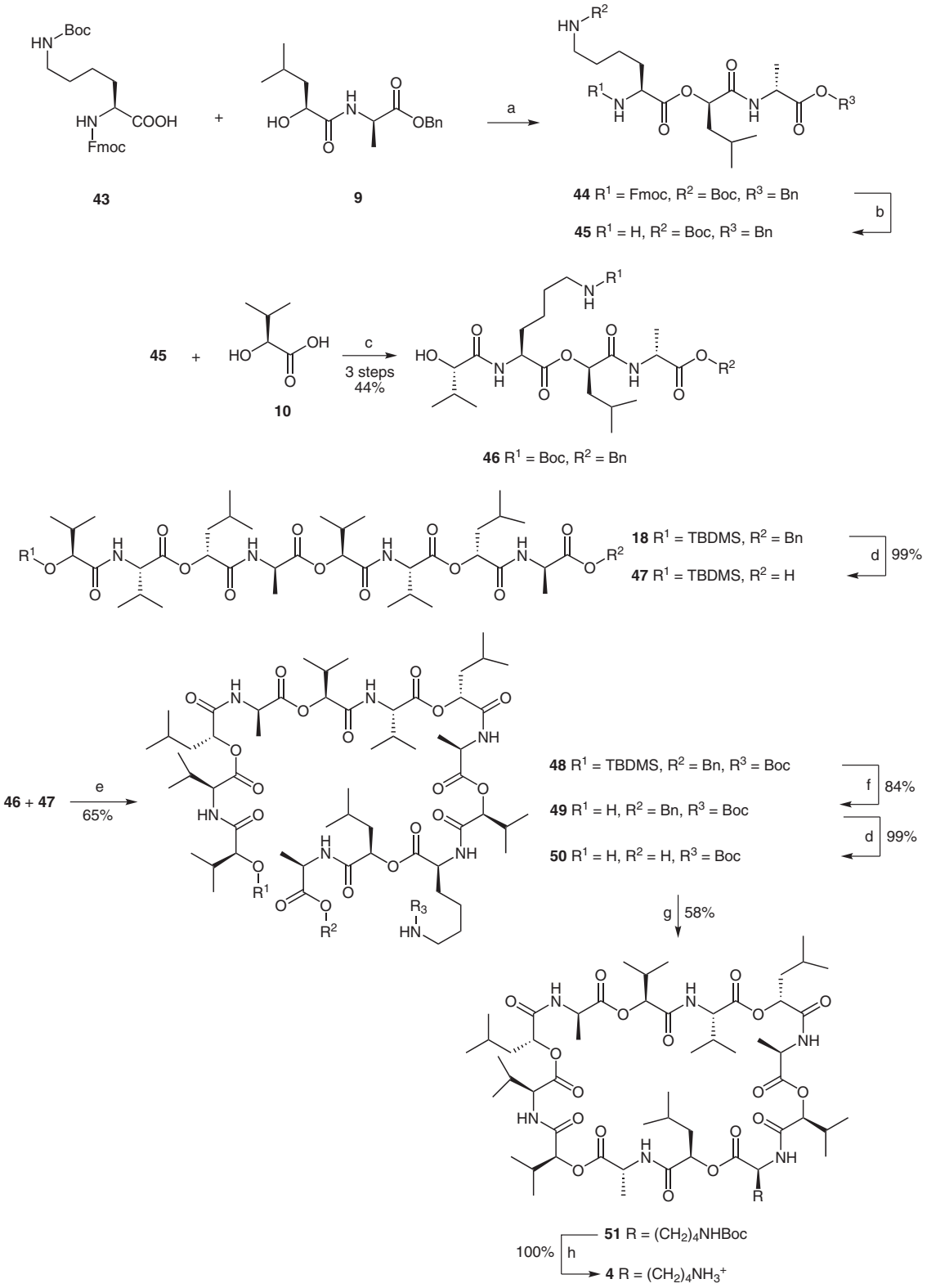
Table 1 The Response of Vacuoles to Cereulide (**1**) and Lysine-Linked Cereulide Analogues **2–5** in HEp2-cells.

Emetic[a]	HEp2-cell response (n)[b]
cereulide (**1**)	1200000
cereulide DAK1 (**2**)	1024
cereulide DOLK1 (**3**)	1024
cereulide LVK1 (**4**)	1024
cereulide LOVK1 (**5**)	512

[a] Standard soln in MeOH (1 mg/mL).
[b] Toxic value (unit = 1/n; 1 unit = 3–5 ng/g).

The responses of vacuoles to synthetic cereulide (**1**) and the four lysine-linked cereulide analogues **2–5** are listed in Table 1. Synthetic cereulide (**1**) showed emetic toxicity against HEp2-cells whereas analogues **2–5** exhibited selective toxicity. The low toxicity demonstrated by lysine-linked analogues **2–5** might be promising for immunological developments. Moreover, cereulide analogues **2–5** demonstrated ionophoric activity towards alkali metal ions and inorganic ammonium ions. Further studies on the ionophoric properties are in progress in terms of self–non-self association and the results will be reported elsewhere on the basis of analytical methods and high-field NMR spectroscopy.

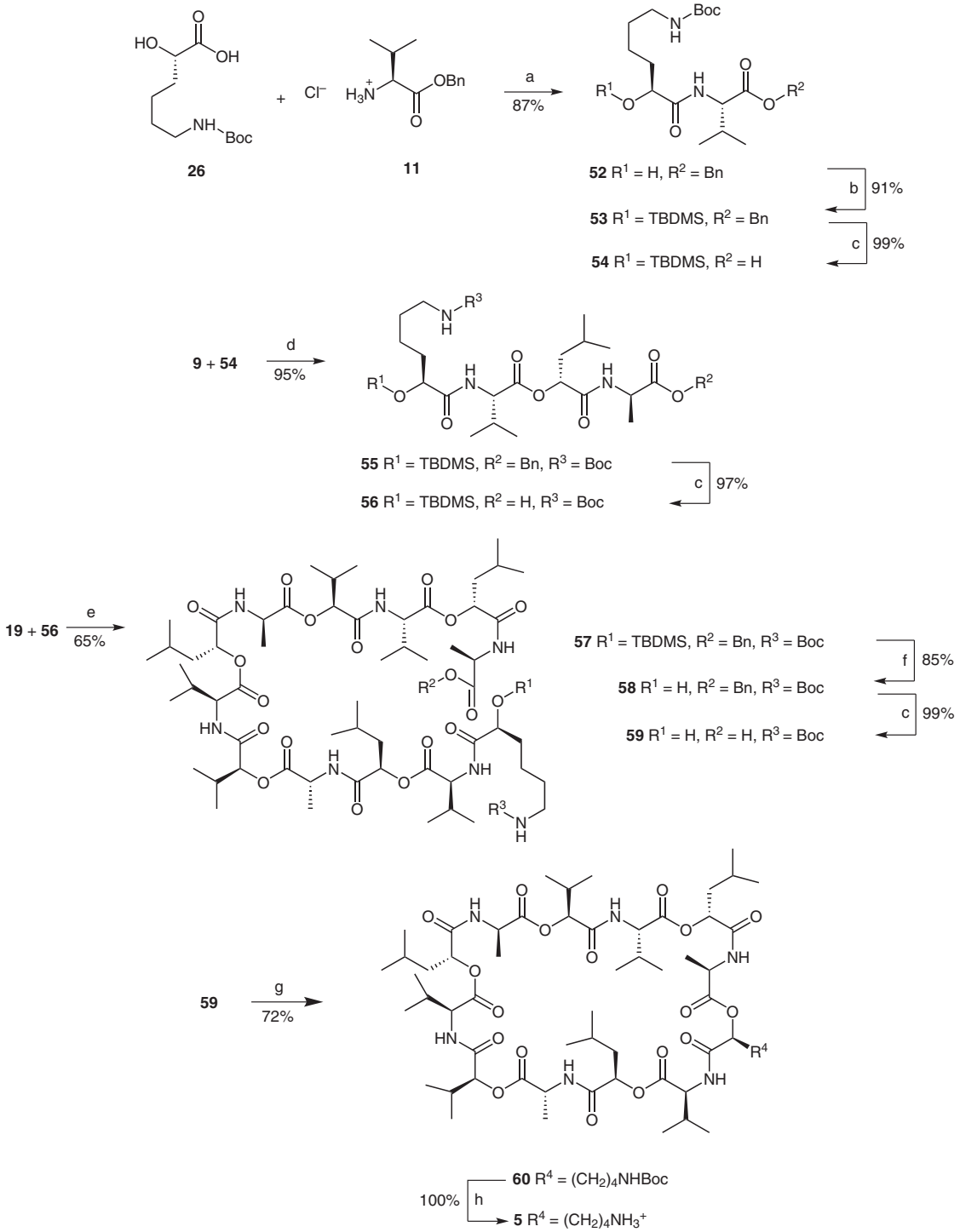
In summary, cereulide (**1**) and the lysine-linked cereulide analogues DAK1 (**2**), DOLK1 (**3**), LVK1 (**4**) and LOVK1 (**5**) have been synthesized in good overall yields. The cereulide analogues were prepared by replacement of one of the original amino acid or oxy acid residues in cereulide by either a lysine or oxy-lysine residue. Cereulide DAK1 (**2**) was prepared by replacement of a D-alanine residue with a D-lysine residue; cereulide DOLK1 (**3**) was synthesized by replacement of D-*O*-leucine with D-*O*-lysine; cereulide LVK1 (**4**) was obtained by replacement of L-valine with L-lysine; cereulide LOVK1 (**5**) was constructed by replacement of L-*O*-valine with L-*O*-lysine. The L-*O*-lysine residue is obtained easily by diazotization of L-lysine·0.5 H_2SO_4. All four lysine-linked cereulide analogues demonstrated non-emetic toxicity towards HEp2-



Scheme 6 Synthesis of cereulide LVK1 (**4**). *Reagents and conditions*: (a) DIAD, Ph_3P, THF, r.t.; (b) Et_2NH–MeCN (1:1), –10 °C; (c) HATU, HOBt, DIPEA, DMF, –10 °C to r.t.; (d) H_2, 10% Pd/C, THF, r.t.; (e) *p*-toluyl chloride, Et_3N, DMAP, toluene, r.t.; (f) 70% HF/py, THF, r.t.; (g) MNBAN, DMAP, CH_2Cl_2, (*c* 1.5 mM), r.t.; (h) TFA–CH_2Cl_2 (1:1), 0 °C.

cells. The development of an enzyme-linked immunosorbent assay (ELISA) for cereulide is in progress.

Melting points were determined using a Yanaco MP-S3 apparatus and are uncorrected. Infrared (IR) spectra were recorded in a NaCl cell using a JASCO FT/IR-6100 FT-IR spectrometer. Proton and carbon NMR spectra were obtained using a Bruker AMX-400 spec-



Scheme 7 Synthesis of cereulide LOVK1 (**5**). *Reagents and conditions*: (a) EDCI, HOBt, DIPEA, THF, 0 °C to r.t.; (b) TBDMSCl, imidazole, DMF, r.t.; (c) H_2, 10% Pd/C, THF, r.t.; (d) DIAD, Ph_3P, THF, r.t.; (e) *p*-toluyl chloride, Et_3N, DMAP, toluene, r.t.; (f) 70% HF/py, THF, r.t.; (g) MNBAN, DMAP, CH_2Cl_2, (*c* 1.5 mM), r.t.; (h) TFA–CH_2Cl_2 (1:1), 0 °C.

trometer at 400 MHz and 101 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS). Deuterochloroform ($CDCl_3$) was used as solvent. The following multiplicity abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet, br t = broad triplet, dd = doublet of doublets and qd = quartet of doublets. Coupling constants (*J*) are reported in Hertz (Hz). EI mass spectra and FAB mass spectra were obtained using a JEOL JMS-700 spectrometer. High-resolution (HR) mass spectra were measured with a JEOL JMS-700 or a Q-TOF mass spectrometer (Micromass, Manchester, UK) equipped with a Z-spray type ESI ion source. All analyses were performed in positive ion mode. Elemental analyses were performed by Analytical Laboratory, Graduate School of Bioagricultural Science (Nagoya University, Japan). Optical rotations were obtained using a JASCO DIP-370 digital polarimeter. High-performance liquid chromatography (or high-pressure liquid chromatography, HPLC) was performed on a JASCO Gulliver system composed of two PU-980 pumps, a UV-970 UV/

VIS detector and an 807-IT integrator. The apparatus was equipped with a Devolosil ODS-5 column (4.6 × 250 mm). Analytical thin layer chromatography (TLC) was conducted on precoated plates (silica gel 60 F-254, layer thickness = 0.25 mm, Merck). Silica gel column chromatography was performed using Silica Gel 60 (40-50 m, spherical, Merck). The components were detected by visualization under ultraviolet light at λ 254 nm and 365 nm and/or by development using phosphomolybdic acid [25 g in EtOH (500 mL)], followed by heating on a hot plate. The organic solvents utilized for extraction and as eluents for column chromatography were of commercial grade and those used for crystallization were of analytical grade. The vacuole response assay was run using an aliquot (25 L of a two-fold serially diluted sample) which was placed in each well of a 96-well microtiter plate as described by Hughes et al.[1f] The titer was recorded as the inverse of dilution in the last well showing vacuole formation.[21]

D-Alanine Benzyl Ester Hydrochloride (7)

To a soln of D-alanine (**6**) (6.83 g, 76.7 mmol) in freshly distilled BnOH (120 mL) was slowly added $SOCl_2$ (27 mL, 383 mmol) over a 20 min period. The reaction mixture was then stirred at 0 °C for 2 h before being heated to r.t. and stirred for 24 h. The mixture was carefully evaporated to dryness under reduced pressure to give a crude residue which was crystallized from EtOH–Et_2O. Crystalline compound **7** was collected by filtration and washed with Et_2O prior to being dried under vacuum to give D-alanine benzyl ester hydrochloride (**7**) as a white solid; yield: 15.73 g (95%); mp 138–140 °C.

$[\alpha]_D^{27}$ +20.96 (*c* 0.73, $CHCl_3$).

IR (NaCl film): 3054, 2986, 1746, 1604 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.71 (d, *J* = 7.2 Hz, 3 H), 4.29 (m, 1 H), 5.17 (ABq, 2 H), 7.30 (m, 5 H), 8.78 (br s, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.0, 49.4, 68.0, 128.2, 128.6, 134.6, 170.0.

HRMS (FAB+): *m*/*z* $[M]^+$ calcd for $C_{10}H_{14}ClNO_2$: 215.0713; found: 215.0751.

Anal. Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.70; H, 6.53; N, 6.40.

L-*O*-Leucine-D-alanine Benzyl Ester (9)

To a soln of L-*O*-leucine (**8**) (1.23 g, 9.3 mmol), D-alanine benzyl ester hydrochloride (**7**) (2.00 g, 9.3 mmol) and HOBt (1.88 g, 13.9 mmol) in anhyd THF (50 mL) at 0 °C was added a soln of DIPEA (4.90 mL, 28.1 mmol) and EDCI (2.67 g, 13.9 mmol) in anhyd THF (40 mL). The reaction mixture was stirred at 0 °C for 2 h before being warmed to r.t. and stirred for 22 h. The soln was then evaporated to dryness under reduced pressure to give the crude product. The residue was dissolved in CH_2Cl_2 (50 mL) and washed sequentially with sat. aq NH_4Cl soln (3 × 15 mL), H_2O (3 × 15 mL) and brine (3 × 15 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a crude residue which was purified by silica gel column chromatography (hexane–EtOAc, 3:1) to afford compound **9** as a white solid; yield: 2.52 g (93%); mp 41–42.5 °C.

$[\alpha]_D^{27}$ –15.66 (*c* 0.53, $CHCl_3$).

IR (NaCl film): 3405, 3055, 2959, 1740, 1664, 1523 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.95 (d, *J* = 6.6 Hz, 6 H), 1.43 (d, *J* = 7.2 Hz, 3 H), 1.49–1.67 (m, 2 H), 1.84 (m, 1 H), 2.79 (m, 1 H), 4.15 (dd, *J* = 9.9, 3.4 Hz, 1 H), 4.64 (qd, *J* = 7.2, 7.2 Hz, 1 H), 5.17 (ABq, 2 H), 7.04 (d, *J* = 7.2 Hz, 1 H), 7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 18.3, 21.3, 23.4, 24.4, 43.6, 47.8, 67.2, 70.7, 128.1, 128.4, 128.6, 135.2, 172.6, 174.0.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{24}NO_4$: 294.1705; found: 294.1720.

Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.77. Found: C, 65.43; H, 7.86; N, 4.68.

L-*O*-Valine-L-valine Benzyl Ester (12)

Compound **12** was prepared from L-*O*-valine (**10**) and L-valine benzyl ester hydrochloride (**11**) according to the same procedure used for the synthesis of **9**. Compound **12** was obtained as a white solid; yield: 5.35 g (95%); mp 39–41 °C.

$[\alpha]_D^{27}$ –35.19 (*c* 0.67, $CHCl_3$).

IR (NaCl film): 3394, 2965, 2933, 2875, 1739, 1657, 1523 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (d, *J* = 7.2 Hz, 6 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 1.03 (d, *J* = 6.9 Hz, 3 H) 2.20 (m, 2 H), 3.09 (br s, 1 H), 4.02 (d, *J* = 3.2 Hz, 1 H), 4.62 (dd, *J* = 9.0, 4.7 Hz, 1 H), 5.17 (ABq, 2 H), 7.07 (d, *J* = 9.0 Hz, 1 H), 7.36 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.6, 17.6, 19.1, 31.1, 31.7, 56.7, 67.1, 76.4, 128.3, 128.4, 128.6, 135.2, 171.9, 173.4.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{26}NO_4$: 308.1862; found: 308.1861.

Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.20; N, 4.56. Found: C, 66.50; H, 8.35; N, 4.59.

L-OTBDMS-Valine-L-valine Benzyl Ester (13)

To a soln of imidazole (3.87 g, 56.8 mmol) in anhyd DMF (40 mL) were added successively TBDMSCl (7.67 g, 50.9 mmol) and L-*O*-valine-L-valine benzyl ester (**12**) (6.69 g, 21.8 mmol) in anhyd DMF (60 mL). The reaction mixture was then heated at 50 °C for 12 h before being cooled to r.t. and diluted with EtOAc (40 mL). The resulting mixture was washed with H_2O (3 × 20 mL) and brine (2 × 20 mL). The organic layer was then dried over Na_2SO_4. Filtration and concentration under reduced pressure gave the crude product which was purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give compound **13** as an oil; yield: 9.18 g (quant.).

$[\alpha]_D^{27}$ –42.00 (*c* 0.85, $CHCl_3$).

IR (NaCl film): 3428, 2962, 2931, 2884, 2859, 1739, 1683, 1507, 1470 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.06 (s, 3 H), 0.08 (s, 3 H), 0.96 (s, 9 H), 0.87–0.99 (m, 12 H), 2.07–2.27 (m, 2 H), 3.98 (d, *J* = 3.1 Hz, 1 H), 4.59 (dd, *J* = 9.1, 4.6 Hz, 1 H), 5.17 (s, 2 H), 7.05 (d, *J* = 9.0 Hz, 1 H), 7.29–7.38 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –5.0, 16.3, 17.6, 18.0, 19.1, 19.4, 25.8, 31.3, 32.7, 56.5, 66.9, 77.7, 128.4, 128.5, 135.4, 171.4, 173.2.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{23}H_{40}NO_4Si$: 422.2727; found: 422.2717.

Anal. Calcd for $C_{23}H_{39}NO_4Si$: C, 65.52; H, 9.32; N, 3.32. Found: C, 65.52; H, 9.43; N, 3.59.

L-OTBDMS-Valine-L-valine-OH (14)

To a soln of compound **13** (9.18 g, 21.8 mmol) in anhyd THF (120 mL) was added 10% Pd/C (0.95 g) and the reaction vessel purged with Ar gas. The reaction was stirred under a H_2 atmosphere (H_2 balloon) for 8 h. Excess H_2 was displaced by air and the catalyst was removed by filtration through Celite. Concentration of the filtrate under reduced pressure gave a crude product which was purified by silica gel short column chromatography (hexane–EtOAc, 1:9) to give L-OTBDMS-valine-L-valine-OH (**14**) as a white solid; yield: 7.15 g (99%); mp 109–111 °C.

$[\alpha]_D^{27}$ –41.68 (*c* 0.54, $CHCl_3$).

IR (NaCl film): 3415, 3055, 2965, 2932, 2859, 1721, 1671, 1637, 1524 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.90 (d, *J* = 6.8 Hz, 3 H), 0.94–1.01 (m, 18 H), 2.05–2.19 (m, 1 H), 2.20–

2.36 (m, 1 H), 4.04 (d, *J* = 3.1 Hz, 1 H), 4.59 (dd, *J* = 9.1, 4.3 Hz, 1 H), 7.11 (d, *J* = 9.1 Hz, 1 H), 7.72–8.40 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –4.9, 16.2, 17.5, 18.0, 19.1, 19.4, 25.8, 31.0, 32.7, 56.5, 77.5, 173.9, 175.7.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{34}NO_4Si$: 332.2257; found: 332.2235.

Anal. Calcd for $C_{16}H_{33}NO_4Si$: C, 57.97; H, 10.03; N, 4.22. Found: C, 58.03; H, 10.29; N, 4.25.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (15)

To a soln of Ph_3P (0.89 g, 3.38 mmol) in anhyd THF (30 mL) was added DIAD (0.66 mL, 3.38 mmol). The reaction mixture was stirred at r.t. for 1 h, cooled to 0 °C and then a soln of compound **14** (0.64 g, 1.93 mmol) in anhyd THF (25 mL) was added. The resulting mixture was stirred at –15 °C for 45 min prior to addition of a soln of compound **9** (0.47 g, 1.61 mmol) in anhyd THF (25 mL). The reaction was stirred at 0 °C for 2 h and then overnight at r.t. Evaporation of the solvent under reduced pressure gave a crude residue which was dissolved in CH_2Cl_2 (100 mL) and washed sequentially with sat. aq $NaHCO_3$ soln (3 × 30 mL), sat. aq NH_4Cl soln (3 × 30 mL) and brine (3 × 30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure and the crude residue purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give compound **15** as an oil; yield: 0.98 g (quant.).

$[\alpha]_D^{27}$ +2.66 (*c* 0.79, $CHCl_3$).

IR (NaCl film): 3429, 3333, 3056, 2961, 2932, 1750, 1667, 1510 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.84–1.03 (m, 27 H), 1.47 (d, *J* = 7.3 Hz, 3 H), 1.66–1.81 (m, 3 H), 2.01–2.19 (m, 2 H), 4.00 (d, *J* = 3.0 Hz, 1 H), 4.26 (t, *J* = 7.2 Hz, 1 H), 4.49–4.61 (m, 1 H), 5.07–5.21 (m, 2 H), 5.25–5.31 (m, 1 H), 7.01 (d, *J* = 7.2 Hz, 1 H), 7.28–7.40 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –5.1, 16.2, 17.4, 18.0, 18.3, 19.1, 19.2, 21.2, 23.3, 24.4, 25.8, 30.1, 32.6, 40.5, 48.1, 58.1, 66.7, 72.9, 77.4, 127.9, 128.2, 129.0, 135.7, 169.8, 171.1, 172.1, 174.1.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{55}N_2O_7Si$: 607.3779; found: 607.3764.

Anal. Calcd for $C_{32}H_{54}N_2O_7Si$: C, 63.33; H, 8.97; N, 4.62. Found: C, 63.19; H, 9.04; N, 4.86.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (16)

To a soln of compound **15** (2.34 g, 3.9 mmol) in THF (20 mL) at –15 °C was added 70% HF/py (8 mL) and the reaction stirred at –15 °C for 15 min and then at r.t. for 24 h. The reaction mixture was quenched with ice (20 mL), the pH adjusted to pH 8–9 with sat. aq $NaHCO_3$ soln, and the aqueous layer extracted with CH_2Cl_2 (5 × 100 mL). The combined organic layer was concentrated to 50 mL, washed with 1 M HCl (3 × 15 mL) and brine (3 × 15 mL) and then dried over Na_2SO_4. Filtration and concentration under reduced pressure gave a crude residue which was purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give compound **16** as an oil; yield: 1.80 g (95%).

$[\alpha]_D^{27}$ –6.75 (*c* 0.76, $CHCl_3$).

IR (NaCl film): 3315, 2962, 2874, 1745, 1657, 1526 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81–1.06 (m, 18 H), 1.45 (d, *J* = 7.3 Hz, 3 H), 1.65–1.83 (m, 3 H), 2.00–2.09 (m, 1 H), 2.09–2.20 (m, 1 H), 2.57–2.77 (m, 1 H), 3.69 (d, *J* = 3.7 Hz, 1 H), 4.30 (t, *J* = 8.2 Hz, 1 H), 4.58–4.68 (m, 1 H), 5.06–5.19 (m, 2 H), 5.26 (dd, *J* = 4.0, 9.4 Hz, 1 H), 6.97 (d, *J* = 8.0 Hz, 1 H), 7.14 (d, *J* = 8.0 Hz, 1 H), 7.28–7.42 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.2, 17.5, 18.6, 18.9, 19.1, 21.2, 23.2, 24.5, 29.8, 31.6, 40.5, 47.8, 58.2, 67.0, 73.2, 76.9, 128.0, 128.3, 128.6, 135.5, 170.0, 171.6, 173.1, 174.6.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{26}H_{41}N_2O_7$: 493.2914; found: 493.2894.

Anal. Calcd for $C_{26}H_{40}N_2O_7$: C, 63.39; H, 8.18; N, 5.69. Found: C, 63.40; H, 8.29; N, 5.89.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine-OH (17)

Compound **17** was prepared from **15** according to the same procedure used for the synthesis of compound **14**. Compound **17** was obtained as a white solid; yield: 0.61 g (99%); mp 47–49 °C.

$[\alpha]_D^{27}$ +11.33 (*c* 0.87, $CHCl_3$).

IR (NaCl film): 3418, 3326, 3057, 2962, 2932, 2875, 2860, 1747, 1666, 1523 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.83–1.06 (m, 27 H), 1.49 (d, *J* = 6.9 Hz, 3 H), 1.65–1.83 (m, 3 H), 1.99–2.21 (m, 2 H), 3.97 (d, *J* = 2.3 Hz, 1 H), 4.15–4.33 (m, 1 H), 4.42–4.55 (m, 1 H), 5.22–5.36 (m, 1 H), 7.09 (d, *J* = 6.7 Hz, 1 H), 7.43–7.59 (m, 1 H), 9.02 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.4, –5.1, 16.2, 17.1, 18.0, 18.3, 19.1, 21.1, 23.2, 24.5, 25.7, 30.0, 32.6, 40.4, 49.0, 58.3, 73.1, 77.2, 170.7, 171.1, 175.0, 175.1.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{25}H_{49}N_2O_7Si$: 517.3309; found: 517.3312.

Anal. Calcd for $C_{25}H_{48}N_2O_7Si$: C, 58.11; H, 9.36; N, 5.42. Found: C, 58.10; H, 9.40; N, 5.44.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (18)

To a soln of compound **17** (0.74 g, 1.4 mmol) in anhyd toluene (20 mL) at r.t. was added Et_3N (0.27 mL, 1.9 mmol). The reaction mixture was stirred at r.t. for 10 min before *p*-toluyl chloride (0.21 mL, 1.6 mmol) was added and stirring was continued for a further 10 min. The mixture was then treated with alcohol **16** (0.63 g, 1.3 mmol) in anhyd toluene (20 mL) followed by the slow addition of DMAP (31.2 mg, 0.26 mmol) in anhyd toluene (2 mL) over a 3 h period. After stirring at r.t. for 5 h the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (60 mL) and washed with sat. aq $NaHCO_3$ soln (3 × 20 mL), sat. aq NH_4Cl soln (3 × 20 mL) and brine (3 × 20 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue purified by silica gel column chromatography (hexane–EtOAc, 3:2) to give compound **18** as a white solid; yield: 1.06 g (83%); mp 46–48 °C.

$[\alpha]_D^{27}$ –0.57 (*c* 1.23, $CHCl_3$).

IR (NaCl film): 3423, 3318, 2962, 2934, 2874, 1750, 1654, 1542 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.85–1.06 (m, 45 H), 1.41 (d, *J* = 7.2 Hz, 3 H), 1.45 (d, *J* = 7.1 Hz, 3 H), 1.61–1.86 (m, 6 H), 1.99–2.11 (m, 2 H), 2.27–2.46 (m, 2 H), 3.91 (d, *J* = 3.1 Hz, 1 H), 4.02 (dd, *J* = 8.2, 6.1 Hz, 1 H), 4.12 (qd, *J* = 7.0, 6.7 Hz, 1 H), 4.41 (t, *J* = 7.8 Hz, 1 H), 4.60 (qd, *J* = 7.5, 7.3 Hz, 1 H), 5.06 (d, *J* = 3.0 Hz, 1 H), 5.10 (d, *J* = 4.1 Hz, 2 H), 5.19 (dd, *J* = 10.1, 2.7 Hz, 1 H), 5.35 (dd, *J* = 10.0, 3.0 Hz, 1 H), 7.00 (d, *J* = 6.0 Hz, 1 H), 7.29–7.36 (m, 5 H), 7.65 (d, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 8.3 Hz, 1 H), 8.01 (d, *J* = 6.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.0, 16.1, 16.4, 17.5, 18.0, 18.9, 19.0, 19.3, 20.8, 21.2, 23.1, 23.4, 24.3, 24.5, 25.7, 29.7, 30.1, 30.2, 32.7, 40.5, 41.1, 47.9, 49.6, 58.6, 59.1, 66.6, 72.7, 72.9, 77.5, 78.7, 127.9, 128.0, 128.4, 135.8, 169.9, 170.0, 170.4, 170.7, 171.5, 171.7, 172.1, 174.9.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{51}H_{87}N_4O_{13}Si$: 991.6039; found: 991.6005.

Anal. Calcd for $C_{51}H_{86}N_4O_{13}Si$: C, 61.79; H, 8.74; N, 5.65. Found: C, 61.79; H, 8.74; N, 5.51.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (19)

Compound **19** was prepared from **18** according to the same procedure used for the synthesis of compound **16**. Compound **19** was obtained as a white solid; yield: 0.45 g (92%); mp 57–59 °C.

$[\alpha]_D^{28}$ –1.95 (*c* 0.98, $CHCl_3$).

IR (NaCl film): 3314, 3066, 2963, 2874, 1749, 1654, 1542 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81–1.08 (m, 36 H), 1.46 (d, *J* = 7.2 Hz, 3 H), 1.47 (d, *J* = 7.3 Hz, 3 H), 1.62–1.83 (m, 6 H), 2.00–2.23 (m, 3 H), 2.31–2.44 (m, 1 H), 3.87 (br s, 1 H), 3.97 (br s, 1 H), 4.06 (dd, *J* = 9.4, 6.6 Hz, 1 H), 4.23 (dd, *J* = 9.6, 7.7 Hz, 1 H), 4.51–4.60 (m, 1 H), 5.05–5.18 (m, 4 H), 5.31–5.38 (m, 1 H), 7.30–7.38 (m, 6 H), 7.45 (d, *J* = 7.6 Hz, 1 H), 7.53 (d, *J* = 6.5 Hz, 1 H), 7.63 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 7.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.2, 16.4, 17.0, 17.4, 18.2, 18.6, 19.1, 19.2, 19.3, 19.4, 21.0, 21.2, 23.3, 24.4, 24.6, 28.6, 29.1, 31.4, 32.1, 40.3, 40.8, 47.8, 47.9, 59.6, 59.8, 67.1, 73.0, 73.9, 76.2, 79.1, 128.1, 128.3, 128.5, 135.5, 170.5, 170.6, 171.4, 171.5, 173.0, 173.4, 175.9.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{45}H_{73}N_4O_{13}$: 877.5174; found: 877.5157.

Anal. Calcd for $C_{45}H_{72}N_4O_{13}$: C, 61.62; H, 8.27; N, 6.39. Found: C, 61.61; H, 8.12; N, 6.26.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (20)

To a soln of compound **17** (0.10 g, 0.19 mmol) in anhyd toluene (20 mL) at r.t. was added Et_3N (0.04 mL, 0.29 mmol). The reaction mixture was stirred at r.t. for 10 min before *p*-toluyl chloride (25 L, 0.19 mmol) was added and stirring continued for a further 10 min. The mixture was then treated with alcohol **19** (0.13 g, 0.14 mmol) in anhyd toluene (6 mL) followed by the slow addition of DMAP (13.8 mg, 0.11 mmol) in anhyd toluene (12 mL) over a 12 h period. After stirring at r.t. for 5 h the reaction mixture was filtered and concentrated under reduced pressure. The residue was dissolved in EtOAc (20 mL) and washed with sat. aq $NaHCO_3$ soln (2 × 10 mL), sat. aq NH_4Cl soln (2 × 10 mL) and brine (2 × 10 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue purified by silica gel column chromatography (hexane–EtOAc, 2:1) to give compound **20** as a white solid; yield: 0.14 g (68%, 76% conversion); mp 63–65 °C.

$[\alpha]_D^{26}$ +0.76 (*c* 1.19, $CHCl_3$).

IR (NaCl film): 3424, 3324, 2962, 2934, 2874, 1749, 1649, 1543 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.77–1.18 (m, 63 H), 1.40 (d, *J* = 7.3 Hz, 3 H), 1.45 (d, *J* = 7.0 Hz, 3 H), 1.46 (d, *J* = 7.0 Hz, 3 H), 1.60–1.90 (m, 9 H), 2.00–2.11 (m, 2 H), 2.28–2.44 (m, 4 H), 3.91 (d, *J* = 3.0 Hz, 1 H), 3.94–4.03 (m, 2 H), 4.07–4.15 (m, 1 H), 4.30 (t, *J* = 7.5 Hz, 1 H), 4.50 (qd, *J* = 8.5, 7.3 Hz, 1 H), 4.54–4.65 (m, 1 H), 4.99 (d, *J* = 3.1 Hz, 1 H), 5.03 (d, *J* = 3.0 Hz, 1 H), 5.06–5.13 (m, 3 H), 5.21 (dd, *J* = 10.8, 1.6 Hz, 1 H), 5.36 (dd, *J* = 10.2, 2.7 Hz, 1 H), 7.02 (d, *J* = 5.5 Hz, 1 H), 7.27–7.34 (m, 5 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.82 (d, *J* = 8.8 Hz, 1 H), 7.85 (d, *J* = 7.7 Hz, 1 H), 8.23 (d, *J* = 5.9 Hz, 1 H), 8.29 (d, *J* = 6.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.1, 16.1, 16.2, 16.5, 17.6, 18.0, 18.9, 19.0, 19.2, 19.3, 20.8, 21.2, 23.1, 23.2, 23.3, 24.3, 24.4, 25.7, 29.6, 29.8, 30.1, 30.2, 30.4, 32.7, 40.5, 41.1, 41.2, 47.9, 49.4, 49.7, 58.3, 58.8, 59.2, 66.6, 72.7, 72.9, 77.4, 78.9, 79.0, 128.0, 128.1, 128.4, 135.8, 169.7, 169.9, 170.3, 170.5, 170.8, 171.5, 172.0, 172.1, 172.4, 175.0.

ESI-MS: *m/z* [M + H]$^+$ calcd for $C_{70}H_{119}N_6O_{19}Si$: 1375.8281; found: 1375.9428.

Anal. Calcd for $C_{70}H_{118}N_6O_{19}Si$: C, 61.11; H, 8.64; N, 6.11. Found: C, 61.08; H, 8.74; N, 6.24.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (21)

Compound **21** was prepared from benzyl ester **20** according to the same procedure used for the synthesis of compound **16**. Product **21** was obtained as a white solid; yield: 0.30 g (94%); mp 72–74 °C.

$[\alpha]_D^{28}$ –1.18 (*c* 1.79, $CHCl_3$).

IR (NaCl film): 3414, 2962, 1736, 1648, 1560, 1543 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.82–1.07 (m, 54 H), 1.39 (d, *J* = 7.2 Hz, 3 H), 1.47 (d, *J* = 6.8 Hz, 3 H), 1.48 (d, *J* = 6.6 Hz, 3 H), 1.60–1.85 (m, 9 H), 2.02–2.16 (m, 2 H), 2.21–2.45 (m, 4 H), 3.75 (d, *J* = 5.0 Hz, 1 H), 3.85–3.91 (m, 1 H), 4.03 (dd, *J* = 8.8, 6.4 Hz, 1 H), 4.07–4.18 (m, 2 H), 4.31–4.45 (m, 2 H), 4.47–4.56 (m, 1 H), 4.93 (d, *J* = 3.4 Hz, 1 H), 5.05 (d, *J* = 3.0 Hz, 1 H), 5.11 (s, 2 H), 5.16–5.25 (m, 2 H), 5.35 (dd, *J* = 10.0, 2.4 Hz, 1 H), 7.28–7.35 (m, 5 H), 7.39 (d, *J* = 6.2 Hz, 1 H), 7.64 (d, *J* = 7.5 Hz, 1 H), 7.70 (d, *J* = 7.2 Hz, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 8.00 (d, *J* = 6.5 Hz, 1 H), 8.12 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.9, 16.1, 16.4, 16.9, 17.4, 18.6, 18.7, 18.9, 19.1, 19.2, 19.3, 19.4, 20.9, 21.1, 21.2, 23.1, 23.3, 24.3, 24.4, 24.5, 28.9, 29.3, 30.0, 30.2, 30.7, 31.8, 40.6, 40.9, 48.3, 48.9, 49.6, 58.6, 59.4, 59.7, 66.7, 72.6, 72.8, 73.2, 76.2, 78.8, 79.1, 128.0, 128.4, 135.8, 170.0, 170.7, 171.1, 171.3, 171.7, 171.8, 172.0, 172.1, 172.3, 175.3.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{64}H_{105}N_6O_{19}$: 1261.7435; found: 1261.7482.

Anal. Calcd for $C_{64}H_{104}N_6O_{19}$: C, 60.93; H, 8.31; N, 6.66. Found: C, 60.91; H, 8.24; N, 6.52.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-OH (22)

Compound **22** was prepared from **21** according to the same procedure used for the synthesis of compound **14**. Compound **22** was obtained as a white solid; yield: 0.26 g (quant.); mp 102–104 °C.

$[\alpha]_D^{26}$ +12.52 (*c* 0.62, $CHCl_3$).

IR (NaCl film): 3317, 3060, 2965, 2875, 1749, 1651, 1545 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.84–1.07 (m, 54 H), 1.43 (d, *J* = 7.2 Hz, 3 H), 1.48 (d, *J* = 7.2 Hz, 3 H), 1.51 (d, *J* = 7.2 Hz, 3 H), 1.63–1.85 (m, 9 H), 2.05–2.18 (m, 2 H), 2.22–2.43 (m, 4 H), 3.92 (d, *J* = 3.4 Hz, 1 H), 4.03–4.09 (m, 2 H), 4.27–4.37 (m, 2 H), 4.40–4.49 (m, 2 H), 4.96 (d, *J* = 3.3 Hz, 1 H), 5.06 (d, *J* = 3.1 Hz, 1 H), 5.16–5.26 (m, 3 H), 7.48 (d, *J* = 8.0 Hz, 1 H), 7.52 (d, *J* = 6.7 Hz, 1 H), 7.69 (d, *J* = 7.3 Hz, 1 H), 7.74 (d, *J* = 6.8 Hz, 1 H), 7.96 (d, *J* = 6.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.9, 16.2, 16.4, 16.6, 16.8, 16.9, 18.5, 18.8, 19.0, 19.1, 19.3, 19.5, 21.1, 21.2, 23.2, 23.3, 24.4, 24.5, 28.5, 29.0, 29.7, 30.4, 30.8, 31.7, 40.5, 40.6, 40.8, 48.0, 48.6, 49.4, 58.9, 59.3, 60.0, 72.9, 73.0, 73.4, 76.4, 78.7, 78.9, 170.4, 170.5, 171.0, 171.2, 171.8, 171.9, 172.4, 173.3, 175.8.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{57}H_{99}N_6O_{19}$: 1171.6965; found: 1171.6962.

Anal. Calcd for $C_{57}H_{98}N_6O_{19}$: C, 58.44; H, 8.43; N, 7.17. Found: C, 58.35; H, 8.22; N, 7.15.

Cereulide (1)

To a soln of *m*-nitrobenzoic anhydride (43.4 mg, 0.13 mmol) and DMAP (31.3 mg, 0.26 mmol) in anhyd CH_2Cl_2 (35 mL) at r.t. was added slowly a soln of compound **22** (106.6 mg, 0.09 mmol) in anhyd CH_2Cl_2 (22 mL) via a mechanically driven syringe over a 7 h period. The reaction mixture was then stirred for a further 34 h at r.t. The resulting mixture was evaporated to ca. 20 mL under reduced pressure and then washed with sat. aq $NaHCO_3$ soln (2 × 10 mL), sat. aq NH_4Cl soln (2 × 10 mL) and brine (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the residue purified by silica gel column chromatography (hexane–EtOAc, 4:1) to give cereulide (**1**) as a yellow-white solid; yield: 77.1 mg (73%); mp 196–199 °C.

$[\alpha]_D^{26}$ +3.37 (*c* 1.03, $CHCl_3$) (H^+ form); $[\alpha]_D^{27}$ –1.69 (*c* 1.36, $CHCl_3$) (K^+ form); $[\alpha]_D^{26}$ –1.15 (*c* 1.22, $CHCl_3$) (NH_4^+ form).

IR (NaCl film): 3298, 2963, 2874, 1755, 1655, 1541 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ (H^+ form) = 0.86–1.01 (m, 45 H), 1.06 (d, *J* = 6.6 Hz, 9 H), 1.45 (d, *J* = 7.2 Hz, 9 H), 1.61–1.82 (m, 9 H), 2.26–2.37 (m, 6 H), 4.10 (dd, *J* = 9.6, 7.5 Hz, 3 H), 4.36 (qd, *J* = 6.9, 6.9 Hz, 3 H), 5.00 (d, *J* = 3.3 Hz, 3 H), 5.31 (dd, *J* = 8.1, 4.8 Hz, 3 H), 7.79 (d, *J* = 6.3 Hz, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (H^+ form) = 15.8, 16.9, 18.6, 19.3, 21.2, 23.3, 24.4, 28.7, 30.5, 40.6, 48.8, 59.4, 72.7, 78.7, 170.5, 171.0, 171.5, 171.8.

^1H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.87–1.07 (m, 45 H), 1.15 (d, *J* = 6.4 Hz, 9 H), 1.50 (d, *J* = 7.3 Hz, 9 H), 1.56–1.91 (m, 9 H), 2.20–2.38 (m, 6 H), 3.84 (dd, *J* = 10.9, 5.1 Hz, 3 H), 4.30 (qd, *J* = 7.1, 4.5 Hz, 3 H), 4.64 (d, *J* = 3.4 Hz, 3 H), 4.79 (dd, *J* = 9.8, 3.6 Hz, 1 H), 8.24 (d, *J* = 5.1 Hz, 3 H), 8.34 (d, *J* = 4.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 16.6, 18.6, 19.2, 20.2, 21.1, 23.1, 24.3, 28.5, 30.1, 40.8, 50.3, 61.7, 73.7, 79.7, 171.4, 172.2, 175.7, 176.2.

^1H NMR ($CDCl_3$, 400 MHz): δ (NH_4^+ form) = 0.87–1.07 (m, 45 H), 1.14 (d, *J* = 6.4 Hz, 9 H), 1.50 (d, *J* = 7.2 Hz, 9 H), 1.60–1.90 (m, 9 H), 2.19–2.39 (m, 6 H), 3.83 (dd, *J* = 10.7, 5.0 Hz, 3 H), 4.27 (qd, *J* = 7.5, 4.5 Hz, 3 H), 4.69 (d, *J* = 3.4 Hz, 3 H), 4.84 (dd, *J* = 9.7, 3.9 Hz, 3 H), 8.07 (d, *J* = 5.1 Hz, 1 H), 8.14 (d, *J* = 4.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (NH_4^+ form) = 15.3, 16.6, 18.6, 19.1, 20.1, 21.1, 23.0, 24.3, 28.6, 30.2, 40.9, 50.1, 61.5, 73.9, 79.6, 171.3, 172.2, 175.6, 176.0.

HRMS (FAB+): *m*/*z* $[M]^+$ calcd for $C_{57}H_{97}N_6O_{18}$ (H^+ form): 1153.6859; found: 1153.6886.

Anal. Calcd for $C_{57}H_{97}N_6O_{18}$ (H^+ form): C, 59.30; H, 8.47; N, 7.28. Found: C, 59.30; H, 8.28; N, 7.06.

L-Lysine·0.5H_2SO_4 (24)

A soln of L-lysine (**23**) (7.0 g, 47.9 mmol) in H_2O (40 mL) was neutralized with 10% H_2SO_4 at r.t. The mixture was then evaporated under vacuum and the residue crystallized from EtOH–H_2O to afford L-lysine·0.5H_2SO_4 (**24**) as colorless crystals; yield: 9.0 g (96%) which were used immediately for the next step; mp 270–275 °C (dec.).

$[\alpha]_D^{26}$ +10.44 (*c* 1.20, H_2O).

IR (NaCl film): 3019, 1718, 1582, 1517 cm^{-1}.

^1H NMR (D_2O, 400 MHz): δ = 1.53 (m, 2 H), 1.76 (m, 2 H), 1.96 (m, 2 H), 3.06 (t, *J* = 7.6 Hz, 2 H), 3.86 (t, *J* = 6.1 Hz, 1 H).

^{13}C NMR (D_2O, 101 MHz): δ = 21.4, 26.4, 29.7, 39.1, 54.1, 174.1.

LRMS (FAB+): *m*/*z* $[M]^+$ calcd for $C_6H_{15}N_2O_4S_{0.5}$: 195.0892; found: 195.1248.

Anal. Calcd for $C_6H_{15}N_2O_4S_{0.5}$: C, 36.91; H, 7.74; N, 14.35. Found: C, 36.90; H, 7.54; N, 14.12.

L-*O*-Lysine (25)

To a soln of compound **24** (8.97 g, 45.9 mmol) in 10% H_2SO_4 (120 mL) was added $NaNO_2$ (11.7 g, 169.6 mmol) in H_2O (45 mL) gradually over a period of 2 h with stirring at 45–50 °C. The mixture was then stirred at the same temperature for 3 h. Excess nitrous acid present in the reaction mixture was neutralized with urea and the reaction mixture was poured onto an ion-exchange column (Amberlite IR-120, H^+ form, 100 mL). The column was washed thoroughly with H_2O, after which the product was eluted with aq NH_4OH soln until the eluent displayed a negative ninhydrin test. The combined elute was evaporated in vacuo to give a pale yellow semi-solid which was recrystallized from MeOH–Et_2O to afford L-*O*-lysine (**25**) as a white powder; yield: 3.20 g (45% based on **23**); mp 190–192 °C.

$[\alpha]_D^{27}$ –11.86 (*c* 1.20, H_2O).

IR (NaCl film): 3019, 1523, 1474, 1420, 1323 cm^{-1}.

^1H NMR (D_2O, 400 MHz): δ = 1.43 (m, 2 H), 1.70 (m, 4 H), 2.99 (t, *J* = 7.4 Hz, 2 H), 4.03 (m, 1 H).

^{13}C NMR (D_2O, 101 MHz): δ = 21.3, 26.6, 33.2, 39.3, 71.9, 181.3.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_6H_{14}NO_3$: 148.0974; found: 148.0969.

Anal. Calcd for $C_6H_{13}NO_3$: C, 48.97; H, 8.90; N, 9.52. Found: C, 48.82; H, 8.79; N, 9.62.

L-*O*-Lysine(Boc)-OH (26)

To a stirred soln of compound **25** (0.80 g, 5.4 mmol) in 1 M NaOH (12 mL) and 1,4-dioxane (12 mL) was added $(Boc)_2O$ (2.37 g, 10.9 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h before being concentrated to half the original volume. The remainder was extracted with Et_2O (2 × 20 mL) to remove any organic impurities. The aqueous layer was acidified to pH 2 with 1 M HCl and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (20 mL) before being dried with $MgSO_4$ and concentrated to give L-*O*-lysine(Boc)-OH (**26**) as an oil; yield: 1.14 g (85%).

$[\alpha]_D^{27}$ –0.36 (*c* 1.12, CH_3OH).

IR (NaCl film): 3347, 1704, 1523, 1367 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.51 (m, 13 H), 1.80 (m, 2 H), 3.12 (m, 2 H), 4.25 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 28.4 (2), 33.4, 67.0 (2), 70.0, 156.5, 177.8.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{22}NO_5$: 248.1498; found: 248.1493.

Fmoc-D-Lysine(Boc) Benzyl Ester (28)

Compound **28** was prepared from commercially available compound **27** and BnOH according to the same procedure used for the synthesis of compound **15**. Compound **28** was obtained as a white solid; yield: 1.00 g (98%); mp 65–66 °C.

$[\alpha]_D^{26}$ +3.64 (*c* 0.55, $CHCl_3$).

IR (NaCl film): 3019, 1715, 1508, 1451 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 1.24–1.51 (m, 12 H), 1.55–1.78 (m, 2 H), 1.79–1.93 (m, 1 H), 3.06 (m, 2 H), 4.21 (t, *J* = 7.0 Hz, 1 H), 4.31–4.57 (m, 4 H), 5.18 (ABq, 2 H), 5.39 (br s, 1 H), 7.27–7.44 (m, 9 H), 7.60 (d, *J* = 7.4 Hz, 2 H), 7.76 (d, *J* = 7.5 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 22.3, 28.4, 29.6, 32.2, 40.1, 47.1, 53.8, 67.0, 67.2, 119.9, 125.1, 127.0, 127.7, 128.4, 128.5, 128.6, 135.2, 141.3, 143.7, 155.9, 156.0, 172.3.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{33}H_{39}N_2O_6$: 559.2808; found: 559.2770.

Anal. Calcd for $C_{33}H_{38}N_2O_6$: C, 70.95; H, 6.86; N, 5.01. Found: C, 70.97; H, 6.86; N, 5.07.

L-*O*-Leucine-D-lysine(Boc) Benzyl Ester (29)

To a soln of compound **28** (0.76 g, 1.35 mmol) in MeCN (15 mL) at –10 °C was added Et_2NH (15 mL). The reaction mixture was then stirred at –10 °C for 1 h to ensure complete removal of the Fmoc-protecting group before being concentrated under vacuum. The residue was azeotroped to dryness with MeCN (2 × 10 mL) and the product was dissolved in DMF (20 mL). In another flask, a soln of L-*O*-leucine (**8**) (0.23 g, 1.76 mmol) in DMF (15 mL) was treated with HOBt (0.22 g, 1.63 mmol) and HATU (0.62 g, 1.63 mmol) in DMF (10 mL). After 10 min, this mixture and DIPEA (0.50 mL, 2.84 mmol) were added sequentially to the deprotected amino ester at –10 °C. The mixture was stirred at –10 °C for 2 h before warming to r.t. and stirring for 22 h. Evaporation under reduced pressure gave a residue which was dissolved in EtOAc (30 mL) and washed sequentially with sat. aq $NaHCO_3$ soln (3 × 15 mL), sat. aq NH_4Cl soln (3 × 15 mL), H_2O (3 × 15 mL) and brine (3 × 15 mL). The organic layer was then dried over Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product which was purified by silica gel column chromatography (hexane–EtOAc, 7:3) to afford compound **29** as a white solid; yield: 0.41 g (68% over two steps); mp 98 °C.

$[\alpha]_D^{26}$ –15.24 (*c* 1.24, $CHCl_3$).

IR (NaCl film): 3019, 1736, 1698, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.94 (s, 3 H), 0.95 (s, 3 H), 1.25–1.36 (m, 2 H), 1.37–1.48 (m, 11 H), 1.48–1.65 (m, 2 H), 1.66–1.76 (m, 1 H), 1.81–1.94 (m, 2 H), 2.98–3.08 (m, 2 H), 3.34 (br s, 1 H), 4.16 (dd, *J* = 9.8, 3.5 Hz, 1 H), 4.52–4.71 (m, 2 H), 5.17 (m, 2 H), 7.10 (d, *J* = 8.4 Hz, 1 H), 7.29–7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 21.4, 22.4, 23.4, 24.5, 28.4, 29.5, 31.7, 40.2, 43.5, 51.6, 67.1, 70.7, 128.3, 128.5, 128.6, 135.3, 156.1, 172.0, 174.6.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{24}H_{39}N_2O_6$: 451.2808; found: 451.2775.

Anal. Calcd for $C_{24}H_{38}N_2O_6$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.82; H, 8.57; N, 6.41.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-lysine(Boc) Benzyl Ester (30)

Compound **30** was prepared from compounds **29** and **14** according to the same procedure used for the synthesis of compound **15**. Compound **30** was obtained as an oil; yield: 0.58 g (89%).

IR (NaCl film): 3019, 1748, 1667, 1510, 1470 cm^{-1}.

$[\alpha]_D^{26}$ +0.95 (*c* 2.74, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.84–1.03 (m, 27 H), 1.22–1.39 (m, 2 H), 1.43 (s, 9 H), 1.48–1.92 (m, 7 H), 2.01–2.20 (m, 2 H), 2.94–3.19 (m, 2 H), 3.97 (d, *J* = 2.9 Hz, 1 H), 4.25 (t, *J* = 7.2 Hz, 1 H), 4.46–4.54 (m, 1 H), 4.67 (br s, 1 H), 5.07–5.19 (m, 2 H), 5.25–5.32 (m, 1 H), 7.00 (d, *J* = 7.0 Hz, 1 H), 7.27–7.39 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –5.1, 16.2, 18.0, 18.3, 19.2, 21.2, 21.7, 22.8, 23.3, 24.4, 25.8, 28.4, 29.3, 29.4, 30.0, 31.0, 32.5, 40.6, 52.2, 58.1, 66.7, 73.0, 128.0, 128.2, 128.5, 135.7, 156.0, 170.1, 171.1, 171.6, 174.2.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{40}H_{70}N_3O_9Si$: 764.4881; found: 764.4893.

Anal. Calcd for $C_{40}H_{69}N_3O_9Si$: C, 62.88; H, 9.10; N, 5.50. Found: C, 62.89; H, 9.24; N, 5.76.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-lysine(Boc)-OH (31)

Compound **31** was prepared from compound **30** according to the same procedure used for the synthesis of compound **14**. Compound **31** was obtained as a white solid; yield: 0.47 g (quant.); mp 75–77 °C.

$[\alpha]_D^{26}$ +11.85 (*c* 0.65, $CHCl_3$).

IR (NaCl film): 3019, 1752, 1670, 1515 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.84–1.03 (m, 27 H), 1.43 (s, 9 H), 1.29–1.62 (m, 4 H), 1.62–2.25 (m, 7 H), 2.97–3.17 (m, 2 H), 3.89–4.08 (m, 1 H), 4.19–4.50 (m, 2 H), 4.60–4.85 (m, 1 H), 5.10–5.31 (m, 1 H), 7.00–7.22 (m, 1 H), 7.28–7.45 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.0, 16.1, 17.9, 19.3, 21.2, 23.2, 24.6, 25.7, 28.4, 29.4, 30.1, 32.5, 40.3, 40.6, 53.1, 57.4, 73.6, 78.8, 156.0, 170.1, 170.7.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{33}H_{64}N_3O_9Si$: 674.4412; found: 674.4431.

Anal. Calcd for $C_{33}H_{63}N_3O_9Si$: C, 58.81; H, 9.42; N, 6.23. Found: C, 58.80; H, 9.46; N, 6.18.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-lysine(Boc)-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (32)

Compound **32** was prepared from compounds **19** and **31** according to the same procedure used for the synthesis of compound **20**. Compound **32** was obtained as a white solid; yield: 0.13 g (61%, 75% conversion); mp 63–65 °C.

$[\alpha]_D^{26}$ +4.75 (*c* 0.61, $CHCl_3$).

IR (NaCl film): 3019, 1752, 1656, 1533, 1468 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (s, 3 H), 0.11 (s, 3 H), 0.85–1.06 (m, 63 H), 1.43 (s, 9 H), 1.29–1.83 (m, 19 H), 1.84–2.14 (m, 4 H), 2.25–2.47 (m, 4 H), 3.00–3.20 (m, 2 H), 3.92–4.14 (m, 5 H), 4.41–4.48 (m, 1 H), 4.53–4.62 (m, 1 H), 4.63–4.75 (m, 1 H), 5.00 (d, *J* = 3.1 Hz, 1 H), 5.04 (d, *J* = 3.0 Hz, 1 H), 5.08–5.16 (m, 3 H), 5.22–5.29 (m, 1 H), 5.32–5.40 (m, 1 H), 7.02 (d, *J* = 6.0 Hz, 1 H), 7.27–7.35 (m, 5 H), 7.66 (d, *J* = 7.7 Hz, 1 H), 7.80 (d, *J* = 8.4 Hz, 1 H), 7.93–7.98 (m, 1 H), 8.01 (d, *J* = 5.6 Hz, 1 H), 8.28 (d, *J* = 6.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –5.1, 16.2, 16.3, 16.5, 17.5, 18.0, 18.7, 19.0, 19.1, 19.3, 19.4, 19.6, 20.8, 21.1, 21.2, 23.1, 23.3, 23.4, 24.3, 24.4, 25.7, 28.4, 29.2, 29.5, 29.7, 30.1, 30.2, 30.3, 32.7, 40.5, 40.6, 41.1, 48.0, 49.6, 54.3, 58.5, 59.0, 60.1, 66.5, 72.6, 72.7, 72.8, 77.2, 78.2, 78.8, 128.0, 128.4, 135.9, 155.9, 169.8, 170.1, 170.5, 170.7, 170.8, 171.1, 171.3, 171.8, 172.1, 174.9.

HRMS (FAB+): *m/z* [M + H]$^+$ calcd for $C_{78}H_{134}N_7O_{21}Si$: 1532.9402; found: 1532.9390.

Anal. Calcd for $C_{78}H_{133}N_7O_{21}Si$: C, 61.11; H, 8.74; N, 6.40. Found: C, 61.34; H, 8.58; N, 6.22.

L-*O*-Valine-L-valine-D-*O*-leucine-D-lysine(Boc)-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (33)

Compound **33** was prepared from compound **32** according to the same procedure used for the synthesis of compound **16**. Compound **33** was obtained as a white solid; yield: 0.11 g (91%); mp 74–76 °C.

$[\alpha]_D^{26}$ +13.49 (*c* 0.63, $CHCl_3$).

IR (NaCl film): 3312, 1749, 1652, 1535, 1466 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86–1.05 (m, 54 H), 1.40 (d, *J* = 7.3 Hz, 3 H), 1.44 (s, 9 H), 1.50 (d, *J* = 7.1 Hz, 3 H), 1.16–1.53 (m, 4 H), 1.60–1.92 (m, 10 H), 1.95–2.16 (m, 3 H), 2.20–2.45 (m, 4 H), 2.94–3.18 (m, 2 H), 3.84–3.95 (m, 1 H), 3.95–4.14 (m, 4 H),

4.44–4.59 (m, 2 H), 4.61–4.79 (m, 1 H), 4.86 (d, *J* = 3.6 Hz, 1 H), 5.05 (d, *J* = 3.1 Hz, 1 H), 5.10 (s, 2 H), 5.14–5.22 (m, 2 H), 5.37 (dd, *J* = 10.1, 2.6 Hz, 1 H), 7.28–7.34 (m, 5 H), 7.40–7.51 (m, 1 H), 7.67 (d, *J* = 7.6 Hz, 1 H), 7.81 (d, *J* = 8.5 Hz, 1 H), 7.89–7.99 (m, 1 H), 8.02–8.15 (m, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 14.1, 15.8, 16.4, 16.5, 16.9, 17.5, 18.9, 19.0, 19.2, 19.3, 19.6, 20.8, 20.9, 21.2, 22.6, 23.1, 23.3, 24.3, 24.5, 28.4, 28.9, 29.4, 29.5, 30.1, 30.3, 30.4, 31.6, 31.8, 40.4, 40.7, 40.8, 41.1, 48.2, 49.7, 54.1, 58.4, 59.4, 59.9, 66.6, 72.6, 72.7, 73.1, 75.9, 77.2, 78.9, 79.3, 128.0, 128.1, 128.4, 135.8, 156.5, 169.9, 170.0, 170.7, 170.9, 171.0, 171.5, 171.9, 172.1, 172.2, 176.1.

HRMS (FAB+): *m*/*z* [M + H]$^+$ calcd for $C_{72}H_{120}N_7O_{21}$: 1418.8537; found: 1418.8552.

Anal. Calcd for $C_{72}H_{119}N_7O_{21}$: C, 60.95; H, 8.45; N, 6.91. Found: C, 60.98; H, 8.39; N, 6.85.

L-*O*-Valine-L-valine-D-*O*-leucine-D-lysine(Boc)-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-l-valine-D-*O*-leucine-D-alanine-OH (34)

Compound **34** was prepared from compound **33** according to the same procedure used for the synthesis of compound **14**. Compound **34** was obtained as a white solid; yield: 0.09 g (98%); mp 101–103 °C.

$[\alpha]_D^{24}$ +10.22 (*c* 3.24, $CHCl_3$).

IR (NaCl film): 3313, 1749, 1655, 1536, 1466 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.79–1.11 (m, 54 H), 1.44 (s, 9 H), 1.50 (d, *J* = 7.0 Hz, 3 H), 1.19–1.56 (m, 7 H), 1.60–2.00 (m, 10 H), 2.03–2.19 (m, 3 H), 2.23–2.46 (m, 4 H), 2.95–3.27 (m, 2 H), 3.85–3.95 (m, 1 H), 4.00–4.23 (m, 4 H), 4.24–4.54 (m, 3 H), 4.85–5.03 (m, 2 H), 5.04–5.27 (m, 3 H), 7.43–7.55 (m, 1 H), 7.59–7.75 (m, 2 H), 7.84–8.01 (s, 2 H), 8.02–8.14 (s, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.0, 16.3, 16.5, 16.8, 18.8, 18.9, 19.0, 19.1, 19.2, 19.5, 21.0, 21.1, 21.2, 23.1, 23.2, 23.2, 24.3, 24.4, 28.4, 28.8, 29.2, 29.4, 29.5, 29.6, 29.8, 30.2, 30.3, 31.7, 40.1, 40.5, 40.7, 48.4, 48.5, 49.3, 53.9, 58.6, 59.3, 59.8, 72.8, 73.1, 73.3, 77.2, 78.6, 79.1, 156.3, 170.3, 171.0, 171.1, 171.5, 171.7, 172.0, 176.3.

HRMS (FAB+): *m*/*z* [M + H]$^+$ calcd for $C_{65}H_{114}N_7O_{21}$: 1328.8068; found: 1328.8059.

Anal. Calcd for $C_{65}H_{113}N_7O_{21}$: C, 58.76; H, 8.57; N, 7.38. Found: C, 58.77; H, 8.71; N, 7.34.

Cereulide DAK1-*N*-Boc (35)

Cereulide DAK1-*N*-Boc **35** was prepared from compound **34** according to the same procedure used for the synthesis of cereulide (**1**). Compound **35** was obtained as a yellow-white solid; yield: 61.8 mg (73%); mp 82–84 °C.

$[\alpha]_D^{27}$ +7.87 (*c* 1.36, $CHCl_3$) (H^+ form); $[\alpha]_D^{27}$ –1.63 (*c* 1.47, $CHCl_3$) (K^+ form); $[\alpha]_D^{27}$ –1.55 (*c* 1.41, $CHCl_3$) (NH_4^+ form).

IR (NaCl film): 3311, 1754, 1657, 1539, 1467 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (H^+ form) = 0.79–1.11 (m, 54 H), 1.24–1.37 (m, 1 H), 1.44 (s, 9 H), 1.38–1.58 (m, 8 H), 1.60–2.01 (m, 12 H), 2.21–2.41 (m, 6 H), 3.01–3.16 (m, 2 H), 4.01–4.21 (m, 3 H), 4.22–4.39 (m, 3 H), 4.74–4.90 (m, 1 H), 4.98 (d, *J* = 3.3 Hz, 2 H), 5.02 (d, *J* = 3.2 Hz, 1 H), 5.23–5.37 (m, 3 H), 7.63–7.94 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (H^+ form) = 15.7, 15.8, 16.8, 17.0, 18.6, 18.7, 19.1, 19.3, 19.4, 21.2, 21.3, 23.1, 23.3, 24.4, 28.4, 28.6, 28.8, 28.9, 29.3, 29.4, 30.4, 30.5, 40.0, 40.4, 40.5, 40.6, 48.8, 49.0, 53.4, 59.1, 59.3, 59.6, 72.7, 72.8, 78.4, 78.8, 78.9, 156.0, 170.3, 170.4, 170.5, 170.8, 170.9, 171.0, 171.1, 171.3, 171.6, 171.8, 172.2.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.80–1.17 (m, 54 H), 1.23–1.37 (m, 1 H), 1.42 (s, 9 H), 1.47–1.70 (m, 14 H), 1.71–1.95 (m, 6 H), 2.16–2.40 (m, 6 H), 3.05–3.20 (m, 2 H), 3.78–3.89 (m, 3 H), 4.11–4.19 (m, 1 H), 4.24–4.35 (m, 2 H), 4.59–4.69 (m, 3 H), 4.79 (dd, *J* = 9.8, 3.1 Hz, 3 H), 4.89–5.03 (m, 1 H), 8.18–8.42 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 16.6, 18.6, 18.9, 19.2, 20.2, 21.1, 23.0, 23.3, 24.3, 28.4, 28.5, 29.6, 29.9, 30.1, 30.2, 40.0, 40.8, 50.3, 55.2, 61.7, 73.7, 77.2, 78.9, 79.7, 79.9, 156.1, 171.4, 171.5, 172.2, 172.3, 175.6, 175.7, 175.8, 176.1, 176.1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (NH_4^+ form) = 0.75–1.18 (m, 54 H), 1.23–1.37 (m, 1 H), 1.42 (s, 9 H), 1.47–1.60 (m, 7 H), 1.61–1.99 (m, 13 H), 2.16–2.41 (m, 6 H), 3.03–3.22 (m, 2 H), 3.74–3.89 (m, 3 H), 4.09–4.17 (m, 1 H), 4.21–4.32 (m, 2 H), 4.63–4.74 (m, 3 H), 4.79–4.87 (m, 3 H), 4.88–5.05 (m, 1 H), 7.94–8.26 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (NH_4^+ form) = 15.2, 15.3, 16.5, 16.6, 18.6, 18.9, 19.1, 19.2, 20.1, 21.1, 23.0, 23.2, 24.3, 28.4, 28.6, 29.6, 29.8, 30.2, 39.9, 40.8, 40.9, 50.1, 54.9, 61.5, 61.7, 73.8, 77.2, 78.9, 79.6, 79.7, 156.1, 171.2, 171.3, 171.4, 172.1, 172.2, 175.5, 175.6, 175.7, 175.8, 175.9.

HRMS (FAB+): *m*/*z* [M]$^+$ calcd for $C_{65}H_{112}N_7O_{20}$ (H^+ form): 1310.7962; found: 1310.7979.

Anal. Calcd for $C_{65}H_{112}N_7O_{20}$ (H^+ form): C, 59.52; H, 8.61; N, 7.48. Found: C, 59.41; H, 8.40; N, 7.63.

Cereulide DAK1 (2)

To a stirred soln of cereulide DAK1-*N*-Boc **35** (31.0 mg, 23.7 mol) in anhyd CH_2Cl_2 (2.5 mL) at 0 °C was slowly added TFA (2.5 mL). The reaction mixture was stirred for a further 40 min at the same temperature before being evaporated under reduced pressure to give cereulide DAK1 (**2**) as a yellow-white solid; yield: 28.7 mg (quant.); mp 114–117 °C.

IR (NaCl film): 3294, 1749, 1655, 1540, 1468 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.68–1.20 (m, 54 H), 1.34–2.07 (m, 21 H), 2.14–2.44 (m, 6 H), 2.95–3.22 (m, 2 H), 3.77–3.91 (m, 3 H), 4.13–4.21 (m, 1 H), 4.22–4.33 (m, 2 H), 4.62–4.71 (m, 3 H), 4.72–4.83 (m, 3 H), 7.76–7.99 (m, 3 H), 8.07–8.47 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 15.3, 16.7, 16.8, 16.9, 18.6, 18.9, 19.2, 20.2, 21.1, 23.1, 23.4, 24.3, 28.5, 29.6, 30.2, 30.3, 30.9, 40.1, 40.8, 50.3, 55.2, 61.6, 61.7, 61.8, 73.5, 73.6, 79.8, 79.9, 80.1, 171.5, 171.6, 171.8, 172.1, 172.3, 175.5, 175.7, 175.8, 175.9.

HRMS (FAB+): *m*/*z* [M]$^+$ calcd for $C_{60}H_{104}N_7O_{18}$ (H^+ form): 1210.7438; found: 1210.7451.

Anal. Calcd for $C_{60}H_{104}N_7O_{18}$ (H^+ form): C, 59.48; H, 8.65; N, 8.09. Found: C, 59.64; H, 8.53; N, 7.93.

L-*O*-Lysine(Boc)-D-alanine Benzyl Ester (36)

Compound **36** was prepared from D-alanine benzyl ester hydrochloride (**7**) and L-*O*-lysine(Boc)-OH (**26**) according to the same procedure used for the synthesis of compound **9**. Compound **36** was obtained as a white solid; yield: 1.67 g (80%); mp 71–71.5 °C.

$[\alpha]_D^{26}$ –10.44 (*c* 0.68, $CHCl_3$).

IR (NaCl film): 3019, 1683, 1519 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31–1.56 (m, 16 H), 1.61–1.76 (m, 1 H), 1.81–1.96 (m, 1 H), 3.11 (d, *J* = 5.7 Hz, 2 H), 3.43 (d, *J* = 2.8 Hz, 1 H), 4.07–4.19 (m, 1 H), 4.56–4.74 (m, 2 H), 5.18 (ABq, 2 H), 7.13 (d, *J* = 7.1 Hz, 1 H), 7.28–7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 18.2, 21.2, 28.4, 29.8, 33.6, 39.6, 47.8, 67.1, 71.8, 79.4, 128.1, 128.4, 128.6, 135.4, 156.6, 172.6, 173.6.

HRMS (FAB+): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{33}N_2O_6$: 409.2339; found: 409.2364.

Anal. Calcd for $C_{21}H_{32}N_2O_6$: C, 61.75; H, 7.90; N, 6.86. Found: C, 61.76; H, 7.95; N, 7.03.

L-OTBDMS-Valine-L-valine-D-*O*-lysine(Boc)-D-alanine Benzyl Ester (37)

Compound **37** was prepared from compounds **36** and **14** according to the same procedure used for the synthesis of compound **15**. Compound **37** was obtained as a white solid; yield: 1.82 g (quant.); mp 87–88.5 °C.

$[\alpha]_D^{26}$ –2.49 (*c* 1.00, $CHCl_3$).

IR (NaCl film): 3019, 1748, 1668, 1509 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.85–1.03 (m, 21 H), 1.32–1.54 (m, 16 H), 1.62–1.75 (m, 1 H), 1.81–2.00 (m, 2 H), 2.02–2.19 (m, 2 H), 3.08 (d, *J* = 5.1 Hz, 1 H), 3.95 (d, *J* = 3.0 Hz, 1 H), 4.26 (t, *J* = 7.1 Hz, 1 H), 4.48–4.64 (m, 2 H), 5.07–5.22 (m, 2 H), 5.26 (dd, *J* = 7.3, 4.5 Hz, 1 H), 7.00 (d, *J* = 7.3 Hz, 1 H), 7.28–7.42 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.2, –5.1, 16.2, 17.4, 18.0, 18.3, 19.1, 19.2, 22.1, 25.7, 28.4, 29.5, 30.1, 31.2, 32.6, 48.1, 58.1, 66.7, 73.9, 77.4, 127.9, 128.2, 128.5, 135.7, 155.9, 169.2, 170.9, 172.0, 174.1.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{37}H_{64}N_3O_9Si$: 722.4412; found: 722.4368.

Anal. Calcd for $C_{37}H_{63}N_3O_9Si$: C, 61.55; H, 8.80; N, 5.82. Found: C, 61.55; H, 8.88; N, 5.83.

L-OTBDMS-Valine-L-valine-D-*O*-lysine(Boc)-D-alanine-OH (38)

Compound **38** was prepared from compound **37** according to the same procedure used for the synthesis of compound **14**. Compound **38** was obtained as a white solid; yield: 1.41 g (98%); mp 70–72 °C.

$[\alpha]_D^{27}$ +1.29 (*c* 0.70, $CHCl_3$).

IR (NaCl film): 3417, 1668, 1515, 1462, 1392 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.84–1.05 (m, 21 H), 1.35–1.55 (m, 16 H), 1.81–2.00 (m, 2 H), 2.01–2.18 (m, 2 H), 3.10 (dd, *J* = 4.6, 0.8 Hz, 2 H), 3.93–3.99 (m, 1 H), 4.17–4.26 (m, 1 H), 4.42–4.51 (m, 1 H), 4.52–4.63 (m, 1 H), 5.18–5.26 (m, 1 H), 7.08 (d, *J* = 6.6 Hz, 1 H), 7.45–7.61 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.1, 16.2, 17.6, 18.0, 18.1, 19.2, 21.0, 22.3, 25.7, 28.4, 29.5, 30.2, 31.2, 32.6, 40.2, 49.0, 57.9, 74.3, 79.1, 155.9, 170.8.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{30}H_{58}N_3O_9Si$: 632.3942; found: 632.3912.

Anal. Calcd for $C_{30}H_{57}N_3O_9Si$: C, 57.02; H, 9.09; N, 6.65. Found: C, 56.92; H, 9.05; N, 6.53.

L-OTBDMS-Valine-L-valine-D-*O*-lysine(Boc)-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (39)

Compound **39** was prepared from compounds **19** and **38** according to the same procedure used for the synthesis of compound **20**. Compound **39** was obtained as a white solid; yield: 0.19 g (74%); mp 68–69 °C.

$[\alpha]_D^{27}$ –2.42 (*c* 0.99, $CHCl_3$).

IR (NaCl film): 3322, 1749, 1652, 1539, 1458 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.10 (s, 3 H), 0.83–1.08 (m, 57 H), 1.43 (s, 9 H), 1.35–1.52 (m, 11 H), 1.58–1.98 (m, 10 H), 1.99–2.13 (m, 2 H), 2.23–2.44 (m, 4 H), 3.09 (d, *J* = 4.8 Hz, 2 H), 3.92 (d, *J* = 3.0 Hz, 1 H), 3.97–4.07 (m, 2 H), 4.13–4.21 (m, 2 H), 4.62–4.43 (m, 3 H), 5.00 (d, *J* = 3.2 Hz, 1 H), 5.03 (d, *J* = 3.0 Hz, 1 H), 5.09–5.13 (m, 3 H), 5.16–5.22 (m, 1 H), 5.36 (dd, *J* = 10.1, 2.7 Hz, 1 H), 7.02 (d, *J* = 5.8 Hz, 1 H), 7.27–7.37 (m, 5 H), 7.68 (d, *J* = 7.8 Hz, 1 H), 7.77–7.88 (m, 2 H), 8.12 (d, *J* = 5.7 Hz, 1 H), 8.22 (d, *J* = 6.2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.1, 16.2, 16.5, 17.5, 18.0, 18.8, 18.9, 19.0, 19.1, 19.3, 20.8, 21.2, 22.5, 23.1, 23.3, 24.3, 24.4, 25.7, 28.4, 29.5, 29.6, 30.1, 30.3, 31.1, 32.7, 40.2, 40.9, 41.1, 48.0, 49.5, 49.6, 58.4, 59.0, 59.3, 66.6, 72.7, 72.9, 73.8, 77.4, 78.6, 78.9, 128.0, 128.4, 135.8, 155.9, 169.8, 170.0, 170.5, 170.6, 170.7, 170.9, 171.2, 171.3, 172.1, 172.2, 174.9.

HRMS (ESI-MS+): *m*/*z* $[M + H]^+$ calcd for $C_{75}H_{128}N_7O_{21}Si$: 1490.8933; found: 1490.8940.

Anal. Calcd for $C_{75}H_{127}N_7O_{21}Si$: C, 60.42; H, 8.59; N, 6.58. Found: C, 60.40; H, 8.33; N, 6.47.

L-*O*-Valine-L-valine-D-*O*-lysine(Boc)-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (40)

Compound **40** was prepared from compound **39** according to the same procedure used for the synthesis of compound **16**. Compound **40** was obtained as a white solid; yield: 0.13 g (85%); mp 81–83 °C.

$[\alpha]_D^{27}$ –3.01 (*c* 0.66, $CHCl_3$).

IR (NaCl film): 3314, 1750, 1651, 1539, 1456 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.84–1.06 (m, 48 H), 1.44 (s, 9 H), 1.36–1.51 (m, 11 H), 1.59–1.96 (m, 10 H), 2.04–2.15 (m, 2 H), 2.21–2.45 (m, 4 H), 3.09 (d, *J* = 5.7 Hz, 2 H), 3.89 (d, *J* = 3.2 Hz, 1 H), 4.04–4.14 (m, 3 H), 4.36–4.45 (m, 2 H), 4.46–4.59 (m, 2 H), 4.92 (d, *J* = 3.6 Hz, 1 H), 5.05 (d, *J* = 3.1 Hz, 1 H), 5.12 (s, 2 H), 5.14–5.23 (m, 2 H), 5.35 (dd, *J* = 10.0, 2.7 Hz, 1 H), 7.31 (m, 6 H), 7.41 (d, *J* = 6.6 Hz, 1 H), 7.65 (d, *J* = 7.5 Hz, 2 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 6.3 Hz, 1 H), 8.07 (d, *J* = 6.0 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.9, 16.2, 16.4, 16.5, 16.9, 17.3, 18.6, 18.8, 18.9, 19.0, 19.1, 19.3, 19.5, 21.0, 21.2, 22.3, 23.1, 23.3, 24.3, 24.5, 28.4, 28.7, 29.4, 29.6, 30.1, 30.2, 30.6, 31.1, 31.8, 40.3, 40.8, 40.9, 48.3, 48.8, 49.6, 58.6, 59.1, 60.0, 66.6, 72.6, 72.8, 74.0, 76.2, 77.2, 78.8, 79.0, 128.0, 128.4, 135.8, 156.0, 170.0, 170.8, 170.9, 171.1, 171.3, 171.9, 172.0, 172.1, 175.3.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{69}H_{114}N_7O_{21}$: 1376.8068; found: 1376.8074.

Anal. Calcd for $C_{69}H_{113}N_7O_{21}$: C, 60.20; H, 8.27; N, 7.12. Found: C, 60.39; H, 8.10; N, 7.37.

L-*O*-Valine-L-valine-D-*O*-lysine(Boc)-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-OH (41)

Compound **41** was prepared from compound **40** according to the same procedure used for the synthesis of compound **14**. Compound **41** was obtained as a white solid; yield: 0.10 g (quant.); mp 114–116 °C.

$[\alpha]_D^{25}$ +4.82 (*c* 0.56, $CHCl_3$).

IR (NaCl film): 3315, 1750, 1655, 1542, 1465 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.74–1.11 (m, 48 H), 1.43 (s, 9 H), 1.33–1.58 (m, 11 H), 1.60–1.99 (m, 10 H), 2.06–2.20 (m, 2 H), 2.23–2.45 (m, 4 H), 2.96–3.20 (m, 2 H), 3.80–5.35 (m, 13 H), 7.34–8.45 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.8, 16.3, 16.5, 16.7, 18.7, 18.9, 19.2, 19.3, 21.2, 22.4, 23.2, 24.4, 28.4, 29.1, 29.5, 30.2, 30.4, 31.0, 31.8, 40.2, 40.8, 49.3, 59.4, 73.2, 74.5, 77.2, 79.1, 155.9, 171.1.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{62}H_{108}N_7O_{21}$: 1286.7598; found: 1286.7640.

Anal. Calcd for $C_{62}H_{107}N_7O_{21}$: C, 57.88; H, 8.38; N, 7.62. Found: C, 57.71; H, 8.47; N, 7.89.

Cereulide DOLK1-*N*-Boc (42)

Cereulide DOLK1-*N*-Boc **42** was prepared from compound **41** according to the same procedure used for the synthesis of cereulide (**1**). Compound **42** was obtained as a yellow-white solid; yield: 17.7 mg (47%); mp 83–85 °C.

$[\alpha]_D^{27}$ +0.79 (*c* 1.65, $CHCl_3$) (H^+ form); $[\alpha]_D^{27}$ –0.28 (*c* 1.80, $CHCl_3$) (K^+ form); $[\alpha]_D^{26}$ –0.11 (*c* 1.90, $CHCl_3$) (NH_4^+ form).

IR (NaCl film): 3304, 1751, 1658, 1537, 1467 cm^{-1}

^1H NMR ($CDCl_3$, 400 MHz): δ (H^+ form) = 0.81–1.08 (m, 48 H), 1.31–1.52 (m, 13 H), 1.60 (s, 9 H), 1.56–2.01 (m, 8 H), 2.23–2.39 (m, 6 H), 3.00–3.15 (m, 2 H), 4.02–4.17 (m, 3 H), 4.32–4.42 (m, 3 H), 4.55–4.72 (m, 1 H), 4.97–5.06 (m, 3 H), 5.24–5.33 (m, 3 H), 7.68–7.91 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (H^+ form) = 15.8, 16.8, 16.9, 18.5, 18.6, 19.2, 19.3, 19.4, 21.3, 21.5, 21.9, 23.3, 24.4, 24.5, 28.4, 28.6, 28.7, 29.3, 30.5, 30.9, 40.7, 48.9, 59.2, 59.4, 59.7, 72.7, 72.8, 73.6, 77.2, 78.6, 78.8, 155.9, 170.1, 170.5, 170.6, 170.9, 171.1, 171.2, 171.5, 171.7, 171.8, 171.9.

^1H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.79–1.19 (m, 48 H), 1.38–1.58 (m, 18 H), 1.59–1.95 (m, 10 H), 2.17–2.42 (m, 6 H), 3.02–3.21 (m, 2 H), 3.76–3.92 (m, 3 H), 4.24–4.35 (m, 3 H), 4.63 (d, *J* = 3.0 Hz, 3 H), 4.73–4.92 (m, 4 H), 8.16–8.38 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 16.6, 18.6, 19.1, 19.3, 20.2, 21.1, 22.5, 23.0, 24.3, 28.4, 28.5, 29.6, 30.1, 31.3, 40.2, 40.8, 50.1, 50.2, 50.3, 61.6, 61.7, 61.8, 73.6, 73.7, 74.9, 77.2, 79.6, 79.7, 156.1, 171.3, 171.4, 171.7, 172.2, 172.2, 172.3, 175.6, 176.2.

^1H NMR ($CDCl_3$, 400 MHz): δ (NH_4^+ form) = 0.74–1.21 (m, 48 H), 1.34–1.97 (m, 26 H), 1.99–2.42 (m, 8 H), 3.02–3.21 (m, 2 H), 3.74–3.90 (m, 3 H), 4.19–4.37 (m, 3 H), 4.68 (d, *J* = 2.5 Hz, 3 H), 4.75–4.92 (m, 3 H), 5.73–6.12 (m, 4 H), 7.94–8.21 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (NH_4^+ form) = 15.2, 16.6, 18.6, 19.1, 19.2, 20.0, 20.1, 21.1, 22.5, 23.0, 24.3, 28.4, 28.5, 28.6, 29.5, 30.2, 31.4, 40.2, 40.8, 40.9, 50.0, 50.1, 61.4, 61.5, 73.8, 75.1, 76.8, 77.2, 79.6, 79.6, 156.1, 171.2, 171.6, 172.1, 172.2, 175.4, 175.5, 175.9.

HRMS (FAB+): *m*/*z* $[M]^+$ calcd for $C_{62}H_{106}N_7O_{20}$ (H^+ form): 1268.7493; found: 1268.7472.

Anal. Calcd for $C_{62}H_{106}N_7O_{20}$ (H^+ form): C, 58.66; H, 8.42; N, 7.72. Found: C, 58.50; H, 8.34; N, 7.86.

Cereulide DOLK1 (3)

Cereulide DOLK1 (**3**) was prepared from compound **42** according to the same procedure used for the synthesis of cereulide DAK1 (**2**). Compound **3** was obtained as a yellow-white solid; yield: 17.3 mg (quant.); mp 127–130 °C.

IR (NaCl film): 3306, 1749, 1655, 1539, 1469 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.79–1.20 (m, 48 H), 1.44–1.52 (m, 9 H), 1.53–1.69 (m, 4 H), 1.70–2.01 (m, 8 H), 2.15–2.39 (m, 6 H), 2.95–3.13 (m, 2 H), 3.76–3.93 (m, 3 H), 4.23–4.39 (m, 3 H), 4.61 (dd, *J* = 6.3, 3.2 Hz, 3 H), 4.78–4.87 (m, 3 H), 7.73–8.00 (m, 3 H), 8.15 (d, *J* = 5.1 Hz, 1 H), 8.22–8.35 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 16.6, 18.7, 19.2, 19.5, 20.1, 20.2, 20.3, 21.2, 22.4, 23.1, 24.3, 26.6, 28.4, 28.5, 28.6, 30.1, 31.2, 40.0, 40.8, 40.9, 50.1, 50.2, 50.3, 61.6, 61.8, 61.9, 73.6, 73.8, 74.9, 79.5, 79.6, 79.7, 171.0, 171.4, 171.6, 172.3, 172.6, 175.4, 175.5, 175.6, 176.2, 176.4.

HRMS (FAB+): *m*/*z* $[M]^+$ calcd for $C_{57}H_{98}N_7O_{18}$ (H^+ form): 1168.6968; found: 1168.6935.

Anal. Calcd for $C_{57}H_{98}N_7O_{18}$ (H^+ form): C, 58.54; H, 8.45; N, 8.38. Found: C, 58.53; H, 8.42; N, 8.44.

L-*O*-Valine-L-lysine(Boc)-D-*O*-leucine-D-alanine Benzyl Ester (46)

L-Lysine(Boc)-D-*O*-leucine-D-alanine benzyl ester (**45**) was prepared from commercially available compound **43** and L-*O*-leucine-D-alanine benzyl ester (**9**) according to the same procedure used for the synthesis of compound **15** followed by Fmoc-deprotection. Compound **46** was prepared from L-lysine(Boc)-D-*O*-leucine-D-alanine benzyl ester (**45**) and L-*O*-valine (**10**) according to the same procedure used for the synthesis of **29**. Compound **46** was obtained as a white solid; yield: 0.40 g (44% over three steps); mp 36–38 °C.

$[\alpha]_D^{27}$ –1.94 (*c* 1.18, $CHCl_3$).

IR (NaCl film): 3336, 1744, 1669, 1514, 1456 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (d, *J* = 6.8 Hz, 3 H), 0.92 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.98 (d, *J* = 6.9 Hz, 3 H), 1.20–1.29 (m, 1 H), 1.32–1.57 (m, 15 H), 1.62–1.95 (m, 5 H), 2.03–2.14 (m, 1 H), 2.95–3.17 (m, 3 H), 3.80 (dd, *J* = 5.2, 3.7 Hz, 1 H), 4.46 (dd, *J* = 14.3, 7.3 Hz, 1 H), 4.55–4.65 (m, 1 H), 5.10–5.19 (m, 2 H), 5.26 (t, *J* = 6.7 Hz, 1 H), 7.09 (d, *J* = 7.3 Hz, 1 H), 7.23 (d, *J* = 7.8 Hz, 1 H), 7.29–7.39 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.9, 17.5, 19.0, 21.4, 22.7, 23.1, 24.6, 28.4, 29.6, 30.6, 31.7, 40.0, 40.5, 47.9, 52.4, 67.1, 73.3, 76.4, 79.2, 128.0, 128.3, 128.6, 135.4, 156.1, 169.9, 171.6, 172.9, 174.5.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{32}H_{52}N_3O_9$: 622.3704; found: 622.3680.

Anal. Calcd for $C_{32}H_{51}N_3O_9$: C, 61.82; H, 8.27; N, 6.76. Found: C, 61.82; H, 8.19; N, 6.93.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-OH (47)

Compound **47** was prepared from compound **18** according to the same procedure used for the synthesis of compound **14**. Compound **47** was obtained as a white solid; yield: 0.09 g (99%); mp 98–100 °C.

$[\alpha]_D^{27}$ +3.72 (*c* 1.58, $CHCl_3$).

IR (NaCl film): 3317, 1752, 1661, 1522, 1469 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.11 (s, 6 H), 0.79–1.09 (m, 45 H), 1.34–1.58 (m, 6 H), 1.60–1.87 (m, 6 H), 1.98–2.19 (m, 2 H), 2.22–2.47 (m, 2 H), 3.92–3.98 (m, 1 H), 4.01–4.25 (m, 1 H), 4.28–4.70 (m, 3 H), 5.02–5.17 (m, 1 H), 5.19–5.40 (m, 2 H), 6.98–7.24 (m, 1 H), 7.30–7.81 (m, 2 H), 7.87–8.10 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.1, 16.0, 16.6, 18.0, 18.5, 18.8, 19.1, 21.0, 21.3, 23.1, 23.4, 24.3, 25.8, 29.7, 30.5, 32.5, 40.3, 40.7, 49.0, 49.2, 58.6, 67.4, 72.8, 73.2, 77.5, 78.4, 171.2, 171.3, 174.8.

HRMS (FAB+): *m*/*z* $[M + H]^+$ calcd for $C_{44}H_{81}N_4O_{13}Si$: 901.5569; found: 901.5616.

Anal. Calcd for $C_{44}H_{80}N_4O_{13}Si$: C, 58.64; H, 8.95; N, 6.22. Found: C, 58.66; H, 8.93; N, 6.08.

L-OTBDMS-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-lysine(Boc)-D-*O*-leucine-D-alanine Benzyl Ester (48)

Compound **48** was prepared from compounds **46** and **47** according to the same procedure used for the synthesis of compound **20**. Compound **48** was obtained as a white solid; yield 0.08 g (65%); mp 64–66 °C.

$[\alpha]_D^{27}$ –0.79 (*c* 0.50, $CHCl_3$).

IR (NaCl film): 3311, 1749, 1654, 1543, 1458 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.09 (s, 3 H), 0.11 (s, 3 H), 0.83–1.10 (m, 57 H), 1.42 (s, 9 H), 1.36–1.51 (m, 12 H), 1.62–1.87 (m, 11 H), 1.88–2.12 (m, 4 H), 2.26–2.47 (m, 3 H), 3.09 (d, *J* = 5.8 Hz, 1 H), 3.91 (d, *J* = 3.1 Hz, 1 H), 3.95–4.07 (m, 2 H), 4.08–4.16 (m,

1 H), 4.25 (t, *J* = 7.5 Hz, 1 H), 4.38–4.50 (m, 1 H), 4.57–4.68 (m, 1 H), 4.70–4.80 (m, 1 H), 4.99 (d, *J* = 3.2 Hz, 1 H), 5.03 (d, *J* = 2.8 Hz, 1 H), 5.08–5.14 (m, 3 H), 5.19 (dd, *J* = 10.9, 2.7 Hz, 1 H), 5.28 (dd, *J* = 9.5, 2.7 Hz, 1 H), 7.02 (d, *J* = 5.6 Hz, 1 H), 7.28–7.36 (m, 5 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 7.5 Hz, 1 H), 7.95 (d, *J* = 8.0 Hz, 1 H), 8.21 (d, *J* = 5.9 Hz, 1 H), 8.28 (d, *J* = 6.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –5.0, 16.2, 16.3, 16.5, 17.7, 18.0, 18.9, 19.0, 19.3, 20.8, 20.9, 21.2, 23.1, 23.2, 23.3, 24.3, 24.4, 25.7, 28.4, 29.1, 29.6, 29.7, 30.0, 30.2, 30.9, 32.7, 40.2, 40.5, 40.8, 40.9, 41.1, 47.8, 49.5, 49.7, 52.6, 59.0, 59.2, 66.7, 72.7, 72.9, 73.0, 77.5, 78.8, 128.0, 128.4, 135.8, 155.9, 169.9, 170.4, 170.5, 170.8, 170.9, 171.5, 172.0, 172.2, 172.5, 173.0, 174.9.

HRMS (ESI-MS+): *m*/*z* [M + H]$^+$ calcd for $C_{76}H_{130}N_7O_{21}Si$: 1504.9089; found: 1504.9108.

Anal. Calcd for $C_{76}H_{129}N_7O_{21}Si$: C, 60.65; H, 8.64; N, 6.51. Found: C, 60.66; H, 8.65; N, 6.37.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-lysine(Boc)-D-*O*-leucine-D-alanine Benzyl Ester (49)

Compound **49** was prepared from compound **48** according to the same procedure used for the synthesis of compound **16**. Compound **49** was obtained as a white solid; yield: 0.04 g (84%); mp 75–77 °C.

$[\alpha]_D^{26}$ –3.86 (*c* 1.74, $CHCl_3$).

IR (NaCl film): 3313, 1750, 1650, 1542, 1457 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.81–1.09 (m, 48 H), 1.19–1.87 (m, 13 H), 1.38–1.52 (m, 9 H), 1.42 (s, 9 H), 1.88–1.99 (m, 2 H), 2.02–2.17 (m, 2 H), 2.22–2.45 (m, 3 H), 3.08 (d, *J* = 5.5 Hz, 2 H), 3.82–4.00 (m, 2 H), 4.04 (dd, *J* = 8.7, 6.3 Hz, 1 H), 4.08–4.19 (m, 2 H), 4.31–4.39 (m, 2 H), 4.47–4.67 (m, 1 H), 4.73–4.85 (m, 1 H), 4.97 (d, *J* = 3.3 Hz, 1 H), 5.04 (d, *J* = 2.9 Hz, 1 H), 5.13 (s, 2 H), 5.14–5.22 (m, 2 H), 5.28 (dd, *J* = 9.0, 4.2 Hz, 1 H), 7.28–7.43 (m, 6 H), 7.67–7.80 (m, 2 H), 7.87 (d, *J* = 7.5 Hz, 1 H), 8.02 (d, *J* = 6.1 Hz, 1 H), 8.16 (d, *J* = 5.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 15.9, 16.1, 16.2, 16.3, 16.8, 17.4, 18.6, 18.7, 18.9, 19.0, 19.1, 19.2, 19.5, 21.0, 21.2, 22.6, 23.1, 23.2, 23.3, 23.4, 24.3, 24.4, 24.5, 28.4, 28.9, 29.1, 29.3, 29.9, 30.0, 30.2, 30.6, 31.8, 40.2, 40.6, 40.7, 48.1, 48.9, 49.5, 53.0, 59.3, 59.8, 66.7, 72.6, 73.0, 73.1, 76.2, 78.7, 78.8, 127.9, 128.0, 128.4, 135.8, 156.0, 169.9, 170.5, 170.6, 171.1, 171.6, 171.8, 172.2, 172.9, 175.4.

HRMS (FAB+): *m*/*z* [M + H]$^+$ calcd for $C_{70}H_{116}N_7O_{21}$: 1390.8224; found: 1390.8206.

Anal. Calcd for $C_{70}H_{115}N_7O_{21}$: C, 60.46; H, 8.33; N, 7.05. Found: C, 60.42; H, 8.26; N, 6.97.

L-*O*-Valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-lysine(Boc)-D-*O*-leucine-D-alanine-OH (50)

Compound **50** was prepared from compound **49** according to the same procedure used for the synthesis of compound **14**. Compound **50** was obtained as a white solid; yield: 22.5 mg (99%); mp 103–105 °C.

$[\alpha]_D^{25}$ +5.61 (*c* 1.27, $CHCl_3$).

IR (NaCl film): 3312, 1749, 1654, 1540, 1458 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.78–1.13 (m, 48 H), 1.30–2.48 (m, 37 H), 2.98–3.21 (m, 2 H), 3.82–4.64 (m, 7 H), 4.75–5.32 (m, 7 H), 7.39–8.19 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.0, 16.3, 16.4, 16.8, 18.6, 18.9, 19.1, 19.3, 19.5, 21.1, 21.3, 23.1, 23.2, 23.3, 24.3, 24.5, 28.4, 29.2, 29.3, 30.1, 30.5, 30.9, 31.8, 40.1, 40.6, 40.7, 49.1, 49.3, 52.7, 52.8, 59.4, 72.9, 73.4, 78.6, 79.0, 156.1, 170.3, 171.1, 171.2, 171.8, 172.0.

HRMS (FAB+): *m*/*z* [M + H]$^+$ calcd for $C_{63}H_{110}N_7O_{21}$: 1300.7755; found: 1300.7709.

Anal. Calcd for $C_{63}H_{109}N_7O_{21}$: C, 58.18; H, 8.45; N, 7.54. Found: C, 58.02; H, 8.38; N, 7.67.

Cereulide LVK1-*N*-Boc (51)

Cereulide LVK1-*N*-Boc (**51**) was prepared from compound **50** according to the same procedure used for the synthesis of cereulide (**1**). Compound **50** was obtained as yellow-white solid; yield: 13.8 mg (58%); mp 89–91 °C.

$[\alpha]_D^{27}$ +4.84 (*c* 0.62, $CHCl_3$) (H^+ form); $[\alpha]_D^{26}$ +5.00 (*c* 0.58, $CHCl_3$) (K^+ form); $[\alpha]_D^{27}$ +3.97 (*c* 0.63, $CHCl_3$) (NH_4^+ form).

IR (NaCl film): 3316, 1752, 1657, 1539, 1465 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (H^+ form) = 0.86–1.08 (m, 48 H), 1.44 (s, 9 H), 1.24–1.55 (m, 11 H), 1.60–1.79 (m, 11 H), 1.80–1.94 (m, 2 H), 2.21–2.41 (m, 5 H), 3.02–3.19 (m, 2 H), 4.01–4.12 (m, 2 H), 4.30–4.45 (m, 4 H), 4.75–4.90 (m, 1 H), 4.97 (d, *J* = 3.4 Hz, 1 H), 5.00 (d, *J* = 3.2 Hz, 1 H), 5.03 (d, *J* = 3.2 Hz, 1 H), 5.21–5.26 (m, 1 H), 5.27–5.33 (m, 2 H), 7.70 (dd, *J* = 6.1, 3.0 Hz, 2 H), 7.77 (d, *J* = 7.2 Hz, 2 H), 7.83 (dd, *J* = 6.6, 3.8 Hz, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (H^+ form) = 15.7, 15.8, 15.9, 16.8, 16.9, 18.5, 18.6, 19.2, 19.3, 19.4, 21.3, 21.6, 22.8, 23.1, 23.3, 23.4, 24.4, 24.6, 28.4, 28.5, 28.7, 29.2, 29.5, 30.4, 30.5, 30.6, 39.9, 40.5, 40.6, 48.7, 48.8, 52.8, 59.3, 59.6, 72.6, 72.8, 73.1, 78.5, 78.6, 78.8, 156.0, 170.4, 170.5, 170.7, 170.9, 171.2, 171.5, 171.7, 172.1.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.84–1.17 (m, 48 H), 1.22–1.70 (m, 33 H), 2.18–2.41 (m, 5 H), 3.02–3.22 (m, 2 H), 3.84 (dd, *J* = 10.9, 5.0 Hz, 2 H), 4.13–4.23 (m, 1 H), 4.24–4.34 (m, 3 H), 4.64 (t, *J* = 3.3 Hz, 3 H), 4.72–4.86 (m, 4 H), 8.13 (d, *J* = 4.4 Hz, 1 H), 8.21–8.32 (m, 4 H), 8.37 (d, *J* = 4.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.1, 15.2, 16.6, 16.8, 18.6, 19.2, 20.2, 21.0, 21.5, 22.8, 23.1, 23.2, 23.3, 24.3, 24.5, 28.4, 28.5, 29.1, 29.7, 30.1, 39.9, 40.5, 40.7, 40.8, 50.1, 50.2, 50.3, 54.9, 61.7, 73.6, 73.8, 74.0, 79.5, 79.6, 79.7, 156.0, 171.3, 171.4, 172.2, 172.3, 172.4, 175.6, 175.7, 176.1, 176.2.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (NH_4^+ form) = 0.79–1.19 (m, 48 H), 1.22–2.00 (m, 33 H), 2.18–2.40 (m, 5 H), 3.00–3.25 (m, 2 H), 3.82 (dd, *J* = 10.6, 4.5 Hz, 2 H), 4.10–4.21 (m, 1 H), 4.22–4.33 (m, 3 H), 4.69 (dd, *J* = 5.1, 2.9 Hz, 3 H), 4.74–4.89 (m, 4 H), 5.73–6.16 (m, 4 H), 7.91–7.98 (m, 1 H), 8.00–8.13 (m, 4 H), 8.16 (d, *J* = 4.3 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (NH_4^+ form) = 15.2, 15.3, 16.5, 16.7, 18.6, 19.1, 20.1, 21.0, 21.1, 21.5, 22.7, 23.0, 23.1, 23.3, 24.3, 24.5, 28.4, 28.6, 29.2, 29.7, 30.2, 39.9, 40.6, 40.8, 40.9, 50.0, 50.1, 54.7, 61.5, 73.8, 74.0, 74.3, 79.5, 79.6, 156.0, 171.1, 171.3, 172.1, 172.2, 172.3, 175.5, 175.6, 175.8, 176.0.

HRMS (FAB+): *m*/*z* [M]$^+$ calcd for $C_{63}H_{108}N_7O_{20}$ (H^+ form): 1282.7649; found: 1282.7639.

Anal. Calcd for $C_{63}H_{108}N_7O_{20}$ (H^+ form): C, 58.95; H, 8.48; N, 7.64. Found: C, 58.82; H, 8.23; N, 7.59.

Cereulide LVK1 (4)

Cereulide LVK1 (**4**) was prepared from compound **51** according to the same procedure used for the synthesis of cereulide DAK1 (**2**). Compound **4** was obtained as yellow-white solid; yield: 10.2 mg (quant.); mp 125–128 °C.

IR (NaCl film): 3302, 1749, 1656, 1540, 1467 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.80–1.17 (m, 48 H), 1.22–1.41 (m, 1 H), 1.42–1.54 (m, 10 H), 1.58–2.06 (m, 13 H), 2.19–2.40 (m, 5 H), 2.96–3.18 (m, 2 H), 3.77–3.88 (m, 2 H), 4.18–4.39 (m, 4 H), 4.58–4.65 (m, 3 H), 4.75–4.88 (m, 3 H), 8.05–7.66 (m, 3 H), 8.13 (d, *J* = 4.6 Hz, 1 H), 8.15 (d, *J* = 4.8 Hz, 1 H), 8.23

(d, *J* = 5.2 Hz, 1 H), 8.26 (d, *J* = 4.5 Hz, 1 H), 8.32 (d, *J* = 5.1 Hz, 1 H), 8.35 (d, *J* = 4.5 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.1, 15.2, 16.5, 16.9, 18.7, 19.3, 20.2, 20.3, 21.2, 21.3, 21.7, 22.8, 23.1, 23.2, 23.3, 24.3, 24.5, 26.8, 28.5, 28.9, 30.1, 39.9, 40.6, 40.7, 40.9, 50.0, 50.3, 54.8, 61.7, 61.8, 73.7, 74.2, 74.3, 79.4, 79.5, 79.6, 171.1, 171.5, 172.3, 172.5, 172.6, 175.4, 175.5, 175.6, 176.2, 176.3.

HRMS (FAB+): *m/z* $[M]^+$ calcd for $C_{58}H_{100}N_7O_{18}$ (H^+ form): 1182.7125; found: 1182.7114.

Anal. Calcd for $C_{58}H_{100}N_7O_{18}$ (H^+ form): C, 58.86; H, 8.52; N, 8.28. Found: C, 59.06; H, 8.21; N, 8.12.

L-*O*-Lysine(Boc)-L-valine Benzyl Ester (52)

Compound **52** was prepared from L-valine benzyl ester hydrochloride (**11**) and L-*O*-Lysine(Boc)-OH (**26**) according to the same procedure used for the synthesis of compound **9**. Compound **52** was obtained as an oil; yield: 1.19 g (87%).

$[\alpha]_D^{27}$ –22.12 (*c* 0.52, $CHCl_3$).

IR (NaCl film): 3397, 1738, 1672, 1522, 1456 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 (d, *J* = 6.9 Hz, 3 H), 0.93 (d, *J* = 6.9 Hz, 3 H), 1.32–1.56 (m, 12 H), 1.61–1.77 (m, 2 H), 1.80–1.95 (m, 2 H), 2.15–2.29 (m, 1 H), 3.02–3.22 (m, 2 H), 3.25–3.40 (m, 1 H), 4.09–4.19 (m, 1 H), 4.53–4.71 (m, 2 H), 5.17 (ABq, 2 H), 7.11 (d, *J* = 7.8 Hz, 1 H), 7.30–7.40 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 17.6, 19.1, 21.5, 28.4, 29.8, 31.2, 33.9, 39.7, 56.7, 67.1, 71.9, 79.3, 128.3, 128.4, 128.6, 135.3, 156.4, 171.7, 173.9.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{23}H_{37}N_2O_6$: 437.2652; found: 437.2610.

Anal. Calcd for $C_{23}H_{36}N_2O_6$: C, 63.28; H, 8.31; N, 6.42. Found: C, 63.20; H, 8.31; N, 6.60.

L-OTBDMS-Lysine(Boc)-L-valine Benzyl Ester (53)

To a soln of imidazole (0.25 g, 3.61 mmol) in anhyd DMF (20 mL) at 0 °C were added successively TBDMSCl (0.47 g, 3.13 mmol) and L-*O*-lysine(Boc)-L-valine benzyl ester (**52**) (0.89 g, 2.04 mmol) in anhyd DMF (15 mL). The reaction mixture was then stirred at 0 °C for 5 h before being heated to r.t. and stirred for 8 h. The mixture was diluted with EtOAc (80 mL) before being washed with H_2O (3 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure, and the residue purified by silica gel column chromatography (hexane–EtOAc, 7:3) to give compound **53** as an oil; yield: 1.02 g (91%).

$[\alpha]_D^{27}$ –20.00 (*c* 1.10, $CHCl_3$).

IR (NaCl film): 3348, 1739, 1714, 1685, 1510 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.07 (s, 3 H), 0.09 (s, 3 H), 0.94 (s, 9 H), 0.82–0.98 (m, 6 H), 1.43 (s, 9 H), 1.24–1.53 (m, 3 H), 1.56–1.63 (m, 1 H), 1.64–1.74 (m, 1 H), 1.75–1.86 (m, 1 H), 2.15–2.26 (m, 1 H), 3.00–3.17 (m, 2 H), 4.16 (t, *J* = 5.0 Hz, 1 H), 4.49 (br s, 1 H), 4.59 (dd, *J* = 9.4, 4.6 Hz, 1 H), 5.16 (s, 2 H), 7.15 (d, *J* = 9.3 Hz, 1 H), 7.28–7.41 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –4.9, 17.5, 17.9, 19.1, 21.4, 25.7, 28.4, 29.9, 31.3, 34.9, 40.4, 56.4, 66.9, 73.2, 128.4, 128.6, 135.4, 155.9, 171.3, 173.4.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{29}H_{51}N_2O_6Si$: 551.3516; found: 551.3490.

Anal. Calcd for $C_{29}H_{50}N_2O_6Si$: C, 63.24; H, 9.15; N, 5.09. Found: C, 63.24; H, 9.07; N, 5.21.

L-OTBDMS-Lysine(Boc)-L-valine-OH (54)

Compound **54** was prepared from compound **53** according to the same procedure used for the synthesis of compound **14**. Compound **54** was obtained as an oil; yield: 0.53 g (99%).

$[\alpha]_D^{27}$ –13.62 (*c* 1.28, $CHCl_3$).

IR (NaCl film): 3410, 1713, 1666, 1521, 1471 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.097 (s, 3 H), 0.102 (s, 3 H), 0.94 (s, 9 H), 0.86–1.05 (m, 6 H), 1.43 (s, 9 H), 1.22–1.56 (m, 4 H), 1.62–1.86 (m, 2 H), 2.20–2.34 (m, 1 H), 3.10 (dd, *J* = 3.2, 1.8 Hz, 2 H), 4.19 (t, *J* = 5.0 Hz, 1 H), 4.47–4.59 (m, 2 H), 7.18 (d, *J* = 9.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.4, –4.9, 17.4, 17.9, 19.2, 21.4, 25.7, 28.4, 29.9, 30.9, 34.8, 40.4, 56.4, 73.2, 79.1, 156.0, 173.9, 175.1.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{22}H_{45}N_2O_6Si$: 461.3047; found: 461.3061.

Anal. Calcd for $C_{22}H_{44}N_2O_6Si$: C, 57.36; H, 9.63; N, 6.08. Found: C, 57.37; H, 9.72; N, 6.11.

L-OTBDMS-Lysine(Boc)-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (55)

Compound **55** was prepared from compounds **9** and **54** according to the same procedure used for the synthesis of compound **15**. Compound **55** was obtained as an oil; yield: 0.63 g (95%).

$[\alpha]_D^{27}$ +7.35 (*c* 0.33, $CHCl_3$).

IR (NaCl film): 3323, 1747, 1674, 1518, 1456 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.08 (s, 3 H), 0.09 (s, 3 H), 0.94 (s, 9 H), 0.87–1.04 (m, 12 H), 1.21–1.35 (m, 2 H), 1.43 (s, 9 H), 1.36–1.52 (m, 4 H), 1.56–1.83 (m, 6 H), 2.09–2.22 (m, 1 H), 3.00–3.17 (m, 2 H), 4.13 (t, *J* = 4.9 Hz, 1 H), 4.30 (t, *J* = 7.1 Hz, 1 H), 4.42–4.61 (m, 2 H), 5.07–5.20 (m, 2 H), 5.27 (dd, *J* = 8.3, 5.0 Hz, 1 H), 7.10 (d, *J* = 7.5 Hz, 1 H), 7.21 (d, *J* = 7.5 Hz, 1 H), 7.28–7.39 (m, 5 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.3, –4.9, 17.5, 17.9, 18.2, 19.1, 21.3, 23.2, 24.4, 25.7, 28.4, 29.9, 30.2, 34.5, 40.5, 48.1, 57.9, 66.7, 73.0, 127.9, 128.2, 128.5, 135.6, 155.9, 169.7, 171.1, 172.1, 174.3.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{38}H_{66}N_3O_9Si$: 736.4568; found: 736.4537.

Anal. Calcd for $C_{38}H_{65}N_3O_9Si$: C, 62.01; H, 8.90; N, 5.71. Found: C, 62.01; H, 8.81; N, 5.73.

L-OTBDMS-Lysine(Boc)-L-valine-D-*O*-leucine-D-alanine-OH (56)

Compound **56** was prepared from compound **55** according to the same procedure used for the synthesis of compound **14**. Compound **56** was obtained as a white solid; yield: 0.46 g (97%); mp 74–76 °C.

$[\alpha]_D^{27}$ +8.87 (*c* 0.97, $CHCl_3$).

IR (NaCl film): 3329, 1747, 1672, 1523, 1462 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (br s, 6 H), 0.94 (s, 9 H), 0.82–1.03 (m, 12 H), 1.26–1.35 (m, 2 H), 1.43 (s, 9 H), 1.35–1.56 (m, 4 H), 1.57–1.89 (m, 6 H), 2.11–2.31 (m, 1 H), 3.09 (br s, 2 H), 4.14–5.44 (m, 5 H), 7.20–7.56 (m, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.4, –4.9, 17.6, 17.9, 18.2, 18.3, 19.2, 21.2, 23.2, 24.5, 25.7, 28.4, 29.8, 30.2, 34.3, 40.3, 40.6, 49.3, 57.4, 72.7, 73.3, 79.1, 156.0, 169.5, 169.7, 170.7, 175.2.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{31}H_{60}N_3O_9Si$: 646.4099; found: 646.4052.

Anal. Calcd for $C_{31}H_{59}N_3O_9Si$: C, 57.65; H, 9.21; N, 6.51. Found: C, 57.48; H, 8.99; N, 6.49.

L-OTBDMS-Lysine(Boc)-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (57)

Compound **57** was prepared from compounds **19** and **56** according to the same procedure used for the synthesis of compound **20**. Compound **57** was obtained as a white solid; yield: 0.13 g (65%, 73% conversion); mp 68–69 °C.

$[\alpha]_D^{27}$ +0.80 (*c* 0.75, $CHCl_3$).

IR (NaCl film): 3316, 1750, 1649, 1542, 1464 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.10 (s, 3 H), 0.11 (s, 3 H), 0.81–1.10 (m, 57 H), 1.21–1.33 (m, 2 H), 1.44 (s, 9 H), 1.36–1.52 (m, 11 H), 1.57–1.90 (m, 11 H), 2.00–2.12 (m, 1 H), 2.27–2.44 (m, 4 H), 3.04–3.15 (m, 2 H), 3.95–4.04 (m, 2 H), 4.07–4.16 (m, 2 H), 4.30 (t, *J* = 7.5 Hz, 1 H), 4.50 (dd, *J* = 8.5, 7.2 Hz, 2 H), 4.64–4.55 (m, 1 H), 4.99 (d, *J* = 3.1 Hz, 1 H), 5.03 (d, *J* = 3.0 Hz, 1 H), 5.04–5.10 (m, 1 H), 5.11 (s, 2 H), 5.21 (dd, *J* = 10.9, 1.6 Hz, 1 H), 5.36 (dd, *J* = 10.2, 2.7 Hz, 1 H), 7.10 (d, *J* = 5.6 Hz, 1 H), 7.27–7.36 (m, 5 H), 7.69 (d, *J* = 7.9 Hz, 1 H), 7.79–7.86 (m, 2 H), 8.12 (d, *J* = 5.8 Hz, 1 H), 8.28 (d, *J* = 6.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = –5.4, –4.9, 16.2, 16.5, 17.6, 17.9, 18.9, 19.0, 19.3, 20.8, 21.2, 21.3, 23.1, 23.2, 23.3, 24.3, 24.4, 25.7, 28.4, 29.6, 29.8, 29.9, 30.1, 30.2, 30.4, 34.5, 40.4, 40.5, 41.0, 41.2, 47.9, 49.4, 49.7, 58.3, 58.8, 59.1, 66.6, 72.7, 72.9, 73.0, 78.9, 79.0, 79.2, 128.0, 128.1, 128.4, 135.8, 155.9, 169.8, 170.0, 170.3, 170.5, 170.6, 170.8, 171.4, 172.0, 172.1, 172.4, 175.2.

HRMS (ESI-MS+): *m/z* $[M + H]^+$ calcd for $C_{76}H_{130}N_7O_{21}Si$: 1504.9089; found: 1504.9108.

Anal. Calcd for $C_{76}H_{129}N_7O_{21}Si$: C, 60.65; H, 8.64; N, 6.51. Found: C, 60.65; H, 8.44; N, 6.43.

L-*O*-Lysine(Boc)-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine Benzyl Ester (58)

Compound **58** was prepared from compound **57** according to the same procedure used for the synthesis of compound **16**. Compound **58** was obtained as a white solid; yield: 0.21 g (85%); mp 61–63 °C.

$[\alpha]_D^{27}$ –1.52 (*c* 0.79, $CHCl_3$).

IR (NaCl film): 3312, 1749, 1651, 1542, 1456 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.81–1.10 (m, 48 H), 1.21–1.54 (m, 22 H), 1.57–1.89 (m, 11 H), 2.00–2.19 (m, 1 H), 2.22–2.46 (m, 4 H), 3.01–3.17 (m, 2 H), 3.97–4.14 (m, 4 H), 4.15–4.23 (m, 1 H), 4.28–4.38 (m, 1 H), 4.41 (t, *J* = 7.71 Hz, 1 H), 4.47–4.56 (m, 1 H), 4.69–4.79 (m, 1 H), 4.95 (d, *J* = 3.4 Hz, 1 H), 5.06 (d, *J* = 3.0 Hz, 1 H), 5.09–5.18 (m, 3 H), 5.20–5.26 (m, 1 H), 5.35 (dd, *J* = 10.0, 2.6 Hz, 1 H), 7.27–7.36 (m, 5 H), 7.44 (d, *J* = 6.2 Hz, 1 H), 7.65–7.75 (m, 2 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.91–8.02 (m, 1 H), 8.15 (d, *J* = 5.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.2, 16.4, 16.9, 17.3, 18.7, 18.9, 19.0, 19.1, 19.2, 19.3, 21.0, 21.2, 21.5, 23.1, 23.3, 24.3, 24.4, 24.5, 28.4, 29.0, 29.3, 29.7, 30.0, 30.1, 30.7, 33.6, 39.9, 40.6, 40.9, 48.3, 48.9, 49.5, 58.6, 59.4, 59.5, 66.7, 71.7, 72.6, 72.8, 73.2, 77.2, 78.8, 79.1, 79.2, 128.0, 128.4, 135.8, 156.4, 170.1, 170.7, 170.9, 171.0, 171.4, 171.6, 171.7, 172.1, 172.3, 175.9.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{70}H_{116}N_7O_{21}$: 1390.8224; found: 1390.8179.

Anal. Calcd for $C_{70}H_{115}N_7O_{21}$: C, 60.46; H, 8.33; N, 7.05. Found: C, 60.46; H, 8.07; N, 6.97.

L-*O*-Lysine(Boc)-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-L-*O*-valine-L-valine-D-*O*-leucine-D-alanine-OH (59)

Compound **59** was prepared from compound **58** according to the same procedure used for the synthesis of compound **14**. Compound **59** was obtained as a white solid; yield: 0.14 g (99%); mp 102–104 °C.

$[\alpha]_D^{26}$ +0.76 (*c* 0.79, $CHCl_3$).

IR (NaCl film): 3314, 1749, 1652, 1542, 1465 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 0.82–1.13 (m, 48 H), 1.23–1.59 (m, 22 H), 1.60–1.89 (m, 11 H), 2.10–2.50 (m, 5 H), 3.04–3.18 (m, 2 H), 3.75–5.55 (m, 14 H), 7.30–8.09 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ = 16.0, 16.3, 16.4, 16.6, 16.8, 17.3, 18.5, 18.8, 19.0, 19.1, 19.3, 19.4, 21.0, 21.1, 21.2, 21.9, 23.1, 23.2, 23.3, 24.4, 24.5, 28.4, 29.1, 29.5, 30.2, 30.7, 40.2, 40.4, 40.6, 40.8, 48.2, 48.7, 49.3, 59.0, 59.5, 59.7, 71.8, 72.9, 73.1, 73.5, 77.2, 78.5, 79.0, 156.2, 170.4, 170.8, 171.7, 176.5.

HRMS (FAB+): *m/z* $[M + H]^+$ calcd for $C_{63}H_{110}N_7O_{21}$: 1300.7755; found: 1300.7726.

Anal. Calcd for $C_{63}H_{109}N_7O_{21}$: C, 58.18; H, 8.45; N, 7.54. Found: C, 58.07; H, 8.32; N, 7.66.

Cereulide LOVK1-*N*-Boc (60)

Cereulide LOVK1-*N*-Boc (**60**) was prepared from compound **59** according to the same procedure used for the synthesis of cereulide (**1**). Compound **60** was obtained as yellow-white solid; yield: 97.2 mg (72%); mp 75–77 °C.

$[\alpha]_D^{27}$ +9.02 (*c* 4.07, $CHCl_3$) (H^+ form); $[\alpha]_D^{25}$ –2.28 (*c* 4.43, $CHCl_3$) (K^+ form); $[\alpha]_D^{25}$ –1.89 (*c* 4.61, $CHCl_3$) (NH_4^+ form).

IR (NaCl film): 3312, 1753, 1657, 1540, 1469 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ (H^+ form) = 0.70–1.11 (m, 48 H), 1.20–1.51 (m, 20 H), 1.58–2.01 (m, 13 H), 2.11–2.40 (m, 5 H), 3.07 (d, *J* = 5.4 Hz, 2 H), 3.94 (dd, *J* = 9.6, 6.5 Hz, 1 H), 4.02 (dd, *J* = 9.6, 6.9 Hz, 1 H), 4.10 (dd, *J* = 9.7, 8.0 Hz, 1 H), 4.22–4.52 (m, 3 H), 4.68 (br s, 1 H), 4.93 (d, *J* = 3.3 Hz, 1 H), 4.97 (d, *J* = 3.1 Hz, 1 H), 5.10–5.19 (m, 2 H), 5.25–5.33 (m, 2 H), 7.64–7.81 (m, 4 H), 7.88 (d, *J* = 6.4 Hz, 1 H), 7.94 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (H^+ form) = 15.6, 15.7, 15.8, 16.7, 16.9, 18.6, 19.2, 19.4, 19.5, 19.6, 21.1, 21.5, 23.2, 23.3, 24.4, 28.4, 28.6, 29.4, 30.3, 30.4, 30.5, 40.2, 40.4, 40.5, 40.6, 48.0, 48.6, 49.1, 59.1, 59.9, 60.1, 72.7, 72.8, 73.1, 74.6, 78.2, 78.8, 155.9, 170.0, 170.8, 171.1, 171.3, 171.4, 171.5, 171.7, 171.8, 172.1.

^1H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.79–1.12 (m, 48 H), 1.32–2.12 (m, 33 H), 2.14–2.33 (m, 5 H), 3.00–3.15 (m, 2 H), 3.71–3.83 (m, 3 H), 4.16–4.30 (m, 3 H), 4.55–4.62 (m, 2 H), 4.67–4.78 (m, 4 H), 4.85–5.00 (m, 1 H), 8.14–8.34 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.0, 15.1, 16.5, 18.5, 19.1, 20.1, 20.9, 22.2, 22.9, 24.2, 28.3, 28.4, 28.5, 29.4, 30.0, 30.9, 40.7, 50.1, 61.6, 61.7, 73.6, 75.3, 77.0, 77.2, 78.7, 79.6, 156.1, 171.3, 172.0, 172.1, 175.6, 176.0.

^1H NMR ($CDCl_3$, 400 MHz): δ (NH_4^+ form) = 0.85–1.18 (m, 48 H), 1.33–2.00 (m, 33 H), 3.01–3.22 (m, 2 H), 3.75–3.88 (m, 3 H), 4.19–4.32 (m, 3 H), 4.66–4.72 (m, 2 H), 4.73–5.04 (m, 5 H), 5.70–6.16 (m, 4 H), 8.00–8.18 (m, 6 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (NH_4^+ form) = 15.1, 15.2, 16.5, 18.5, 19.0, 19.1, 20.0, 20.1, 21.1, 22.2, 22.9, 23.0, 24.2, 28.3, 28.5, 28.6, 29.5, 30.1, 31.1, 40.1, 40.7, 50.0, 61.4, 61.5, 73.8, 75.3, 77.2, 78.8, 79.5, 156.1, 171.2, 171.9, 172.0, 172.1, 175.5, 175.6, 175.7, 175.8.

HRMS (FAB+): *m/z* $[M]^+$ calcd for $C_{63}H_{108}N_7O_{20}$ (H^+ form): 1282.7649; found: 1282.7681.

Anal. Calcd for $C_{63}H_{108}N_7O_{20}$ (H^+ form): C, 58.95; H, 8.48; N, 7.64. Found: C, 58.78; H, 8.36; N, 7.64.

Cereulide LOVK1 (5)

Cereulide LOVK1 (**5**) was prepared from compound **60** according to the same procedure used for the synthesis of cereulide DAK1 (**2**). Compound **5** was obtained as yellow-white solid; yield: 12.3 mg (quant.); mp 123–126 °C.

IR (NaCl film): 3306, 1751, 1655, 1538, 1469 cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ (K^+ form) = 0.81–1.20 (m, 48 H), 1.22–1.42 (m, 2 H), 1.46–1.70 (m, 12 H), 1.71–1.93 (m, 6 H), 1.94–2.18 (m, 4 H), 2.19–2.39 (m, 5 H), 2.94–3.18 (m, 2 H), 3.77–3.89 (m, 3 H), 4.21–4.36 (m, 3 H), 4.65–4.72 (m, 2 H), 4.73–4.83 (m, 4 H), 7.82 (br s, 3 H), 8.17 (d, *J* = 5.2 Hz, 1 H), 8.20–8.29 (m, 3 H), 8.31–8.40 (m, 2 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ (K^+ form) = 15.2, 15.4, 16.6, 16.7, 18.6, 18.7, 19.2, 19.3, 20.2, 20.3, 21.1, 22.4, 23.0, 23.1, 24.3, 26.5, 28.5, 28.6, 29.7, 30.1, 30.2, 31.0, 40.1, 40.8, 50.2, 50.4, 61.7, 61.8, 73.6, 73.8, 75.2, 79.6, 79.8, 171.5, 171.8, 171.9, 172.1, 172.2, 172.3, 175.6, 175.8, 175.9, 176.1.

HRMS (FAB+): *m/z* $[M]^+$ calcd for $C_{58}H_{100}N_7O_{18}$ (H^+ form): 1182.7125; found: 1182.7153.

Anal. Calcd for $C_{58}H_{100}N_7O_{18}$ (H^+ form): C, 58.86; H, 8.52; N, 8.28. Found: C, 59.05; H, 8.54; N, 8.19.

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