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Total Syntheses of Cathepsin D Inhibitory Izenamides A, B, and C and Structural Confirmation of Izenamide B

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Abstract: The first total syntheses of izenamides A, B, and C, which are depsipeptides inhibitor of cathepsin D, were accomplished. In addition, the stereochemistry of izenamide B was confirmed by our syntheses. The key features of our synthetic route involve the avoidance of critical 2,5-diketopiperazine (DKP) formation and the minimization of epimerization during the coupling of amino acids for the target peptides.

Keywords: izenamides; cathepsin D; depsipeptide; total synthesis; structural confirmation

1. Introduction

Cathepsin D is an aspartic protease and has attracted considerable attention from both biologists and chemists due to its interesting biological functions [1,2]. This aspartic protease, which is involved in protein catabolism and required in certain epithelial cells for tissue remodeling and renewal, regulates lysosomal proteolysis and endogenous fibrinolysis [3–6]. Cathepsin D also maintains hormone and antigen processing [7–9]. In particular, cathepsin D is involved in various diseases, including breast cancer metastasis [10–12], atherosclerosis [8,13], Alzheimer's disease [14–16] and neuronal ceroid lipofuscinosis (NCL) [6,17–19]. Therefore, therapeutic modulators of the proteolytic activity of cathepsin D have been extensively investigated for the development of new drugs although there have been few reports regarding inhibitors of cathepsin D [20–24].

Recently, three new depsipeptides, namely, izenamides A (**1**), B (**2**), and C (**3**), were isolated from the marine cyanobacterium 1605-5 by Suenaga and coworkers (Figure 1) [25]. Interestingly, izenamides A (**1**) and B (**2**) were shown to inhibit cathepsin D in vitro. These two depsipeptides consist of seven monomers, including four amino acids, two hydroxy acids, and a γ-amino-β-hydroxy acid called statine. Izenamide C (**3**), which lacks a statine moiety and possesses a glycine unit instead of the alanine seen in izenamides A (**1**) and B (**2**), has no inhibitory activity against cathepsin D. The absolute configuration of the statine moiety in izenamide B (**2**) was indirectly determined by numerous efforts by Suenaga and coworkers [25].

In our pursuit of developing novel cathepsin D inhibitors, we recently became interested in establishing an efficient synthetic route towards izenamides A, B, and C. We were also interested in confirming the structure of izenamide B to ensure the stereochemistry of the statine moiety before we started medicinal chemistry studies. We herein report the first total syntheses of izenamides A, B, and C as well as the structural confirmation of izenamide B.
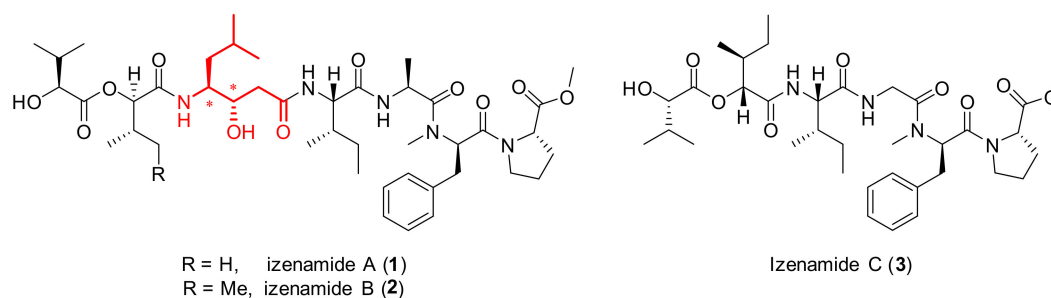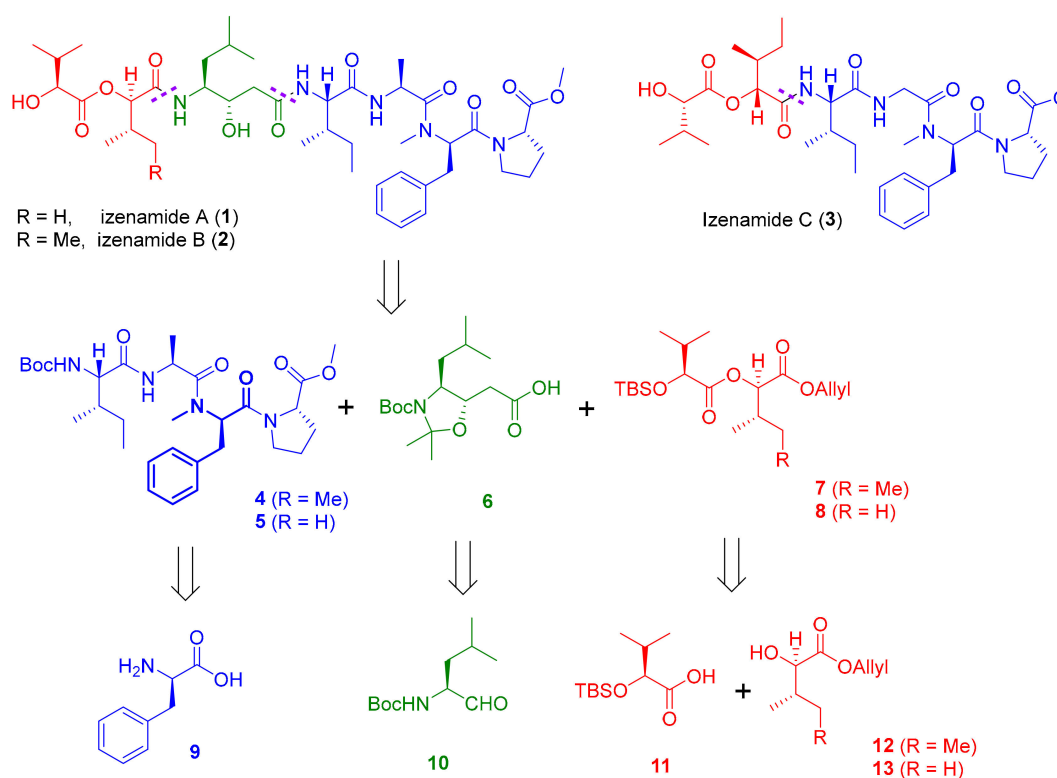
R = H,   izenamide A (**1**)
R = Me, izenamide B (**2**)

Izenamide C (**3**)

Figure 1. Structures of Izenamides.

2. Results and Discussion

2.1. Synthetic Strategy for Izenamides A (1), B (2), and C (3)

Our retrosynthetic analysis is outlined in Scheme 1. We envisioned that the target izenamides could be accessed via a versatile convergent approach. Izenamides A (**1**) and B (**2**) would be synthesized by assembling three fragments, tetrapeptide **4**, statine **6**, and esters **7** or **8**. Considering that izenamide C (**3**) has a very similar structure except for the statine moiety, it could also be convergently synthesized by the amide coupling of tetrapeptide **5** and ester **7**. Tetrapeptides **4** and **5** were anticipated to be derived from commercially available amino acids and *N*Me-D-Phe, which could be obtained from D-Phe (**9**). Protected statine **6** could be prepared from Boc-L-leucinal (**10**) through the known procedure [26,27]. Esters **7** and **8** can be conveniently obtained by the esterification of protected hydroxy acids **11** and **12** (or **13**).

R = H,   izenamide A (**1**)
R = Me, izenamide B (**2**)

Izenamide C (**3**)

4 (R = Me)
5 (R = H)

6

7 (R = Me)
8 (R = H)

9

10

11

12 (R = Me)
**13** (R = H)

Scheme 1. Retrosynthetic analysis for the synthesis of izenamides **1, 2** and **3**.

2.2. Syntheses of Fragments

The synthesis of izenamides commenced with synthesizing tetrapeptides **4** and **5**. Initially, *N*Me-D-Phe **16** was prepared from commercially available D-Phe (**9**) as shown in Scheme 2. Amine

protection of D-Phe **9** with Boc anhydride and *N*-methylation of resulting carbamate **14** afforded acid **15**, which was esterified to produce desired monomer **16** in 84% yield over three steps.
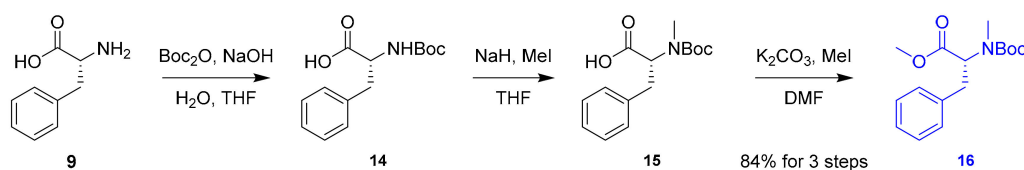

Scheme 2. Preparation of NMe-D-Phe monomer **16**.

With monomer **16** in hand, we turned our attention to the synthesis of tetrapeptides **4** and **5** (Scheme 3). To avoid facile DKP formation upon sequential elongation from the *C*-terminal *N*Me-Phe and Pro residue, we synthesized tetrapeptides **4** and **5** according to the optimized sequence of fragment couplings. Amidation of L-alanine methyl ester hydrochloride (**17**) and glycine methyl ester hydrochloride (**18**) with Boc-Ile-OH followed by ester hydrolysis with LiOH afforded dipeptides **21** and **22** in high yields. Deprotection of **16** and coupling of resulting free amine **23** with acids **21** and **22** produced tripeptides **24** and **25** in 77 and 87% yields over two steps, respectively. Unfortunately, epimerization was observed during the amidation to form **24**. After thorough optimization of the coupling conditions, amidation in the presence of DEPBT in CH_2Cl_2 at 0 °C provided the best results in terms of high chemical yield and minimal epimerization (2.8:1). Tripeptides **24** and **25** were subjected to hydrolysis and then amidation with L-proline methyl ester hydrochloride to afford tetrapeptides **4** and **5** in 84 and 81% yield over two steps, respectively. In general, the *N*-Me peptide backbone near the *C*-terminal is prone to α-epimerization upon carboxy activation due to steric hindrance and electronic effects [28]. However, we could obtain the desired tetrapeptides without epimerization under the optimized conditions (DEPBT, CH_2Cl_2, 0 °C).
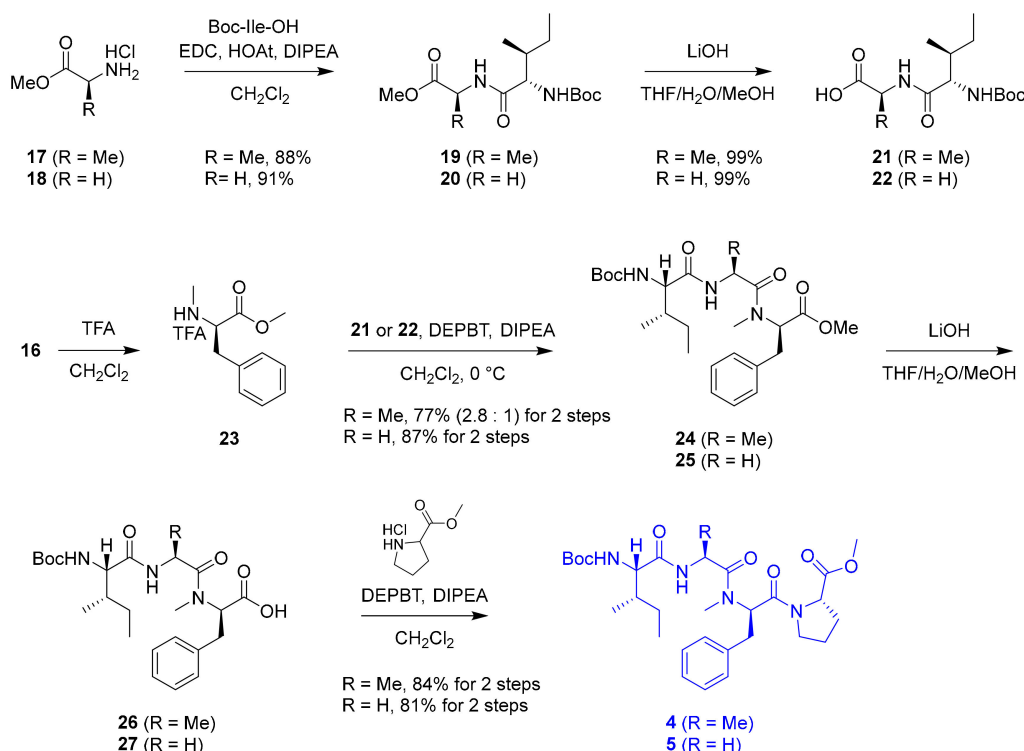

Scheme 3. Synthesis of tetrapeptides **4** and **5**.

Optically pure statine **6** was prepared by the known procedure [26,27] (Scheme 4). An elegant highly diastereoselective allyl addition to *N*-Boc-L-leucinal in the presence of SnCl$_4$ [26] provided desired threo isomer **27**. The reaction of homoallylic alcohol **27** with 2,2-dimethoxypropane in the presence of catalytic PPTS followed by RuO$_4$-mediated oxidative degradation [27] afforded monomer acid **6**.
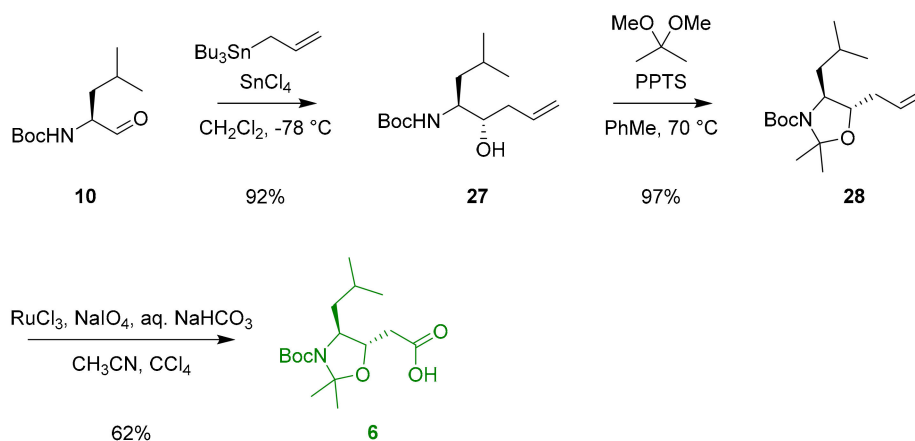

Scheme 4. Synthesis of statine **6**.

The synthesis of esters **7** and **8,** which are the C-terminal fragments of izenamides, began with the preparation of silyl-protected valic acid **11** (Scheme 5). Global TBS-protection of commercially available L-valic acid (**29**) and hydrolysis of resulting silyl ester **30** produced *C*-terminal acid **11** in 94% yield over 2 steps. D-Allo-isoleucic acid **32** [29], which was prepared through the diazotization of commercially available D-allo-Ile (**31**), and D-valic acid (**33**) were converted to corresponding allyl esters **12** (64% for 2 steps) and **13** (91%), respectively. The EDC-mediated esterification of acid **11** with alcohol **12** afforded ester **7**. Unfortunately, a satisfactory yield for this esterification was not achieved due the production of undesired esters by inevitable silyl transfer between hydroxyl groups.
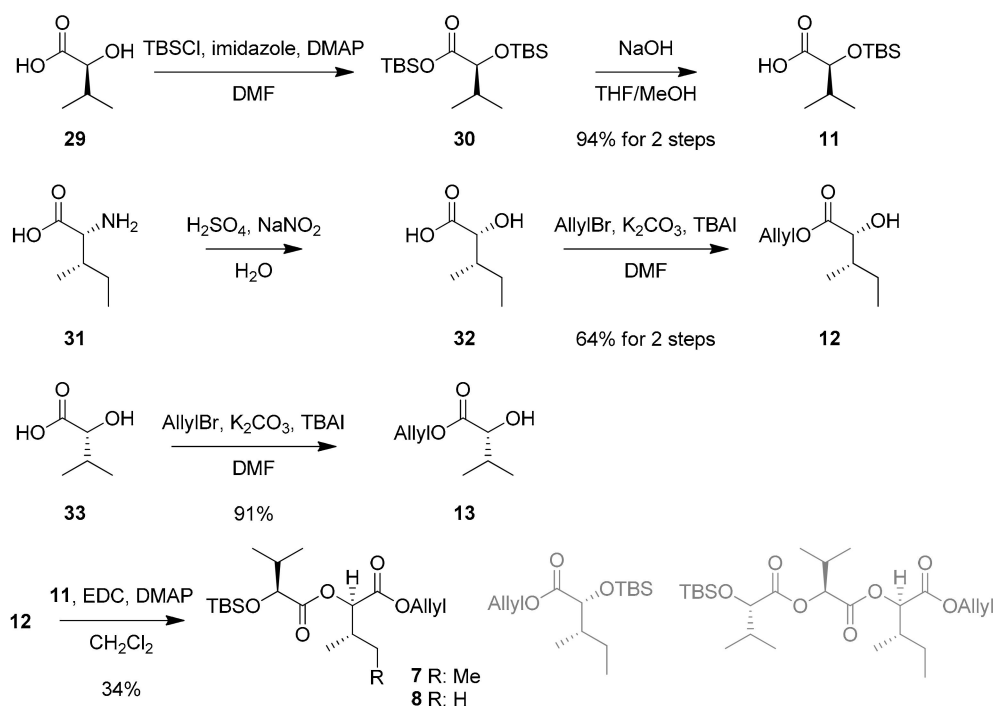
**Scheme 5.** Synthesis of Ester **7**.

Therefore, we decided to change the TBS protecting group to a bulkier TBDPS group, which was anticipated to minimize silyl transfer (Scheme 6). To our delight, the silyl transfer was minimized in the coupling reactions, and fragments **36** and **37** were obtained in 92% and 94% yields, respectively. Finally, allyl deprotection of esters **36** and **37** with *N*-Me-aniline in the presence of Pd(0) produced acids **38** in 88% and **39** in 92% yield, respectively.
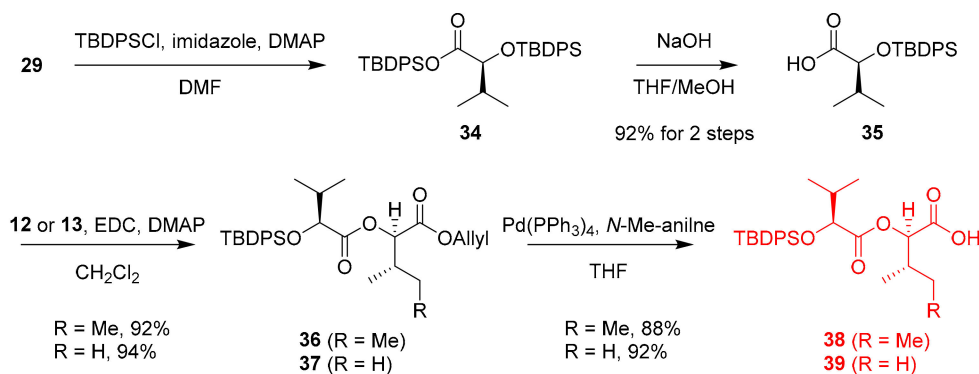
**Scheme 6.** Synthesis of fragments **38** and **39** with minimized silyl transfer.

2.3. Completion of the Syntheses

We finally assembled the prepared fragments of izenamide C as shown in Scheme 7. The EDC-mediated amide coupling of amine **40**, which was prepared from tetrapeptide **5**, with acid **38** followed by silyl-deprotection produced izenamide C (**3**) in 81% over 3 steps.
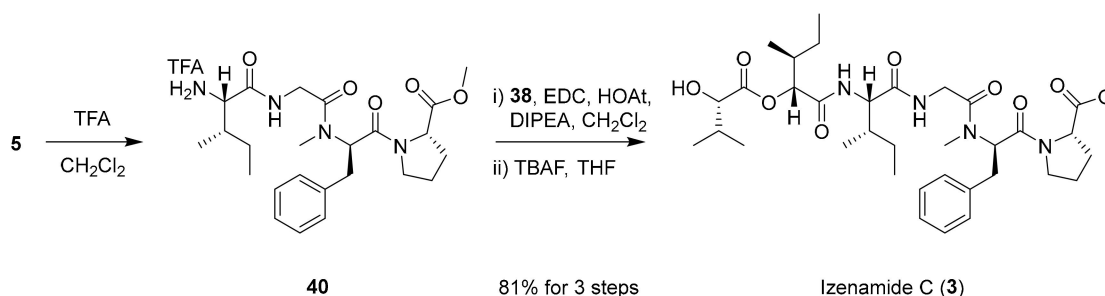
Scheme 7. Completion of the synthesis of izenamide C (**3**).

The completed synthesis of izenamides A (**1**) and B (**2**) is illustrated in Scheme 8. Boc-deprotection of tetrapeptide **4** with TFA and amide coupling with acid **6** afforded pentapeptide **42** in 77% yield over two steps. Global deprotection under acidic conditions followed by amidation of the resulting amine with acids **39** or **38** produced the corresponding heptapeptides. Finally, desilylation of heptapeptides afforded izenamides A (**1**) and B (**2**) in 66% and 61% over 3 steps, respectively. Spectral data of the synthesized depsipeptides **1**, **2**, and **3** were all identical with the reported data of natural **1**, **2** and **3** [25]. Moreover, the absolute configuration of the statine moiety in **2** was identical to that of **1**. The ^{1}H and ^{13}C NMR spectra of some compounds are in the Supplementary Materials.
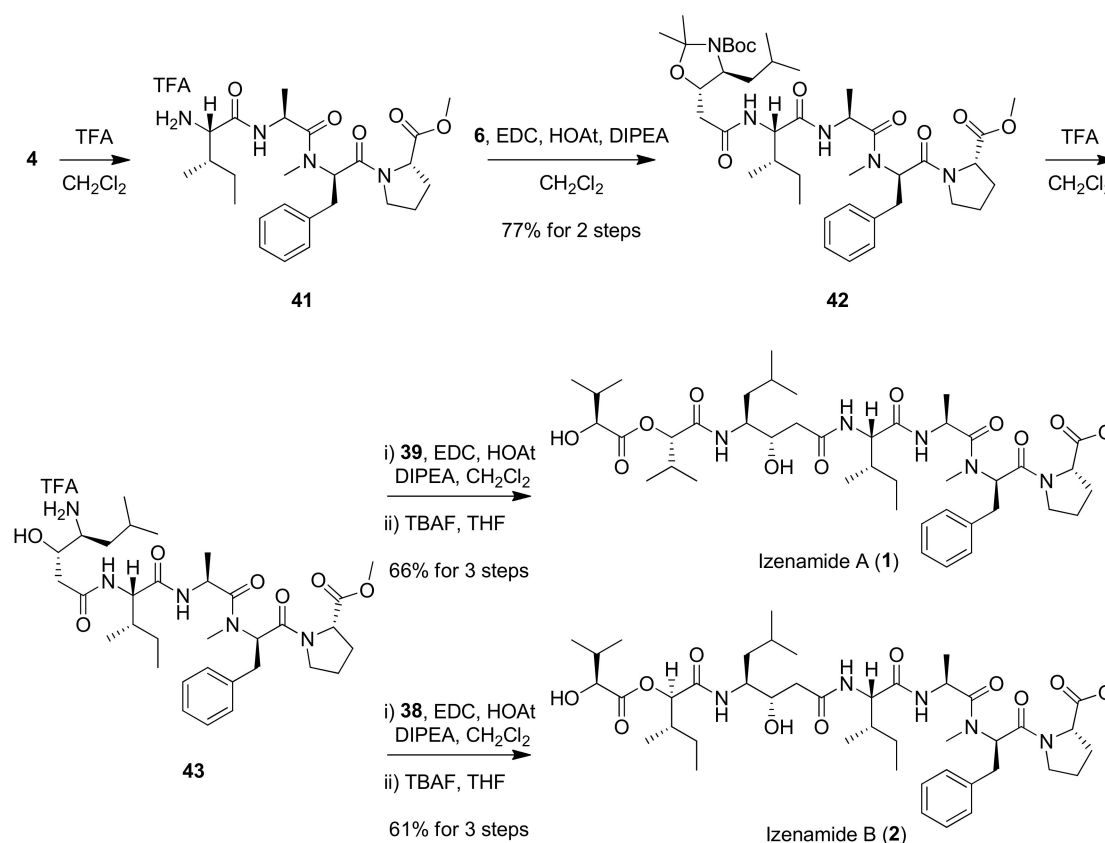
Scheme 8. Completion of the syntheses of izenamides A (**1**) and B (**2**).

3. Materials and Methods

3.1. General Information

Unless noted otherwise, all starting materials and reagents were obtained from commercial suppliers (Sigma-Aldrich, St. Louis, MO, USA; TCI, Tokyo, Japan; Combi-Blocks, San Diego, CA, USA) and were used without further purification. Tetrahydrofuran and Et_2O were distilled from sodium benzophenone ketyl. Dichloromethane, chloroform and acetonitrile were freshly distilled from calcium hydride. All solvents used for routine isolation of products and chromatography were reagent grade and glass distilled. Reaction flasks were dried at 100 °C. Air and moisture sensitive reactions were performed under argon atmosphere. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck, Kenilworth, NJ, USA) with the indicated solvents. Thin-layer chromatography was performed using 0.25 mm silica gel plates (Merck, Kenilworth, NJ, USA). Optical rotations were measured with JASCO P-2000 digital polarimeter (Tokyo, Japan) at ambient temperature using cylindrical cell of 10 mm or 100 mm pathlength. Infrared spectra were recorded on a JASCO FT-IR-4200 spectrometer (Tokyo, Japan). High resolution mass spectra were obtained with JEOL JMS-700 (Tokyo, Japan) and Agilent Q TOF 6530 (Santa Clara, CA, USA) instruments. ^{1}H and ^{13}C NMR spectra were recorded using BRUKER AVANCE-800 (Billerica, MA, USA). Chemical shifts are expressed in parts per million (ppm, δ) downfield from tetramethylsilane and are referenced to the deuterated solvent (CHCl$_3$, ^{1}H δ 7.24, ^{13}C δ 77.0; MeOH-d_4, ^{1}H δ 3.30, ^{13}C δ 49.00). ^{1}H-NMR data were reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and/or multiple resonances; br, broad signal), coupling constant in hertz (Hz) and number of protons.

3.2. Experimental Part

Boc-NMe-ᴅ-Phe-OMe (**16**). To a solution of ᴅ-Phe **9** (1.7 g, 10.3 mmol) and Boc$_2$O (3.5 mL, 15.4 mmol) in a mixture THF and H$_2$O (1:1, 50 mL) was added NaOH (0.6 g, 15.4 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. To a solution of above crude Boc-ᴅ-Phe-OH **14** (10.3 mmol) in dry THF (20 mL) was added NaH (60% dispersion in mineral oil, 2.1 g, 51.5 mmol) at room temperature. After stirring for 1 h, iodomethane (3.2 mL, 51.5 mmol) was added to the reaction mixture. The reaction mixture was stirred for 12 h, quenched with 1*N* HCl, and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude acid **15** (10.3 mmol) in dry DMF (20 mL) were added iodomethane (1.3 mL, 20.6 mmol) and K$_2$CO$_3$ (2.8 g, 20.6 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with Et$_2$O. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:20) to give 2.5 g (84% for 3 steps) of ester **16** as a colorless oil. $[\alpha]_D^{20}$ = +109.84 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$, 3:2 mixture of two rotamers). Major rotamer δ 7.28–7.20 (m, 2H), 7.19–7.07 (m, 3H), 4.50 (dd, *J* = 10.4, 3.8 Hz, 1H), 3.70 (s, 3H), 3.23 (dd, *J* = 14.2, 4.4 Hz, 1H), 3.01–2.94 (m, 1H), 2.68 (s, 3H), 1.29 (s, 9H), minor rotamer δ 7.28–7.20 (m, 2H), 7.19–7.07 (m, 3H), 4.89 (dd, *J* = 10.6, 5.2 Hz, 1H), 3.68 (s, 3H), 3.27 (dd, *J* = 14.4, 5.1 Hz, 1H), 3.01–2.94 (m, 1H), 2.66 (s, 3H), 1.33 (s, 9H); ^{13}C-NMR (200 MHz, CDCl$_3$, 3:2 mixture of two rotamers). Major rotamer δ 171.4, 154.8, 137.5, 128.9, 128.4, 126.5, 80.1, 61.5, 52.0, 35.4, 32.4, 28.0, minor rotamer δ 171.7, 155.6, 137.2, 128.8, 128.2, 126.3, 79.8, 59.4, 52.0, 34.9, 31.8, 28.1; IR (thin film, neat) ν_{max} 2977, 1746, 1698, 1393, 1332, 1227, 1145, 751 cm^{-1}; LR-MS (ESI+) *m/z* 316 (M + Na$^+$); HR-MS (ESI+) calcd for C$_{16}$H$_{23}$NNaO$_4$ (M + Na$^+$) 316.1519; found 316.1523.

Boc-L-Ile-L-Ala-OH (**21**). To a solution of ʟ-alanine methyl ester hydrochloride **17** (1.7 g, 12.2 mmol), Boc-ʟ-Ile-OH (2.3 g, 9.9 mmol), DIPEA (5.2 mL, 29.8 mmol), and HOAt (1.4 g, 10.4 mmol) in CH$_2$Cl$_2$ (40 mL) was added EDC·HCl (3.8 g, 19.9 mmol) at room temperature. After stirring for 4 h, the reaction mixture was quenched with 1*N* HCl, extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:2 to 1:1) to give 2.8 g (88%) of dipeptide **19** as white solid. $[\alpha]_D^{20}$ = +16.54 (*c* 1.00, CHCl$_3$); ^{1}H NMR (800 MHz, CDCl$_3$) δ 6.40 (s, 1H), 5.03 (d, *J* = 6.7 Hz, 1H), 4.56 (dq, *J* = 7.2, 7.1 Hz, 1H), 3.94 (t, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 1.88–1.81 (m, 1H), 1.53–1.44 (m, 1H), 1.42 (s, 9H), 1.39 (d, *J* = 7.2 Hz, 3H), 1.17–1.09 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (200 MHz, CDCl$_3$) δ 173.1, 171.1, 155.7, 79.9, 59.1, 52.4, 48.0, 37.3, 28.3, 24.7, 18.3, 15.4, 11.4; IR (thin film, neat) ν_{max} 3313, 2977, 1751, 1682, 1651, 1528, 1367, 1252, 870 cm^{-1}; LR-MS (ESI+) *m/z* 317 (M + H$^+$); HR-MS (ESI+) calcd for C$_{15}$H$_{29}$N$_2$O$_5$ (M + H$^+$) 317.2071; found 317.2072. To a solution of Boc-ʟ-Ile-**ʟ**-Ala-OMe **19** (2.0 g, 6.3 mmol) in a mixture of THF, MeOH and H$_2$O (1:1:1, 10 mL) was added LiOH·H$_2$O (0.6 g, 14.3 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was dried over MgSO$_4$ and concentrated *in vacuo* to afford 1.9 g (99%) of Boc-ʟ-Ile-ʟ-Ala-OH **21** as a white solid. The free acid **21** was used in the next step without further purification.

Boc-L-Ile-Gly-OH (**22**). To a solution of glycine methyl ester hydrochloride **18** (1.5 g, 11.9 mmol), Boc-ʟ-Ile-OH (2.3 g, 9.9 mmol), DIPEA (5.2 mL, 29.8 mmol), and HOAt (1.4 g, 10.4 mmol) in CH$_2$Cl$_2$ (40 mL) was added EDC·HCl (3.8 g, 19.9 mmol) at room temperature. After stirring for 5 h, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:2 to 1:1) to give 2.7 g (91%) of dipeptide **20** as a white solid. $[\alpha]_D^{20}$ = −5.85 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 6.81 (s, 1H), 5.17 (d, *J* = 7.5 Hz, 1H), 4.08–3.91 (m, 3H), 3.70 (s, 3H), 1.84 (s, 1H), 1.51–1.45 (m, 1H), 1.39 (s, 9H), 1.13–1.06 (m, 1H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 172.1, 170.1,

155.8, 79.9, 59.0, 52.2, 41.0, 37.2, 28.2, 24.6, 15.4, 11.3; IR (thin film, neat) ν_{max} 3324, 2968, 1759, 1687, 1661, 1527, 1367, 1173, 862 cm^{-1}; LR-MS (ESI+) *m/z* 303 (M + H$^+$); HR-MS (ESI+) calcd for C$_{14}$H$_{27}$N$_2$O$_5$ (M + H$^+$) 303.1914; found 303.1923. To a solution of Boc-L-Ile-Gly-OMe **20** (2.0 g, 6.6 mmol) in a mixture of THF, MeOH, and H$_2$O (1:1:1, 33 mL) was added LiOH·H$_2$O (0.6 g, 14.3 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was dried over MgSO$_4$ and concentrated *in vacuo* to afford 1.9 g (99%) of Boc-L-Ile-Gly-OH **22** as white solid. The free acid **22** was used in the next step without further purification.

*Boc-*L*-Ile-*L*-Ala-NMe-*D*-Phe-OMe* (**24**). To a solution of Boc-NMe-D-Phe-OMe **16** (440 mg, 1.5 mmol) in CH$_2$Cl$_2$ (6.0 mL) was added TFA (1.5 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of above amine salt **23** (1.5 mmol), Boc-L-Ile-L-Ala-OH **21** (544 mg, 1.8 mmol), and DIPEA (0.8 mL, 4.6 mmol) in CH$_2$Cl$_2$ (7.5 mL) was added DEPBT (898 mg, 3.0 mmol) at 0 °C. After stirring for overnight at 0 °C, the reaction mixture was quenched with 1*N* HCl, extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:1) to give 407 mg (57% for 2 steps) of tripeptide **24** as white solid and 145 mg (20% for 2 steps) of its epimer as white solid. $[\alpha]_D^{20}$ = +61.58 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$, a mixture of rotamers) Major rotamer δ 7.24 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.3 Hz, 2H), 6.81 (d, *J* = 7.1 Hz, 1H), 5.29 (d, *J* = 7.1 Hz, 1H), 4.98 (d, *J* = 8.3 Hz, 1H), 4.69 (dq, *J* = 6.9, 6.8 Hz, 1H), 3.95 (dd, *J* = 7.3, 6.1 Hz, 1H), 3.73 (s, 3H), 3.39 (dd, *J* = 14.8, 5.0 Hz, 1H), 3.01 (dd, *J* = 14.7, 11.8 Hz, 1H), 2.83 (s, 3H), 1.87–1.79 (m, 1H), 1.74–1.64 (m, 1H), 1.40 (s, 9H), 1.12–1.02 (m, 1H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).; ^{13}C-NMR (200 MHz, CDCl$_3$, a mixture of rotamers) Major rotamer δ 172.9, 170.7, 170.5, 155.6, 136.4, 128.7, 128.6, 126.9, 79.8, 59.2, 58.3, 52.4, 45.5, 37.6, 34.7, 32.5, 28.3, 24.6, 17.9, 15.6, 11.5; IR (thin film, neat) ν_{max} 3319, 2970, 1743, 1710, 1637, 1498, 1366, 1173, 1017, 871 cm^{-1}; LR-MS (ESI+) *m/z* 478 (M + H$^+$); HR-MS (ESI+) calcd for C$_{25}$H$_{40}$N$_3$O$_6$ (M + H$^+$) 478.2912; found 478.2915.

*Boc-*L*-Ile-Gly-NMe-*D*-Phe-OMe* (**25**). To a solution of Boc-NMe-D-Phe-OMe **16** (426 mg, 1.5 mmol) in CH$_2$Cl$_2$ (6.0 mL) was added TFA (1.5 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of above amine salt **23** (1.5 mmol), Boc-L-Ile-Gly-OH **22** (502 mg, 1.7 mmol) and DIPEA (0.8 mL, 4.4 mmol) in CH$_2$Cl$_2$ (7.3 mL) was added DEPBT (869 mg, 2.9 mmol) at 0 °C. After stirring overnight at 0 °C, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:1) to give 586 mg (87% for 2 steps) of tripeptide **25** as white solid. $[\alpha]_D^{20}$ = +38.96 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$, a mixture of rotamers) Major rotamer δ 7.21 (t, *J* = 7.5 Hz, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 2H), 6.84 (s, 1H), 5.19 (dd, *J* = 10.7, 5.3 Hz, 1H), 5.10 (d, *J* = 8.4 Hz, 1H), 4.04–4.01 (m, 1H), 3.95 (dd, *J* = 17.9, 3.7 Hz, 1H), 3.81 (dd, *J* = 17.7, 3.1 Hz, 1H), 3.67 (s, 3H), 3.32 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.98 (dd, *J* = 14.6, 10.9 Hz, 1H), 2.74 (s, 3H), 1.81 (s, 1H), 1.44–1.36 (m, 1H), 1.37 (s, 9H), 1.07–1.02 (m, 1H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$, a mixture of rotamers) Major rotamer δ 171.3, 170.6, 168.4, 155.5, 136.4, 128.5, 128.5, 126.8, 79.5, 58.9, 58.7, 52.3, 41.2, 37.5, 34.4, 31.7, 28.1, 24.5, 15.4, 11.4; IR (thin film, neat) ν_{max} 3328, 2967, 1743, 1712, 1643, 1497, 1366, 1172, 1016, 867 cm^{-1}; LR-MS (ESI+) *m/z* 464 (M + H$^+$); HR-MS (ESI+) calcd for C$_{24}$H$_{38}$N$_3$O$_6$ (M + H$^+$) 464.2755; found 464.2751.

*Boc-*L*-Ile-*L*-Ala-NMe-*D*-Phe-*L*-Pro-OMe* (**4**). To a solution of Boc-L-Ile-L-Ala-NMe-D-Phe-OMe **24** (491 mg, 1.0 mmol) in a mixture of THF, MeOH, and H$_2$O (1:1:1, 10 mL) was added LiOH·H$_2$O (86 mg, 2.1 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was dried over MgSO$_4$ and concentrated *in vacuo*. The free acid **26** was used in the next step without further purification. To a solution of above acid **26** (1.0 mmol), L-proline methyl ester hydrochloride (203 mg, 1.3 mmol), and DIPEA (0.6 mL,

3.4 mmol) in CH_2Cl_2 (10 mL) was added DEPBT (615 mg, 2.1 mmol) at 0 °C. After stirring for overnight at 0 °C, the reaction mixture was quenched with 1*N* HCl and extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:1 to 2:1) to give 496 mg (84% for 2 steps) of tetrapeptide **4** as white solid. $[\alpha]_D^{20}$ = +45.90 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (800 MHz, $CDCl_3$, a mixture of rotamers) Major rotamer δ 7.23–7.13 (m, 5H), 6.64 (d, *J* = 7.2 Hz, 1H), 5.66 (dd, *J* = 9.5, 6.4 Hz, 1H), 4.98 (d, *J* = 8.2 Hz, 1H), 4.74 (dq, *J* = 7.1, 6.9 Hz, 1H), 4.42 (t, *J* = 7.5 Hz, 1H), 3.90 (t, *J* = 6.4 Hz, 1H), 3.70 (s, 3H), 3.47–3.42 (m, 1H), 3.22–3.15 (m, 1H), 2.98 (s, 3H), 2.94 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.22–2.17 (m, 1H), 1.97–1.76 (m, 6H), 1.39 (s, 9H), 1.08–1.01 (m, 1H), 0.84 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz, $CDCl_3$, a mixture of rotamers) Major rotamer δ 172.3, 172.2, 170.5, 168.1, 155.5, 136.7, 129.5, 128.2, 126.6, 79.7, 59.2, 59.0, 55.5, 52.2, 46.9, 45.1, 37.6, 34.6, 30.2, 28.8, 28.2, 25.3, 24.6, 17.7, 15.4, 11.5; IR (thin film, neat) ν_{max} 3316, 2971, 1748, 1709, 1643, 1497, 1365, 1245, 1174, 1045, 870 cm^{-1}; LR-MS (ESI+) *m/z* 575 (M + H+); HR-MS (ESI+) calcd for $C_{30}H_{47}N_4O_7$ (M + H+) 575.3439; found 575.3442.

*Boc-*L*-Ile-Gly-NMe-*D*-Phe-*L*-Pro-OMe* (**5**). To a solution of Boc-L-Ile-Gly-*N*Me-D-Phe-OMe **25** (511 mg, 1.0 mmol) in a mixture of THF, MeOH, and H_2O (1:1:1, 11 mL) was added LiOH·H_2O (92 mg, 2.2 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The free acid **27** was used in the next step without further purification. To a solution of above acid **27** (1.1 mmol), L-proline methyl ester hydrochloride (216 mg, 1.4 mmol) and DIPEA (0.6 mL, 3.4 mmol) in CH_2Cl_2 (11 mL) was added DEPBT (660 mg, 2.2 mmol) at 0 °C. After stirring overnight at 0 °C, the reaction mixture was quenched with 1*N* HCl, extracted with CH_2Cl_2. The combined organic layer was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:1 to 2:1) to give 501 mg (81% for 2 steps) of tetrapeptide **5** as a white solid. $[\alpha]_D^{20}$ = +69.20 (*c* 1.00, $CHCl_3$); ^{1}H-NMR (800 MHz, $CDCl_3$, a mixture of rotamers) Major rotamer δ 7.23 (t, *J* = 7.4 Hz, 2H), 7.20 (d, *J* = 6.9 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 6.77 (s, 1H), 5.56 (t, *J* = 7.6 Hz, 1H), 5.00 (d, *J* = 8.0 Hz, 1H), 4.40 (dd, *J* = 8.5, 5.7 Hz, 1H), 4.09–4.01 (m, 1H), 3.92–3.85 (m, 1H), 3.70 (s, 3H), 3.38–3.34 (m, 1H), 3.33–3.29 (m, 1H), 3.25 (dd, *J* = 13.7, 8.0 Hz, 1H), 2.96 (s, *J* = 6.5 Hz, 3H), 2.81 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.16–2.11 (m, 1H), 1.95–1.74 (m, 6H), 1.42 (s, 9H), 1.12–1.02 (m, 1H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H).; ^{13}C-NMR (200 MHz, $CDCl_3$, a mixture of rotamers) Major rotamer δ 172.4, 171.5, 167.9, 167.9, 155.7, 136.9, 129.4, 128.4, 126.7, 79.9, 59.2, 58.9, 56.2, 52.2, 46.8, 41.1, 37.5, 34.9, 29.7, 28.8, 28.3, 25.0, 24.5, 15.6, 11.6; IR (thin film, neat) ν_{max} 3328, 2968, 1748, 1710, 1640, 1497, 1365, 1246, 1174, 1044, 869 cm^{-1}; LR-MS (ESI+) *m/z* 561 (M + H+); HR-MS (ESI+) calcd for $C_{29}H_{45}N_4O_7$ (M + H+) 561.3283; found 561.3290.

Allyl (2R,3S)-2-hydroxy-3-methylpentanoate (**12**). To a solution of D-*allo*-Ile **31** (1.4 g, 10.7 mmol) in dilute sulfuric acid (0.8*N* in H_2O, 26.7 mL, 21.3 mmol) was added $NaNO_2$ (2.2 g, 32.0 mmol) slowly at 0°C. After stirring for 6 h at the same temperature, the reaction mixture was diluted with Et_2O and extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude acid **32** (10.7 mmol) and TBAI (0.79 g, 2.13 mmol) in dry DMF (500 mL) were added allyl bromide (1.8 mL, 21.3 mmol) and K_2CO_3 (3.0 g, 21.3 mmol) at room temperature. After stirring for overnight, the reaction mixture was quenched with 1*N* HCl and extracted with Et_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:10) to give 1.2 g (65% for 2 steps) of ester **12** as a colorless oil. $[\alpha]_D^{20}$ = +45.94 (*c* 0.50, $CHCl_3$); ^{1}H-NMR (800 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 17.1, 10.5, 5.9 Hz, 1H), 5.31 (ddd, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.24 (dd, *J* = 10.4, 2.3, 1.2 Hz, 1H), 4.67 (ddt, *J* = 13.0, 5.9, 1.2 Hz, 1H), 4.63 (ddt, *J* = 13.1, 5.9, 1.3 Hz, 1H), 4.17 (d, *J* = 3.0 Hz, 1H), 2.61 (s, 1H), 1.83–1.75 (m, 1H), 1.50 (ddq, *J* = 13.8, 7.4, 7.2 Hz, 1H), 1.28 (ddq, *J* = 13.7, 7.5, 7.4 Hz, 1H), 0.91 (t, *J* = 7.5 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (200 MHz, $CDCl_3$) δ 175.0, 131.5, 119.1, 72.9, 66.0, 38.5, 25.9, 13.1, 11.8; IR (thin film,

neat) ν_{max} 3524, 2966, 1742, 1461, 1384, 1200, 1138, 934 cm^{-1}; LR-MS (ESI+) *m/z* 173 (M + H$^+$); HR-MS (ESI+) calcd for $C_{29}H_{45}N_4O_7$ (M + H$^+$) 173.1172; found 173.1163.

Allyl (R)-2-hydroxy-3-methylbutanoate (**13**). To a solution of D-valic acid **33** (1.2 g, 10.2 mmol) and TBAI (0.75 g, 2.0 mmol) in dry DMF (25 mL) were added allyl bromide (1.8 mL, 20.3 mmol) and K_2CO_3 (2.8 g, 20.3 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with Et$_2$O. The combined organic layer was washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:20) to give 1.5 g (93%) of ester **13** as a colorless oil. $[\alpha]_D^{20}$ = +24.77 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 5.84 (ddt, *J* = 17.1, 10.6, 5.9 Hz, 1H), 5.26 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.1 Hz, 1H), 4.61 (dd, *J* = 13.1, 5.9 Hz, 1H), 4.57 (dd, *J* = 13.2, 5.9 Hz, 1H), 3.98 (d, *J* = 3.9 Hz, 1H), 2.87 (s, 1H), 2.01 (dtd, *J* = 13.9, 6.9, 3.7 Hz, 1H), 0.94 (d, *J* = 7.3 Hz, 3H), 0.79 (d, *J* = 7.2 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 174.4, 131.4, 118.9, 74.9, 65.8, 32.0, 18.6, 15.8; IR (thin film, neat) ν_{max} 3516, 2968, 1743, 1468, 1372, 1197, 1130, 933 cm^{-1}; LR-MS (ESI+) *m/z* 181 (M + Na$^+$); HR-MS (ESI+) calcd for $C_8H_{14}NaO_3$ (M + Na$^+$) 181.0835; found 181.0834.

(S)-2-((tert-Butyldiphenylsilyl)oxy)-3-methylbutanoic acid (**35**). To a solution of L-valic acid (1.2 g, 10.2 mmol) and DMAP (0.12 g, 1.0 mmol) in dry DMF (5.0 mL) were added imidazole (3.5 g, 50.8 mmol) and TBDPSCl (7.9 mL, 30.5 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with Et$_2$O. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude silyl ether **34** (10.2 mmol) in a mixture of MeOH and H$_2$O (3:1, 40 mL) was added K_2CO_3 (2.1 g, 15.2 mmol) at room temperature. After stirring for 1 h, the reaction mixture was quenched with 1*N* HCl and extracted with Et$_2$O. The combined organic layer was washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:10) to give 1.1 g (92% for 2 steps) of acid **35** as a colorless oil. $[\alpha]_D^{20}$ = −12.98 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 7.64 (d, *J* = 6.9 Hz, 2H), 7.60 (d, *J* = 6.9 Hz, 2H), 7.42 (dt, *J* = 13.4, 7.4 Hz, 2H), 7.39–7.33 (m, 4H), 4.12 (d, *J* = 3.8 Hz, 1H), 1.95–1.85 (m, 1H), 1.11 (s, 9H), 0.88 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 174.4, 135.9, 135.8, 132.7, 132.2, 130.2, 130.1, 127.8, 127.8, 77.4, 33.2, 27.0, 19.4, 17.6, 17.3; IR (thin film, neat) ν_{max} 2962, 1720, 1471, 1428, 1183, 1113, 1071, 939 cm^{-1}; LR-MS (ESI+) *m/z* 355 (M - H$^+$); HR-MS (ESI+) calcd for $C_{21}H_{27}OSi$ (M - H$^+$) 355.1735; found 355.1742.

Allyl (2R,3S)-2-(((S)-2-((tert-Butyldiphenylsilyl)oxy)-3-methylbutanoyl)oxy)-3-methylpentanoate (**36**). To a solution of acid **35** (591 mg, 1.7 mmol), alcohol **12** (238 mg, 1.4 mmol), and DMAP (338 g, 2.8 mmol) in CH$_2$Cl$_2$ (14 mL) was added EDC·HCl (530 g, 2.8 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:20) to give 649 mg (92%) of ester **36** as a colorless oil. $[\alpha]_D^{20}$ = −23.21 (*c* 1.00, CHCl$_3$); ^{1}H NMR (800 MHz, CDCl$_3$) δ 7.67–7.64 (m, 4H), 7.42–7.38 (m, 2H), 7.36–7.33 (m, 4H), 5.84 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.29 (ddd, *J* = 17.2, 2.9, 1.4 Hz, 1H), 5.21 (ddd, *J* = 10.4, 2.3, 1.1 Hz, 1H), 4.82 (d, *J* = 3.5 Hz, 1H), 4.59 (ddt, *J* = 13.1, 5.7, 1.3 Hz, 1H), 4.52 (ddt, *J* = 13.1, 5.9, 1.3 Hz, 1H), 4.25 (d, *J* = 4.3 Hz, 1H), 2.06–1.96 (m, 1H), 1.90–1.85 (m, 1H), 1.36 (ddq, *J* = 13.8, 7.4, 7.3 Hz, 1H), 1.16 (ddq, *J* = 13.7, 7.6, 7.5 Hz, 1H), 1.14 (d, *J* = 7.5 Hz, 3H), 1.10 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 172.0, 169.2, 136.0, 135.9, 133.5, 133.3, 131.7, 129.7, 129.6, 127.5, 127.4, 118.7, 77.6, 75.1, 65.5, 36.7, 33.3, 26.9, 25.7, 19.6, 18.1, 17.1, 14.4, 11.7; IR (thin film, neat) ν_{max} 2965, 1756, 1463, 1428, 1192, 1113, 1008, 935, 822 cm^{-1}; LR-MS (ESI+) *m/z* 528 (M + NH$_4^+$); HR-MS (ESI+) calcd for $C_{30}H_{46}NO_5Si$ (M + NH$_4^+$) 528.3140; found 528.3149.

Allyl (R)-2-(((S)-2-((tert-Butyldiphenylsilyl)oxy)-3-methylbutanoyl)oxy)-3-methylbutanoate (**37**). To a solution of acid **35** (741 g, 2.1 mmol), alcohol **13** (274 mg, 1.7 mmol) and DMAP (423 mg, 3.5 mmol) in CH$_2$Cl$_2$ was added EDC·HCl (664 mg, 3.5 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl, extracted with CH$_2$Cl$_2$. The combined organic layer

was washed with aqueous NaHCO$_3$, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc/Hexane = 1:20) to give 809 mg (94%) of ester **37** as a colorless oil. $[\alpha]_D^{20}$ = +2.49 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 7.64 (td, *J* = 8.4, 1.2 Hz, 4H), 7.40 (tdt, *J* = 7.7, 7.6, 1.3 Hz, 2H), 7.34 (dd, *J* = 7.2, 7.0 Hz, 4H), 5.83 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.28 (dq, *J* = 17.2, 1.4 Hz, 1H), 5.20 (ddt, *J* = 10.4, 1.2, 1.0 Hz, 1H), 4.58 (dt, *J* = 13.1, 5.8, 1.3 Hz, 1H), 4.58 (d, *J* = 4.4 Hz, 1H), 4.51 (ddt, *J* = 13.2, 5.9, 1.2 Hz, 1H), 4.22 (d, *J* = 4.4 Hz, 1H), 2.12–2.06 (m, 1H), 2.05–1.98 (m, 1H), 1.09 (s, 9H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 172.0, 168.9, 136.0, 135.9, 133.4, 133.3, 131.6, 129.7, 129.6, 127.5, 127.4, 118.8, 77.6, 77.0, 65.5, 33.3, 30.1, 26.9, 19.6, 18.5, 18.3, 17.4, 17.2; IR (thin film, neat) ν_{max} 2965, 1754, 1471, 1428, 1185, 1113, 990, 934, 822 cm^{-1}; LR-MS (ESI+) *m/z* 519 (M + Na$^+$); HR-MS (ESI+) calcd for C$_{29}$H$_{40}$NaO$_5$Si (M + Na$^+$) 519.2537; found 519.2543.

(2R,3S)-2-(((S)-2-((tert-Butyldiphenylsilyl)oxy)-3-methylbutanoyl)oxy)-3-methylpentanoic acid (**38**). To a solution of ester **36** (345 mg, 0.7 mmol) and *N*-methylaniline (0.15 mL, 1.4 mmol) in dry THF (6.8 mL) was added Pd(PPh$_3$)$_4$ (78 mg, 0.1 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography through a short pad of silica gel (CH$_2$Cl$_2$/MeOH = 16:1) to afford 280 mg (88%) of the acid **38** as a yellow oil. $[\alpha]_D^{20}$ = −15.06 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 7.64–7.62 (m, 4H), 7.42–7.36 (m, 2H), 7.35–7.29 (m, 4H), 4.84 (d, *J* = 3.3 Hz, 1H), 4.25 (d, *J* = 4.1 Hz, 1H), 2.03–1.97 (m, 1H), 1.89 (dtd, *J* = 7.5, 7.0, 3.3 Hz, 1H), 1.36 (ddq, *J* = 13.9, 7.3, 7.1 Hz, 1H), 1.18 (ddq, *J* = 13.8, 7.6, 7.4 Hz, 1H), 1.09 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.9 Hz, 3H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 174.8, 172.0, 136.0, 135.9, 133.5, 133.3, 129.7, 129.7, 127.5, 127.5, 77.4, 74.4, 36.6, 33.3, 26.9, 25.8, 19.6, 18.4, 17.1, 14.3, 11.7; IR (thin film, neat) ν_{max} 2965, 1760, 1730, 1463, 1428, 1182, 1113, 1000, 822 cm^{-1}; LR-MS (ESI+) *m/z* 488 (M + NH$_4^+$); HR-MS (ESI+) calcd for C$_{27}$H$_{42}$NO$_5$Si (M + NH$_4^+$) 488.2827; found 488.2829.

(R)-2-(((S)-2-((tert-Butyldiphenylsilyl)oxy)-3-methylbutanoyl)oxy)-3-methylbutanoic acid (**39**). To a solution of ester **37** (362 mg, 0.7 mmol) and *N*-methylaniline (0.2 mL, 1.5 mmol) in dry THF (7.3 mL) was added Pd(PPh$_3$)$_4$ (84 mg, 0.1 mmol) at room temperature. After stirring for 2 h, the reaction mixture was quenched with 1*N* HCl and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography through a short pad of silica gel (CH$_2$Cl$_2$/MeOH = 16:1) to afford 306 mg (92%) of the acid **39** as a yellow oil. $[\alpha]_D^{20}$ = −11.79 (*c* 1.00, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$) δ 7.63 (td, *J* = 8.0, 1.1 Hz, 4H), 7.41–7.36 (m, 2H), 7.32 (dt, *J* = 9.0, 7.6 Hz, 4H), 4.61 (d, *J* = 4.3 Hz, 1H), 4.24 (d, *J* = 4.2 Hz, 1H), 2.14–2.09 (m, 1H), 2.06–1.98 (m, 1H), 1.08 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 7.0 Hz, 6H), 0.92 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 173.6, 172.0, 136.0, 135.9, 133.4, 133.3, 129.7, 129.7, 127.5, 127.4, 77.4, 76.3, 33.3, 30.0, 26.9, 19.6, 18.6, 18.4, 17.2, 17.1; IR (thin film, neat) ν_{max} 2965, 1760, 1726, 1470, 1428, 1181, 1113, 999, 822 cm^{-1}; LR-MS (ESI+) *m/z* 474 (M + NH$_4^+$); HR-MS (ESI+) calcd for C$_{26}$H$_{40}$NO$_5$Si (M + NH$_4^+$) 474.2670; found 474.2674.

Izenamide C (**3**). To a solution of Boc-L-Ile-Gly-*N*Me-D-Phe-L-Pro-OMe **5** (34 mg, 0.1 mmol) in CH$_2$Cl$_2$ (0.8 mL) was added TFA (0.2 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. To a solution of above amine salt **40** (0.1 mmol), acid **38** (37 mg, 0.1 mmol), DIPEA (0.1 mL, 0.2 mmol), and HOAt (11 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added EDC·HCl (24 mg, 0.1 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude hexapeptide (0.1 mmol) in THF (1.0 mL) was added TBAF (1M in THF, 0.2 mL, 0.2 mmol) at room temperature. After stirring for 4 h, the reaction mixture was quenched with H$_2$O and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Acetone/Hexane = 1:3) to give 33 mg (83% for 3 steps) of izenamide C (**3**) as white

solid. $[\alpha]_D^{20}$ = +21.50 (*c* 0.10, MeOH); ^{1}H-NMR (800 MHz, CD$_3$OD, a mixture of rotamers) Major rotamer δ 7.25–7.19 (m, 4H), 7.18–7.14 (m, 1H), 5.57 (t, *J* = 7.6 Hz, 1H), 5.06 (d, *J* = 4.5 Hz, 1H), 4.37 (dd, *J* = 8.3, 5.6 Hz, 1H), 4.33 (d, *J* = 7.0 Hz, 1H), 4.15 (d, *J* = 17.0 Hz, 1H), 4.11 (d, *J* = 4.4 Hz, 1H), 3.90 (d, *J* = 17.0 Hz, 1H), 3.70 (s, 3H), 3.44 (dt, *J* = 10.2, 6.9 Hz, 1H), 3.39 (dt, *J* = 10.2, 5.6 Hz, 1H), 3.19 (dd, *J* = 13.7, 7.8 Hz, 1H), 3.02 (s, 3H), 2.84 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.21–2.17 (m, 1H), 2.11 (qqd, *J* = 6.9, 6.8, 4.5 Hz, 1H), 1.97–1.89 (m, 3H), 1.88–1.81 (m, 2H), 1.50–1.43 (m, 1H), 1.44 (ddq, *J* = 13.8, 7.4, 7.3 Hz, 1H), 1.28 (ddq, *J* = 13.7, 7.6, 7.5 Hz, 1H), 1.18–1.11 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (200 MHz, CD$_3$OD, a mixture of rotamers) Major rotamer δ 175.2, 174.0, 173.4, 172.2, 170.2, 170.1, 138.6, 130.5, 129.4, 127.6, 78.0, 76.5, 60.6, 58.9, 57.8, 52.7, 48.3, 41.9, 38.5, 37.9, 35.7, 33.3, 30.5, 29.9, 27.0, 26.0, 25.7, 19.4, 16.9, 16.1, 14.7, 11.8, 11.4; IR (thin film, neat) v_{max} 3317, 2960, 2877, 1744, 1637, 1519, 1447, 1199, 1176, 1137, 1030, 753 cm^{-1}; LR-MS (ESI+) *m/z* 675 (M + H$^+$); HR-MS (ESI+) calcd for C$_{35}$H$_{55}$N$_4$O$_9$ (M + H$^+$) 675.3964; found 675.3949.

Pentapeptide (**42**). To a solution of Boc-L-Ile-L-Ala-*N*Me-D-Phe-L-Pro-OMe **4** (140 mg, 0.2 mmol) in CH$_2$Cl$_2$ (1.6 mL) was added TFA (0.4 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of above amine salt **41** (0.2 mmol), acid **6** (100 mg, 0.3 mmol), DIPEA (0.1 mL, 0.7 mmol), and HOAt (43 mg, 0.3 mmol) in CH$_2$Cl$_2$ (2.4 mL) was added EDC·HCl (93 mg, 0.5 mmol) at room temperature. After stirring overnight, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Acetone/Hexane = 1:3) to give 145 mg (77% for 2 steps) of pentapeptide **42** as white solid. $[\alpha]_D^{20}$ = +67.88 (*c* 0.50, CHCl$_3$); ^{1}H-NMR (800 MHz, CDCl$_3$, a mixture of rotamers) Major rotamer δ 7.23–7.18 (m, 4H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.64 (s, 1H), 6.51 (d, *J* = 6.8 Hz, 1H), 5.66 (dd, *J* = 9.5, 6.5 Hz, 1H), 4.72 (dq, *J* = 7.2, 7.0 Hz, 1H), 4.44 (dd, *J* = 8.1, 6.7 Hz, 1H), 4.27–4.24 (m, 1H), 4.22–4.19 (m, 1H), 3.71 (s, 3H), 3.65–3.60 (m, 1H), 3.48–3.42 (m, 1H), 3.21 (dt, *J* = 10.6, 7.4 Hz, 1H), 3.19 (dd, *J* = 14.5, 6.4 Hz, 1H), 2.98 (s, 3H), 2.95 (dd, *J* = 14.4, 9.6 Hz, 1H), 2.58–2.51 (m, 1H), 2.48–2.40 (m, 1H), 2.23–2.18 (m, 1H), 1.93–1.87 (m, 1H), 1.87–1.75 (m, 4H), 1.61 (s, 3H), 1.52–1.46 (m, 5H), 1.46 (s, 9H), 1.46–1.42 (m, 1H), 1.12–1.02 (m, 1H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 6.9 Hz, 3H); ^{13}C-NMR (200 MHz, CDCl$_3$) δ 172.6, 172.4, 172.2, 169.8, 168.1, 156.3, 136.6, 129.5, 128.3, 126.7, 93.8, 79.3, 70.4, 59.3, 57.7, 55.6, 52.3, 52.2, 46.9, 45.2, 41.6, 40.1, 37.5, 34.7, 30.9, 30.3, 28.8, 28.4, 25.3, 24.9, 24.8, 24.8, 23.1, 22.1, 17.6, 15.3, 11.4; IR (thin film, neat) v_{max} 2961, 2875, 1751, 1700, 1632, 1532, 1455, 1366, 1257, 1175, 1047, 859 cm^{-1}; LR-MS (ESI+) *m/z* 789 (M + NH$_4^+$); HR-MS (ESI+) calcd for C$_{41}$H$_{69}$N$_6$O$_9$ (M + NH$_4^+$) 789.5121; found 789.5134.

Izenamide A (**1**). To a solution of pentapeptide **42** (41 mg, 0.1 mmol) in CH$_2$Cl$_2$ (0.8 mL) was added TFA (0.2 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. To a solution of above amine salt **43** (0.1 mmol), acid **39** (32 mg, 0.1 mmol), DIPEA (0.1 mL, 0.2 mmol), and HOAt (10 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added EDC·HCl (21 mg, 0.1 mmol) at room temperature. After stirring for 6 h, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude heptapeptide (0.1 mmol) in THF (1.0 mL) was added TBAF (1M in THF, 0.2 mL, 0.2 mmol) at room temperature. After stirring for 6 h, the reaction mixture was quenched with H$_2$O and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (Acetone/Hexane = 1:3 to 1:1) to give 29 mg (66% for 3 steps) of izenamide A (**1**) as white solid. $[\alpha]_D^{20}$ = −17.15 (*c* 0.20, MeOH); ^{1}H-NMR (800 MHz, CD$_3$OD, a mixture of rotamers) Major rotamer δ 7.26–7.19 (m, 4H), 7.18–7.13 (m, 1H), 5.69 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.71 (d, *J* = 5.9 Hz, 1H), 4.68 (q, *J* = 7.1 Hz, 1H), 4.41 (dd, *J* = 7.7, 7.4 Hz, 1H), 4.19 (d, *J* = 7.6 Hz, 1H), 4.11 (d, *J* = 4.4 Hz, 1H), 4.00–3.95 (m, 2H), 3.71 (s, 3H), 3.47–3.45 (m, 1H), 3.42–3.37 (m, 1H), 3.11 (dd, *J* = 14.3, 5.9 Hz, 1H), 3.06 (s, 3H),

2.93 (dd, *J* = 14.3, 10.0 Hz, 1H), 2.41–2.34 (m, 2H), 2.29–2.23 (m, 1H), 2.17–2.12 (m, 1H), 2.11–2.07 (m, 1H), 1.97–1.90 (m, 1H), 1.87–1.82 (m, 2H), 1.80–1.73 (m, 1H), 1.60–1.52 (m, 2H), 1.48 (ddd, *J* = 13.4, 7.6, 3.4 Hz, 1H), 1.31 (ddd, *J* = 9.3, 7.5, 4.3 Hz, 1H), 1.13 (ddd, *J* = 13.6, 9.5, 7.3 Hz, 1H), 1.01 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 6H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (200 MHz, CD$_3$OD, a mixture of rotamers) Major rotamer δ 175.8, 174.6, 173.9, 173.8, 173.0, 171.8, 170.4, 138.3, 130.8, 129.3, 127.6, 80.6, 76.4, 71.3, 60.9, 58.7, 57.2, 52.6, 52.2, 48.5, 46.6, 41.4, 41.4, 38.3, 35.6, 33.3, 31.7, 31.1, 30.0, 26.2, 26.0, 25.7, 23.8, 22.2, 19.3, 19.2, 18.1, 17.2, 16.6, 15.8, 11.4; IR (thin film, neat) ν_{max} 3318, 2960, 2878, 1742, 1637, 1544, 1450, 1366, 1265, 1198, 1038, 753 cm^{-1}; LR-MS (ESI+) *m/z* 854 (M + Na$^+$); HR-MS (ESI+) calcd for C$_{43}$H$_{69}$N$_5$NaO$_{11}$ (M + Na$^+$) 854.4886; found 854.4888.

Izenamide B (**2**). To a solution of pentapeptide **42** (46 mg, 0.1 mmol) in CH$_2$Cl$_2$ (0.8 mL) was added TFA (0.2 mL) dropwise at room temperature. After stirring for 1 h, the reaction mixture was concentrated *in vacuo*. To a solution of above amine salt **43** (0.1 mmol), acid **38** (36 mg, 0.1 mmol), DIPEA (0.1 mL, 0.2 mmol), and HOAt (11 mg, 0.1 mmol) in CH$_2$Cl$_2$ (1.0 mL) was added EDC·HCl (23 mg, 0.1 mmol) at room temperature. After stirring for 6 h, the reaction mixture was quenched with 1*N* HCl and extracted with CH$_2$Cl$_2$. The combined organic layer was washed with aqueous NaHCO$_3$, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was used in the next step without further purification. To a solution of crude heptapeptide (0.1 mmol) in THF (1.0 mL) was added TBAF (1M in THF, 0.2 mL, 0.2 mmol) at room temperature. After stirring for 6 h, the reaction mixture was quenched with H$_2$O and extracted with EtOAc. The combined organic layer was washed with brine, dried over MgSO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (Acetone/Hexane = 1:3 to 1:1) to give 31 mg (61% from **S5**) of izenamide B (**2**) as white solid. [α]$_D^{20}$ = −11.62 (*c* 1.30, MeOH); ^{1}H-NMR (800 MHz, CD$_3$OD) δ 7.25–7.19 (m, 4H), 7.18–7.13 (m, 1H), 5.69 (dd, *J* = 10.0, 5.9 Hz, 1H), 4.93 (d, *J* = 4.4 Hz, 1H), 4.67 (q, *J* = 7.0 Hz, 1H), 4.41 (dd, *J* = 7.8, 7.3 Hz, 1H), 4.19 (d, *J* = 7.5 Hz, 1H), 4.13 (d, *J* = 4.3 Hz, 1H), 4.00–3.96 (m, 2H), 3.71 (s, 3H), 3.48–3.44 (m, 1H), 3.42–3.38 (m, 1H), 3.11 (dd, *J* = 14.3, 5.9 Hz, 1H), 3.06 (s, 3H), 2.93 (dd, *J* = 14.3, 10.0 Hz, 1H), 2.41–2.33 (m, 2H), 2.28–2.23 (m, 1H), 2.11–2.07 (m, 1H), 1.96–1.89 (m, 2H), 1.88–1.81 (m, 2H), 1.79–1.74 (m, 1H), 1.59–1.53 (m, 2H), 1.51–1.43 (m, 2H), 1.33–1.27 (m, 2H), 1.18–1.10 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.5 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.82 (d, *J* = 7.1 Hz, 3H); ^{13}C-NMR (200 MHz, CD$_3$OD, a mixture of rotamers) Major rotamer δ 175.7, 174.6, 173.9, 173.8, 173.0, 171.9, 170.3, 138.3, 130.8 129.3 127.6, 78.3, 76.4, 71.4, 60.9, 58.7, 57.2, 52.6, 52.3, 48.5, 46.6, 41.5, 41.4, 38.4, 38.3, 35.6, 33.3, 31.0, 30.0, 27.2, 26.2, 26.1, 25.7, 23.8, 22.2, 19.3, 17.1, 16.6, 15.8, 14.7, 11.9, 11.5; IR (thin film, neat) ν_{max} 3308, 2960, 2877, 1743, 1636, 1533, 1448, 1361, 1265, 1195, 1038, 753 cm^{-1}; LR-MS (ESI+) *m/z* 846 (M + H$^+$); HR-MS (ESI+) calcd for C$_{44}$H$_{72}$N$_5$O$_{11}$ (M + H$^+$) 846.5223; found 846.5229.

4. Conclusions

In conclusion, we have accomplished the first total syntheses of izenamides A (**1**), B (**2**), and C (**3**) and confirmed the stereochemistry of izenamide B, which was originally suggested by Suenaga and coworkers. The key features of the syntheses include the DKP formation-free amide coupling sequence and amidation with minimal epimerization. Our versatile and convergent synthesis of izenamides is expected to be widely utilized for the efficient synthesis of izenamides and their analogs for the development of novel cathepsin D inhibitors. Further studies on the structure-activity relationship of izenamides are currently underway and successful results will be reported in due course.

Conflicts of Interest: The authors declare no conflict of interest.

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Sample Availability: Samples of the compounds **1**–**3**, **4**–**6**, **11**–**13**, **16**, **19**–**22**, **24**–**27**, **35**–**39**, and **42** are available from the authors.