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A Synthesis of All Stereoisomers of Tenuecyclamide A Employing a Fluorous-Fmoc Strategy

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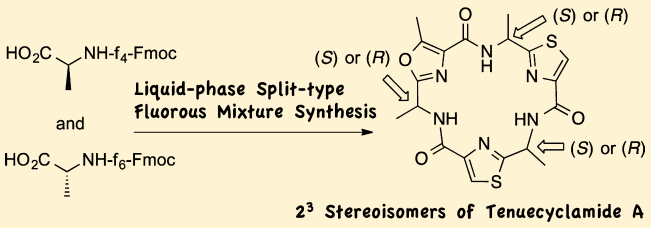
Supporting Information

ABSTRACT: A concise liquid-phase combinatorial synthesis of all stereoisomers of Tenuecyclamide A was achieved using a mixture of D-/L-alanine with each stereoisomer encoded by a different f-Fmoc tag. The synthetic strategy using f-Fmoc reagents as the protecting group for amino acids has been demonstrated to be a useful method for diverse polypeptide analogue synthesis.



INTRODUCTION

Since its introduction in 1997 by Curran et al., fluorous solid-phase extraction (FSPE)[1] has proven to be a highly efficient and widely applicable technique for separating molecules that are tagged with a fluorous domain from other nonfluorous organic molecules.[2] In recent years, the technique has evolved such that molecules can be separated purely on the basis of respective fluorine content regardless of other functionality present in the remainder of the molecule.[3] This salient feature of FSPE allows for liquid-phase combinatorial synthesis called fluorous mixture synthesis (FMS). In this technique, the fluorous tags containing differing amounts of fluorine are installed onto the various starting materials, which are then mixed for the remainder of the synthesis and separated based purely on fluorine content at the end, thereby greatly reducing the number of synthetic steps required to build up a compound library.[4]

A particularly novel application of FMS resides in determining the stereochemical requirements of a molecule for it to impart its biological activity. More specifically, the biological activity of peptides is governed by the configuration at the asymmetric center.[5] From a drug discovery perspective, it is interesting to study the biological activity of the non-natural configuration to ascertain whether or not this modification enhances or diminishes the biological activity or whether or not it elicits an entirely different response. Synthetically, this becomes a daunting task especially in the case of poly peptides where for each additional center there are 2^n possible stereoisomers. FMS, however, is uniquely suited to address this challenge because the various isomers can be individually labeled with different length fluorous tags then mixed together. The mixture can then be carried through the synthesis and then separated at the very end purely based on the fluorine content, thereby deconvoluting the entire mixture. This strategy saves a significant amount of effort because the synthetic steps between the mixing and the demixing do not have to be carried out on each individual isomer yet in the end does provide the entire family of desired stereoisomers isolated individually.

In peptide synthesis, the Fmoc reagent is one of the most well-known nitrogen protecting groups for amino acids.[6] We have previously reported a synthetic route toward two kinds of fluorous-Fmoc reagents (f-Fmoc)[7] and demonstrated that fluorous tagged dipeptides can be separated due to the remarkable differences in their retention times on a fluorous HPLC (f-HPLC) column.[8] Based on the success of this strategy for dipeptides, we planned to use different f-Fmoc reagents with varying amounts of fluorine as both a nitrogen protecting group and a fluorous encoding tag for a liquid-phase combinatorial peptide synthesis. Herein, we report the first example of a FMS for all of the stereoisomers of the biologically active peptide tenuecyclamide A[9c] (**1**) showcasing the f-Fmoc reagents as tools for effective peptide isomer library synthesis.

RESULTS AND DISCUSSION

Tenuecyclamides A (**1a**) and B (**1b**) are cyclic hexapeptides that differ only in configuration at a single stereocenter, and they were both isolated from the cyanobacterium *Nostoc spongiaeforme* var. *tenue* in 1998 (Figure 1).[9] Although the exact stereochemistry was not elucidated at the time of isolation and structural identification, the assignment of the configuration was subsequently achieved by Kelly's group in the work that employed solid-phase peptide synthesis.[10] Tenuecyclamide A (**1a**) was found to inhibit the division of sea urchin embryos with an ED_{100} of 10.8 μM. To date, the biological activity of tenuecyclamide B (**1b**) has not been explored in detail.[9c]

The first step in the synthesis of the tenuecyclamide family was to protect L-alanine (**2a**) and D-alanine (**2b**) using two different f-Fmoc reagents bearing C_4F_9 tags and C_6F_{13} tags,

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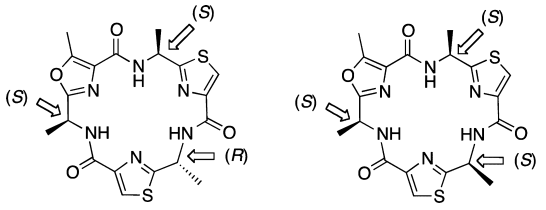
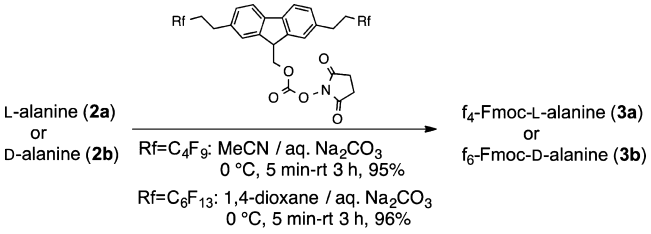


Figure 1. Structure of tenuecyclamide A (**1a**) and B (**1b**).

respectively (Scheme 1). The f_4-Fmoc reagent means bis-C_4F_9 tagged Fmoc, and the f_6-Fmoc reagent means bis-C_6F_{13} tagged

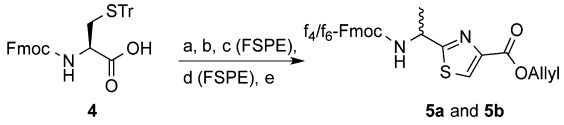
Scheme 1. *N*-Terminal Protection of Both L- and D-Alanine by f-Fmoc Reagents



Fmoc reagent in all of the schemes. In this process, 1,4-dioxane was employed for the f_6-Fmoc protection simply because it afforded greater solubility for the fluorous reagent in comparison to the more commonly used MeCN.

Subsequently, using the synthesis reported by Kelly,[10] we prepared the two isomers of the thiazole-ring unit (**5a** and **5b**) as a mixture, where the two isomers are encoded by a different fluorous tag (Scheme 2). To rapidly purify the reaction

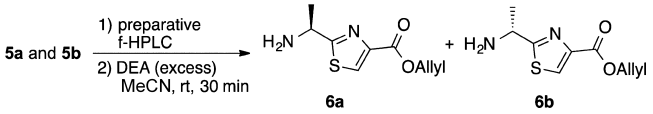
Scheme 2. Preparation of 5a and 5b[a]



[a]Reagents and conditions: (a) 2.0 equiv of allyl alcohol, 1.1 equiv of HOBt, 1.1 equiv of HBTU, 2.1 equiv of DIEA, DMF, rt, 24 h, quant; (b) excess DEA, MeCN; (c) 1.0 equiv each of f_4-Fmoc-L- and f_6-Fmoc-D-alanine, 2.2 equiv of HOBt, 2.2 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 12 h, 95% (two steps); FSPE, 55% aq THF on fluorous silica gel; (d) 18.0 equiv of Ph_3PO, 9.0 equiv of Tf_2O, CH_2Cl_2, 0 °C, 2 h, 90%; FSPE, 70% aq MeOH on fluorous silica gel; (e) activated MnO_2, (10 w/w), $CHCl_3$, reflux, 30 min, 75%.

mixtures and remove organic reagents and byproducts from the desired fluorous tagged thiazoles after the reaction, FSPE was conducted in steps "c" and "d". In practice, the condensation reaction in step "c" was accomplished by using HBTU and HOBt. At the end of the reaction, the crude mixture was loaded onto fluorous silica gel[11] with MeOH, and this was followed by an initial elution with aqueous MeOH which removed the nontagged organic compounds (reagents and reagent by-products) from the reaction mixture while the fluorous tagged components were retained. A second elution with THF washed the fluorous fraction off the column and as a result, the f-Fmoc compounds were isolated in high yields without a tedious purification procedure. The two components of **5a** and **5b** were then separated by preparative f-HPLC[8] using a fluorous HPLC column,[12] and the isolated individual compounds were subsequently deprotected to give the enantiomerically pure thiazoles **6a** and **6b** (Scheme 3).

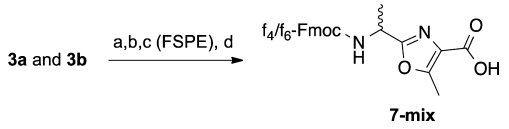
Scheme 3. Preparation of 6a and 6b[a]



[a]Preparative f-HPLC conditions: 0 to 30 min 80% MeCN/H_2O up to 100% MeCN. Flow rate: 7.0 mL/min; 254 nm; **6a**, 80%; **6b**, 80%.

Similarly, a mixture of the oxazole-ring unit (**7-mix**) was prepared from the tagged mixture of L- and D-alanine synthesized previously. Scheme 4 shows the synthetic route

Scheme 4. Preparation of 7-mix[a]

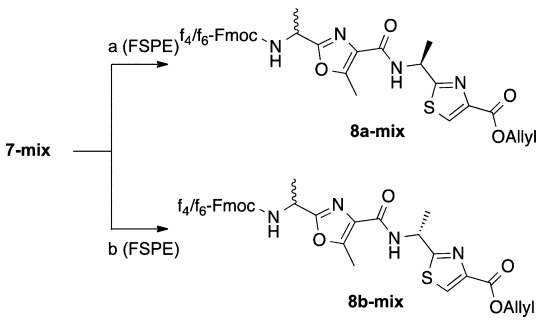


[a]Reagents and conditions: (a) 2.2 equiv of L-threonine-OBn, 4.7 equiv of HOBt, 4.7 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 24 h, quant; (b) 8.0 equiv of Dess–Martin periodinane, CH_2Cl_2, reflux, 2 h, 98%; (c) 18.0 equiv of Ph_3PO, 9.0 equiv of Tf_2O, CH_2Cl_2, 0 °C, 2 h, quant; FSPE, 55% aq THF on fluorous silica gel; (d) H_2, 20 mol % Pd/C, MeOH/THF, rt, 2 h, 94%.

to access **7-mix** as a mixture of two compounds bearing either a C_4F_9 or a C_6F_{13} chain. In this case, FSPE was conducted after step "c" to readily obtain the desired oxazole mixture **7-mix**.

The synthesis then proceeded by splitting the **7-mix** oxazole mixture into two parts, with one part being condensed with **6a** and the other half with **6b**, to give **8a-mix** and **8b-mix**, respectively, each as a mixture of two compounds that are orthogonally tagged (Scheme 5). **8a-mix** and **8b-mix** were then each divided again into two parts to give a total of four compound mixtures (Scheme 6). The allyl protecting groups in all four mixtures were then deprotected separately to reveal the corresponding acid and each mixture was subsequently condensed again with either **6a** or **6b**, respectively. The mixtures were purified by FSPE, and as a result, we obtained

Scheme 5. Preparation of 8a-mix and 8b-mix[a]



[a]Reagents and conditions: (a) 2.4 equiv of **6a**, 4.7 equiv of HOBt, 4.7 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 12 h, 91%; FSPE, 55% aq THF on fluorous silica gel; (b) 2.4 equiv of **6b**, 4.7 equiv of HOBt, 4.7 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 12 h, 98%; FSPE, 55% aq THF on fluorous silica gel.

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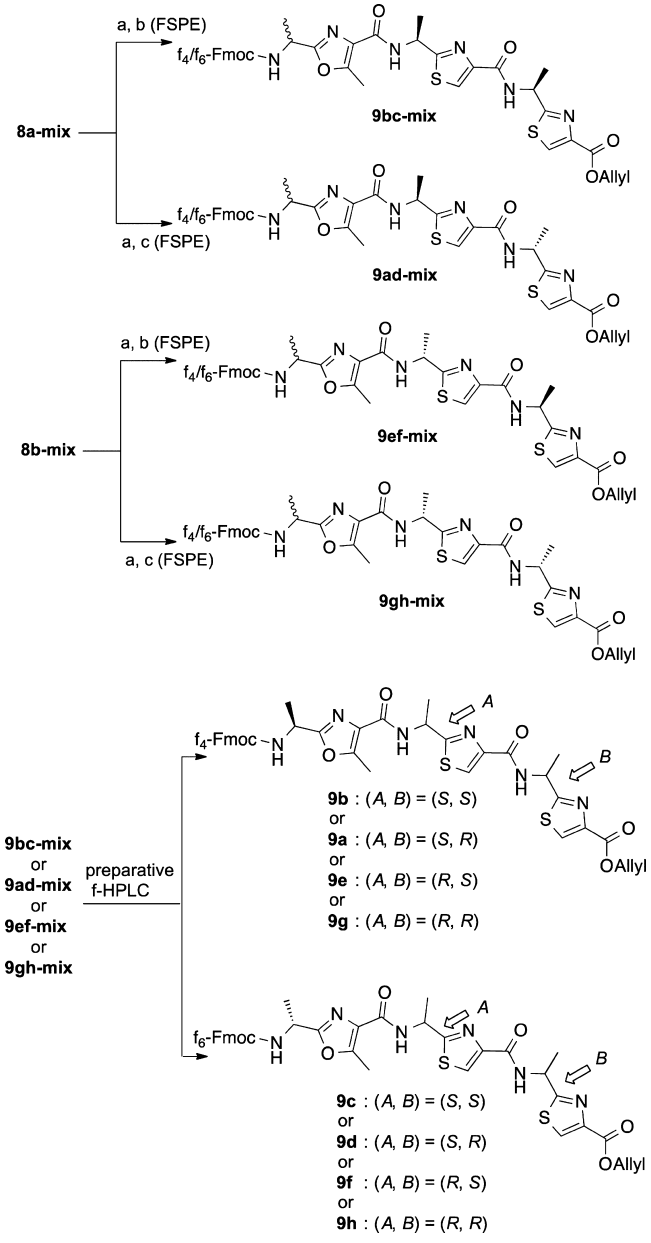
Scheme 6. Preparation of 9bc-mix, 9ad-mix, 9ef-mix, and 9gh-mix and Separation by f-HPLC[a,b]



[a]Reagents and conditions: (a) 20 mol % $Pd(PPh_3)_4$, 2.0 equiv of $PhSiH_3$, CH_2Cl_2, rt, 30 min; (b) 2.4 equiv of **6a**, 4.7 equiv of HOBt, 4.7 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 12 h; FSPE, 50% aq THF on fluorous silica gel; **9bc-mix**, 85%; **9ef-mix**, 87% (two steps); (c) 2.4 equiv of **6b**, 4.7 equiv of HOBt, 4.7 equiv of HBTU, 4.2 equiv of DIEA, DMF, rt, 12 h; FSPE, 50% aq THF on fluorous silica gel; **9ad-mix**, 80%; **9gh-mix**, 82% (two steps). [b]Preparative f-HPLC conditions: 0–7.5 min 80% MeCN/H_2O up to 100% MeCN. Flow rate: 7.0 mL/min.

four pairs of compounds, namely **9bc-mix**, **9ad-mix**, **9ef-mix**, and **9gh-mix**, each containing two compounds with different, and thus chromatographically separable, fluorine content.

As a demonstration, we analyzed the **9bc-mix** by f-HPLC and confirmed that the C_4F_9-Fmoc compound **9b** appeared at 10.8 min, whereas the C_6F_{13}-Fmoc compound **9c** appeared at 23.8 min, a separation of 13.0 min completely dictated by the relative fluorine content of each molecule (Figure 2). With such

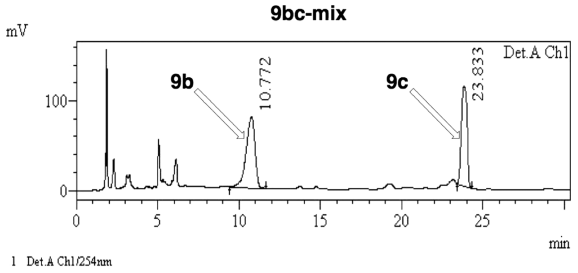


Figure 2. f-HPLC analysis of **9bc-mix**. HPLC conditions: Fluoro*Flash* HPLC column, 4.6 mm i.d., 150 mm length; 0 to 7.5 min 80% MeCN/H_2O up to 100% MeCN. Flow rate: 1.0 mL/min; 254 nm.

remarkable differences in retention time, each component of the four two component mixtures in Scheme 6, **9bc-mix**, **9ad-mix**, **9ef-mix** and **9gh-mix**, were separated to the corresponding individual compounds **9a–h** in almost quantitative yield using preparative f-HPLC (Scheme 6).

After exploring a variety of conditions to effect the key macrolactamization, using fully deprotected **9b** as the test substrate,[13] we identified that employing a fluorous tagged Mukaiyama reagent[14] **10**[15] was superior to other plausible coupling reagents. Further reaction optimization revealed that highly dilute reaction conditions, and syringe-pump addition of the substrate were required to obtain superior yields. The highest yield of 71% (three-step yield) for the macrolactamization was obtained when a DMF solution of **10** was added dropwise over 24 h to a 0.5 mM DMF solution of **9b**. At the end of the cyclization reaction, the byproduct fluorous-pyridone from **10** and other reagents used in the deprotection process were effectively separated from the desired material by precipitation. To achieve this, water was added to the reaction mixture after the coupling, and the resulting suspension was filtered. After a short column chromatography, further purification of the products was not necessary as they were found to be pure by ^1H NMR. Having optimized the lactamization conditions, we were poised to complete the synthesis of all eight stereoisomers of tenuecyclamide A. This was accomplished by treating compounds **9a–h** individually with the fluorous coupling reagent **10** after the f-Fmoc groups had been removed with DEA and the allyl groups had been removed using palladium catalysis. In this manner we synthesized all eight target lactams (**1a–g**) with yields ranging from 41 to 71% over the three step lactamization and deprotection sequence (Scheme 7). The ^1H NMR of both tenuecyclamide A (**1a**) and B (**1b**) obtained here were completely consistent with the data reported by Kelly.[10] In addition, ^1H NMR of both of **1e** and **1g**, were entirely consistent with the report.

■ CONCLUSION

In summary, we have conducted a concise synthesis of all eight stereoisomers of tenuecyclamide A (**1a**) based on an encoding strategy of the amino acid stereocenters using f-Fmoc reagents. If all stereoisomers were synthesized individually by the same linear synthetic route as outlined in this work, 136 synthetic steps would have been required; however, we carried out the syntheses in a mere 52 steps which includes the f-Fmoc protections. We believe that the f-Fmoc strategy will be a useful methods for divergent polypeptide synthesis. Additional studies and the examination of the biological activity of the novel

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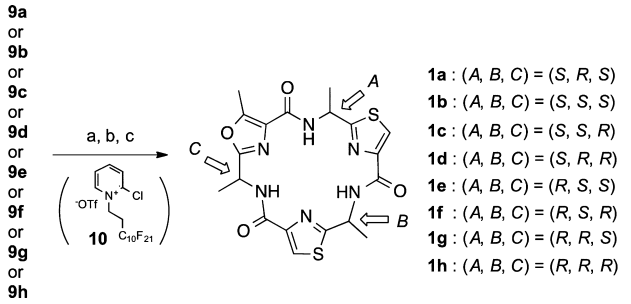
Scheme 7. Intramolecular Cyclization of 9a−h[a]



[a]Reagents and conditions: (a) excess DEA, MeCN, rt, 30 min; (b) 10 mol % $Pd(OAc)_2$, 0.8 equiv of PS-PPh_3, 2.0 equiv of $PhSiH_3$, CH_2Cl_2, rt, 30 min; (c) 5.0−20.0 equiv of fluorous tagged Mukaiyama reagent **10**, DMAP, TEA, DMF, 50 °C, 24 h, high dilution conditions; **1a**, 48%; **1b**, 71%; **1c**, 70%; **1d**, 51%; **1e**, 41%; **1f**, 49%; **1g**, 43%; **1h**, 48% (three steps).

unnatural isomers of tenuecyclamide A obtained by this work (**1c−h**) will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Methods. Except as otherwise indicated, all reactions were carried out under a positive pressure of nitrogen. All the laboratory chemicals were purchased and used without purification. Solvents were removed at a heating bath temperature of 40 °C and reduced pressure by rotary evaporation. Nonvolatile compounds were dried in vacuo at 0.01 mbar. All reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using silica gel plates. Purification by chromatography was performed on silica gel (65−210 Å). NMR spectra were recorded at 270 MHz (^{1}H), 67.8 MHz (^{13}C), and 466 MHz (^{19}F), respectively. Chemical shifts δ are referred in terms of ppm, and *J-coupling* constants are given in Hz. Abbreviations for multiplicity are as follows: s (singlet), d (doublet), t (triplet), q (quadruplet), quin (quintet signal), m (multiplet), br (broad signal). HPLC analysis and separations were performed on Fluoro*Flash* columns (20 mm i.d., 250 mm length and 4.6 mm i.d., 150 mm length), and the oligopeptide analogue were purified by HPLC with UV/vis detector. High-resolution mass spectra were measured by FAB and EI using a magnetic sector analyzer. High-resolution FAB and EI mass spectra were calibrated with Ultramark 1621 and PFK, respectively, prior to data acquisition. Optical rotations were measured at a Na D-line (λ = 589 nm) using a 100 mm cell.

f_4-Fmoc-L-alanine ***3a.*** A solution of f_4-Fmoc-OSu (1.20 g, 1.45 mmol) in MeCN (20 mL) was added to a solution of L-alanine (193 mg, 2.17 mmol) in 10% aq Na_2CO_3 (5 mL) slowly at 0 °C. After 5 min, the reaction mixture was warmed to room temperature and stirred for 3 h. The reaction acidified with 1.0 M HCl aq to pH 2.0. The organic layer was extracted with diethyl ether, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 50:1) to give f_4-Fmoc-L-alanine (1.11 g, 95%): white solid; mp 75−76 °C; $[\alpha]_D^{25}$ = +1.0 (c = 0.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 2H), 7.42 (s, 2H), 7.25 (d, J = 7.8 Hz, 2H), 5.27 (d, J = 7.3 Hz, 1H), 4.44−4.39 (m, 3H), 4.18 (t, J = 6.9 Hz, 1H), 3.02−2.96 (m, 4H), 2.51−2.32 (m, 4H), 1.49 (d, J = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.9, 155.8, 144.6, 144.3, 139.7 (2C), 138.1 (2C), 127.9 (2C), 125.0 (2C), 124.9 (2C), 120.1−111.0 (8C), 67.0, 49.5, 47.0, 26.5 (4C), 18.5; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.87 (4F), −124.27 (4F), −114.66 (4F), −80.91 (6F); HRMS [FAB+] m/z calcd for $C_{30}H_{23}F_{18}NO_4$ 803.1340, found 803.1418.

f_6-Fmoc-D-alanine ***3b.*** f_6-Fmoc-D-alanine was synthesized from f_6-Fmoc-OSu and D-alanine in 96% yield as a white solid by following the procedure used for the synthesis of **f_4-Fmoc-L-alanine 3a**: white solid; mp 112−113 °C; $[\alpha]_D^{25}$ = −1.9 (c = 0.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 2H), 7.42 (s, 2H), 7.25 (d, J = 7.3 Hz, 2H), 5.26 (d, J = 7.8 Hz, 1H), 4.48−4.37 (m, 3H), 4.19 (t, J = 6.6 Hz, 1H), 3.02−2.96 (m, 4H), 2.52−2.32 (m, 4H), 1.49 (d, J = 7.0 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 177.8, 155.9, 144.6, 144.3, 139.7 (2C), 138.1 (2C), 127.9 (2C), 125.0 (2C), 124.9, 124.8, 120.1−106.6 (12C), 67.0, 49.5, 47.0, 26.6 (2C), 26.5 (2C), 18.1; ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.06 (4F), −123.35 (4F), −122.78 (4F), −121.79 (4F), −114.46 (4F), −80.72 (6F); HRMS [FAB+] m/z calcd for $C_{34}H_{23}F_{26}NO_4$ 1003.1212, found 1003.1248.

Fmoc-Cys-S-Tr-OAllyl.[10b] HOBt·H_2O (288 mg, 1.88 mmol) and HBTU (712 mg, 1.88 mmol) were added to a solution of *N*-Fmoc-*S*-trityl-L-cysteine (1.00 g, 1.71 mmol) in DMF (10 mL) at room temperature. After 15 min, allyl alcohol (232 μL, 3.41 mmol) and DIEA (614 μL, 3.76 mmol) were added separately, and the resulting mixture was stirred at the same temperature for 24 h. The reaction mixture was diluted with ethyl acetate and washed with H_2O, saturated aq $NaHCO_3$, and brine, and the organic layer was dried over Na_2SO_4 and then concentrated. The crude residue was purified by silica gel chromatography (EtOAc/hexane =1:3) to give the title compound (1.07 g, quant): white solid; mp 70−72 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.76 (d, J = 7.3 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.41−7.38 (m, 8H), 7.33−7.18 (m, 11H), 5.95−5.80 (m, 1H), 5.33−5.23 (m, 3H), 4.62 (d, J = 5.1 Hz, 2H), 4.38−4.35 (m, 3H), 4.23 (t, J = 7.0 Hz, 1H), 2.68- 2.64 (m, 2H).

f_4/f_6-Fmoc-Ala-Cys-S-Tr-OAllyl. To a solution of *N*-Fmoc-*S*-trityl-L-cysteine-OAllyl (171 mg, 0.274 mmol) in MeCN (4 mL) was added DEA (4 mL) at room temperature. The mixture was stirred at the same temperature for 30 min. After concentration in vacuo, the reaction mixture was azeotroped to dryness with MeCN (3 × 3 mL). In another flask, to a solution mixture of f_4-Fmoc-L-alanine (100 mg, 0.124 mmol) and f_6-Fmoc-D-alanine (125 mg, 0.124 mol) in DMF (4 mL) were added HOBt·H_2O (42 mg, 0.274 mmol) and HBTU (104 mg, 0.274 mol) at room temperature. After 15 min, a solution of the above residue in DMF (2 mL) and DIEA (88 μL, 0.523 mmol) was added. The reaction mixture was stirred at room temperature for 12 h. After the addition of 1.0 M HCl aq and then dilution with ethyl acetate, the organic layer was washed with H_2O, saturated aq $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by FSPE. A column was packed with fluorous silica gel (4.98 g) using 55% aq THF as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 43 mL of 55% aq THF followed by 65 mL of THF. Evaporation of the THF fraction by vacuum centrifuge gave the title product (304 mg, 95%): pale yellow solid; mp 68−74 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 8.1 Hz, 4H), 7.42−7.37 (m, 16H), 7.28−7.15 (m, 22H), 6.45 (d, J = 5.4 Hz, 1H), 6.16 (d, J = 7.8 Hz, 1H), 5.94−5.21 (m, 2H), 5.44−5.21 (m, 6H), 4.59−4.51 (m, 6H), 4.41−4.35 (m, 6H), 4.16 (t, J = 6.5 Hz, 2H), 3.00−2.95 (m, 8H), 2.78−2.58 (m, 4H), 2.49−2.33 (m, 8H), 1.49−1.26 (m, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.00 (4F), −125.85 (4F), −124.23 (4F), −123.29 (4F), −122.72 (4F), −121.75 (4F), −114.65 (4F), −114.38 (4F), −80.92 (6F), −80.66 (6F).

f_4/f_6-Fmoc-thiazoline Ring Unit. To a solution of triphenylphosphine oxide (388 mg, 1.40 mmol) in dry CH_2Cl_2 (3 mL) was added trifluoromethanesulfonic anhydride (0.11 mL, 0.698 mmol) slowly at 0 °C under N_2. After the reaction mixture was stirred at 0 °C for 10 min, a solution of f_4/f_6-Fmoc-alanine-*S*-trityl-L-cysteine-OAllyl (400 mg, 0.155 mmol) in dry CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aq $NaHCO_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude residue was purified by FSPE. A column was packed with fluorous silica gel (22.1 g) using 70% aq MeOH as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 120 mL of 70% aq MeOH followed by 80 mL of THF. The evaporation of the THF fraction by vacuum centrifuge gave the title product (287 mg, 90%): white solid; mp 68−72 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68 (d, J = 8.1 Hz, 4H), 7.44 (s, 4H), 4.32−7.23 (m, 4H), 5.99−5.85 (m, 2H), 5.64 (d, J = 6.8 Hz, 1H), 5.55 (d, J = 7.0 Hz, 1H), 5.39- 5.29 (m, 2H), 5.27−5.23 (m, 2H), 5.18−5.10 (m, 2H), 4.69−4.68 (m, 6H), 4.40 (m, 4H), 4.19 (t, J = 7.0 Hz, 2H), 3.63−3.55 (m, 4H), 3.02−2.96 (m, 8H), 2.52−2.35 (m, 8H), 1.49 (d, J = 4.6 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.99

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(4F), −125.83 (4F), −124.22 (4F), −123.29 (4F), −122.71 (4F), −121.71 (4F), −114.66 (4F), −114.43 (4F), −80.89 (6F), −80.62 (6F).

*Compound **5a** and **5b**.* A solution of ring-closing product (198 mg, 0.0962 mmol) and activated MnO_2 (1982 mg, 10 w/w) in dry $CHCl_3$ (10 mL) was stirred at 60 °C for 30 min under N_2. After MnO_2 was removed by filtration through a pad of Celite and washed with $CHCl_3$, the filtrate was concentrated. The crude residue was purified by silica gel chromatography (EtOAc/hexane = 1/2) to give **5a** and **5b** (148 mg, 75%): white solid; mp 94−104 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.09 (s, 2H), 7.66 (d, J = 7.3 Hz, 4H), 7.43 (s, 4H), 7.23 (d, J = 7.8 Hz, 4H), 6.10−5.95 (m, 2H), 5.67 (d, J = 5.9 Hz, 2H), 5.40 (dd, J = 17.0, 1.4 Hz, 2H), 5.29 (dd, J = 10.5, 1.4 Hz, 2H), 5.19 (quin, J = 6.6 Hz, 2H), 4.84 (d, J = 5.9 Hz, 4H), 4.52−4.37 (m, 4H), 4.16 (t, J = 5.5 Hz, 2H), 3.01−2.95 (m, 8H), 2.51−2.32 (m, 8H), 1.65 (d, J = 5.9 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.00 (4F), −125.85 (4F), −124.22 (4F), −123.26 (4F), −122.69 (4F), −122.0 (4F), −114.73 (4F), −114.47 (4F), −80.88 (6F), −80.63 (6F). Fluorous analytical HPLC (flow rate; 1.0 mL/min; 0 to 30 min: 80% MeCN to 100% MeCN; 30 to 60 min: 100% MeCN): t_R = 22.0 min (f_4-Fmoc-(*S*)-thiazole), 41.9 min (f_6-Fmoc-(*R*)-thiazole).

*Preparative Separation of **5a** and **5b**.* The preparative separation of **5a** and **5b** was carried out on a SHIMADZU HPLC system. Compounds **5a** and **5b** were dissolved in THF (2.0 mL) and filtered through a syringe filter (0.45 μm pore size) prior to injection. The separation was carried out on a Fluoro*Flash* HPLC column, 20 mm i.d., 250 mm length. The separation was achieved by gradient elution with 80% MeCN/H_2O up to 100% MeCN in 30.0 min, followed by isocratic elution with 100% MeCN over 60 min with a constant flow rate of 7.0 mL/min. A UV detector (254 nm) was used to manually identify the peaks. **5a** and **5b** (40 mg) was injected chromatographic run. The yield of the demixing was 80%, and the following two compounds were isolated: **f_4-Fmoc-(*S*)-thiazole-ring unit 5a** (14 mg) and **f_6-Fmoc-(*R*)-thiazole-ring unit 5b** (18 mg).

*f_4-Fmoc-(S)-thiazole-ring unit **5a**:* white solid; mp 110−111 °C; $[\alpha]_D^{25}$= −5.64 (c = 0.13, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.43 (s, 2H), 7.25 (d, J = 7.3 Hz, 2H), 6.11−5.96 (m, 1H), 5.55 (d, J = 5.1 Hz, 1H), 5.41 (dd, J = 17.3, 1.4 Hz, 1H), 5.30 (dd, J = 10.5, 1.4 Hz, 1H), 5.22−5.17 (m, 1H), 4.85 (d, J = 5.9 Hz, 2H), 4.52−4.39 (m, 2H), 4.18 (t, J = 6.2 Hz, 1H), 3.02−2.96 (m, 4H), 2.51−2.32 (m, 4H), 1.66 (d, J = 5.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$), δ 173.7, 160.9, 155.8, 147.0 (2C), 144.6 (2C), 144.3 (2C), 139.8 (2C), 138.1, 131.9 (2C), 128.0, 127.5, 125.1, 125.0, 120.2−110.1 (9C), 67.0, 66.1, 49.4, 47.2, 26.6 (2C), 22.6 (3C); ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.85 (4F), −124.21 (4F), −114.59 (4F), −80.86 (6F); HRMS [FAB+] m/z calcd for $C_{36}H_{29}F_{18}N_2O_4S$ 927.1562, found 927.1513.

*f_6-Fmoc-(R)-thiazole-ring unit **5b**:* white solid; mp 75−76 °C; $[\alpha]_D^{25}$ = +8.24 (c = 0.12, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.68 (d, J = 8.1 Hz, 2H), 7.43 (s, 2H), 7.25 (d, J = 7.8 Hz, 2H), 6.10−5.96 (m, 1H), 5.57 (d, J = 6.5 Hz, 1H), 5.41 (dd, J = 17.0, 1.4 Hz, 1H), 5.30 (dd, J = 10.5, 1.4 Hz, 1H), 5.22−5.17 (m, 1H), 4.85 (d, J = 5.9 Hz, 2H), 4.52−4.39 (m, 2H), 4.17 (d, J = 6.6 Hz, 1H), 3.02−2.96 (m, 4H), 2.51−2.39 (m, 4H), 1.66 (d, J = 5.9 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$), δ 173.6, 160.8, 155.5, 147.0 (2C), 144.5 (2C), 144.4 (2C), 139.7 (2C), 138.1, 131.8 (2C), 128.0, 127.4, 125.0, 124.9, 120.1−108.2 (13C), 66.9, 66.0, 49.3, 47.1, 26.6 (2C), 22.7 (2C), 21.1; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.99 (4F), −123.28 (4F), −122.71 (4F), −121.70 (4F), −114.38 (4F), −80.66 (6F); HRMS [FAB+] m/z calcd for $C_{40}H_{29}F_{26}N_2O_4S$ 1127.1435, found 1127.1387.

*Compound **6a**.* Diethylamine (2 mL) was added to a solution of **f_4-Fmoc-(*S*)-thiazole-ring unit 5a** (10 mg, 0.0108 mmol) in MeCN (2 mL), and the reaction mixture was stirred at room temperature for 30 min. After concentration in vacuo, the reaction mixture was azeotroped to dryness with MeCN (3 × 3 mL). The crude residue was purified by FSPE. A column was packed with fluorous silica gel (0.32 g) using 50% aq THF as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 2 mL of 50% aq THF followed by 4 mL of THF. The evaporation of the THF fraction by vacuum centrifuge gave **6a** as colorless oil, which was used without purification (2.3 mg, quant): colorless oil; $[\alpha]_D^{25}$ = −13.3 (c = 0.265, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12 (s, 1H), 6.11−5.97 (m, 1H), 5.41 (dd, J = 17.0 Hz, 1.4 Hz, 1H), 5.30 (dd, J = 10.5 Hz, 1.4 Hz, 1H), 4.86 (dd, J = 5.9 Hz, 1.4 Hz, 2H), 4.50 (q, J = 6.8 Hz, 1H), 1.86 (s, 2H), 1.55 (d, J = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.9, 161.1, 146.6, 131.9, 127.4, 118.8, 65.9, 49.7, 24.8; HRMS [FAB +] m/z calcd for $C_9H_{13}N_2O_2S$ 213.0698, found 213.0709.

*Compound **6b**.* Compound **6b** was prepared from **f_6-Fmoc-(*R*)-thiazole-ring unit 5b** in quantitative yield as colorless oil by following the procedure used for prepare of **6a**: colorless oil; $[\alpha]_D^{25}$ = +9.86 (c = 0.191, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12 (s, 1H), 6.12−5.97 (m, 1H), 5.41 (dd, J = 17.3 Hz, 1.4 Hz, 1H), 5.29 (dd, J = 10.5 Hz, 1.4 Hz, 1H), 4.85 (dd, J = 5.9 Hz, 1.4 Hz, 2H), 4.50 (q, J = 6.8 Hz, 1H), 1.86 (s, 2H), 1.55 (d, J = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 179.9, 161.1, 146.6, 131.9, 127.4, 118.8, 65.9, 49.7, 24.8; HRMS [FAB+] m/z calcd for calcd for $C_9H_{13}N_2O_2S$ 213.0698, found 213.0688.

f_4/f_6-Fmoc-Ala-Thr-OBn. A solution of f_4-Fmoc-L-alanine (6.00 g, 7.47 mmol) and f_6-Fmoc-D-alanine (7.47 g, 7.47 mmol) in DMF (120 mL) was treated with HOBt·H_2O (5.37 g, 35.10 mmol) and HBTU (13.31 g, 35.10 mmol) at room temperature. After 15 min, H-Thr-OBn·$(COOH)_2$ (4.92 g, 16.43 mmol) and DIEA (5.3 mL, 31.36 mmol) were added to the above reaction mixture. The reaction mixture was stirred at room temperature for 24 h. After the addition of 1.0 M HCl aq and then dilution with ethyl acetate, the organic layer was washed with H_2O, saturated aq $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The crude residue was pass through a short pad of silica gel (EtOAc/hexane =1:3) to obtain the title compounds (15.80 g, 94%): pale yellow solid; mp 115−118 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 4H), 7.42 (s, 4H), 7.32−7.23 (m, 16H), 6.80−6.65 (m, 2H), 5.47−5.42 (m, 2H), 5.23−5.12 (m, 4H), 4.64 (dd, J = 8.4, 1.9 Hz, 2H), 4.40−4.38 (m, 6H), 4.16 (t, J = 6.9 Hz, 2H), 3.02−2.96 (m, 8H), 2.52−2.32 (m, 8H), 2.18−2.02 (m, 2H), 1.46−1.39 (m, 6H), 1.21−1.18 (m, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.04 (4F), −125.89 (4F), −124.25 (4F), −123.30 (4F), −122.74 (4F), −121.77 (4F), −114.69 (4F), −114.46 (4F), −80.89 (6F), −80.65 (6F).

f_4/f_6-Fmoc-Ala-Thr(C═O)-OBn. Dess−Martin periodinane (155 mg, 0.0365 mol) was added to a solution of f_4/f_6-Fmoc-dipeptides (100 mg, 0.0457 mmol) in CH_2Cl_2 (4 mL). The reaction mixture was stirred at 40 °C for 2 h. The reaction was quenched with saturated aq sodium hyposulfite/saturated aq $NaHCO_3$ = 1/1 v/v. The organic layer was washed with saturated aq $NaHCO_3$, dried over Na_2SO_4, and concentrated. The crude residue was passed through a short pad of silica gel to obtain the title compounds (99 mg, 98%): pale yellow solid; mp 86−88 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.68 (d, J = 7.3 Hz, 4H), 7.42 (s, 4H), 7.34−7.33 (m, 12H), 7.25 (d, J = 7.6 Hz, 4H), 5.33−5.15 (m, 8H), 4.44−4.39 (m, 6H), 4.18 (t, J = 6.2 Hz, 2H), 3.03−2.96 (m, 8H), 2.52−2.30 (m, 14H), 1.41 (t, J = 7.3 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.02 (4F), −125.88 (4F), −124.24 (4F), −123.29 (4F), −122.73 (4F), −121.74 (4F), −114.70 (4F), −114.42 (4F), −80.87 (6F), −80.65 (6F).

f_4/f_6-Fmoc-oxazole Ring Unit. To a solution of triphenylphosphine oxide (18.33 g, 65.89 mmol) in dry CH_2Cl_2 (120 mL) was added trifluoromethanesulfonic anhydride (5.1 mL, 32.95 mmol) slowly at 0 °C under N_2. After the reaction mixture was stirred at same temperature for 10 min, a solution of f_4/f_6-Fmoc-oxidative products (8.00 g, 3.66 mmol) in dry CH_2Cl_2 (60 mL) was added to the above reaction mixture. The reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with saturated aq $NaHCO_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated. The crude residue was purified by FSPE. A column was packed with fluorous silica gel (405.0 g) using 55% aq THF as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 1020 mL of 55% aq THF followed by 1120 mL of THF. The evaporation of the THF fraction by vacuum centrifuge gave the title compounds (7.95 g, quant): white solid; mp 81−84 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.67 (d, J = 7.8 Hz, 4H), 7.44−7.23 (m, 18H), 5.53 (d, J = 7.8 Hz, 2H), 5.36 (s, 4H), 5.00 (quin, J = 6.4 Hz, 2H),

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4.42 (d, J = 6.5 Hz, 4H), 4.16 (t, J = 6.9 Hz, 2H), 3.02−2.96 (m, 8H), 2.58 (s, 6H), 2.51−2.32 (m, 8H), 1.56−1.55 (m, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.01 (4F), −125.87 (4F), −124.25 (4F), −123.32 (4F), −122.72 (4F), −121.75 (4F), −114.67 (4F), −114.47 (4F), −80.87 (6F), −80.63 (6F).

Compound ***7-mix***. The ring closing product (**f_4/f_6-Fmoc-oxazole-ring unit**) (1.00 g, 0.465 mmol) and Pd/C (11 mg, 0.0930 mmol) in THF/MeOH (10 mL, 1/1 v/v) was stirred at room temperature for 2 h under H_2 balloon. The catalyst was removed by filtration through a pad of Celite and washed with ethyl acetate. The filtrate was concentrated to give **7-mix** (865 mg, 94%). The residue was immediately used for the next step without further purification: colorless oil; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.66 (d, J = 7.8 Hz, 4H), 7.44−7.41 (m, 4H), 7.23 (d, J = 7.0 Hz, 4H), 5.07−5.02 (m, 2H), 4.40 (d, J = 6.5 Hz, 4H), 4.15 (t, J = 6.6 Hz, 2H), 3.00−2.94 (m, 8H), 2.62 (s, 6H), 2.51−2.25 (m, 8H), 1.58 (d, J = 7.3 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.01 (4F), −125.86 (4F), −124.24 (4F), −123.29 (4F), −122.73 (4F), −121.74 (4F), −114.63 (4F), −114.41 (4F), −80.91 (6F), −80.65 (6F).

Compound ***8a-mix***. A solution of **7-mix** (250 mg, 0.127 mmol) in DMF (4 mL) was treated with HOBt·H_2O (91 mg, 0.597 mmol) and HBTU (226 mg, 0.597 mmol) at room temperature. After 15 min, a solution of **6a** (67 mg, 0.305 mmol) in DMF (4 mL) and DIEA (91 μL, 0.55 mmol) were sequentially added to the above solution. The reaction mixture was stirred at room temperature for 12 h. After the addition of 1.0 M HCl aq and dilution with ethyl acetate, the organic layer was washed with H_2O, saturated aq $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by FSPE. A short column was packed with fluorous silica gel (5.1 g) using 55% aq THF as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 62.9 mL of 55% aq THF followed by 25.0 mL of THF. The evaporation of the THF fraction by vacuum centrifuge gave product **8a-mix** (272 mg, 91%): white solid; mp 123−126 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.70−7.67 (m, 4H), 7.47−7.43 (m, 6H), 7.26−7.24 (m, 4H), 6.09−5.95 (m, 2H), 5.57−5.52 (m, 2H), 5.43−5.27 (m, 6H), 5.05−4.94 (m, 2H), 4.85−4.82 (m, 4H), 4.46−4.44 (m, 4H), 4.21 (t, J = 6.3 Hz, 2H), 3.01−2.96 (m, 8H), 2.62 (s, 6H), 2.51−2.32 (m, 8H), 1.75−1.71 (m, 6H), 1.62−1.53 (m, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.99 (4F), −125.86 (4F), −124.25 (4F), −123.32 (4F), −122.72 (4F), −121.73 (4F), −114.64 (4F), −114.42 (4F), −80.87 (6F), −80.65 (6F).

Compound ***8b-mix***. Compound **8b-mix** was synthesized from **7-mix** and **6b** in 98% yield as a white solid by following the procedure used for the synthesis of **8a-mix**: white solid; mp 121−124 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10−8.07 (m, 2H), 7.68 (d, J = 8.1 Hz, 4H), 7.46−7.43 (m, 6H), 7.25 (d, J = 6.8 Hz, 4H), 6.10−5.94 (m, 2H), 5.54 (quin, J = 7.1 Hz, 2H), 5.43−5.26 (m, 6H), 4.99 (quin, J = 6.4 Hz, 2H), 4.85−4.81 (m, 4H), 4.46−4.44 (m, 4H), 4.20 (t, J = 6.6 Hz, 2H), 3.02−2.96 (m, 8H), 2.61 (s, 6H), 2.50−2.31 (m, 8H), 1.73 (d, J = 6.8 Hz, 6H), 1.53 (d, J = 7.8 Hz, 6H); ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.04 (4F), −125.85 (4F), −124.24 (4F), −123.29 (4F), −122.69 (4F), −121.71 (4F), −114.62 (4F), −114.39 (4F), −80.88 (6F), −80.64 (6F).

Compound ***9bc-mix***. A solution of **8a-mix** (210 mg, 0.0891 mmol) and $Pd(PPh_3)_4$ (21 mg, 0.0178 mmol) in dry CH_2Cl_2 (5 mL) was stirred at room temperature for 10 min in N_2. To the solution mixture was added $PhSiH_3$ (22 μL, 0.178 mmol), and then the mixture was stirred at room temperature for 30 min. The mixture was through a pad of Celite and washed CH_2Cl_2. The filtrate was concentrated. The residue was immediately used for the next step without further purification: A solution of the above residue in DMF (6 mL) was treated with HOBt·H_2O (64 mg, 0.419 mmol) and HBTU (159 mg, 0.419 mmol) at room temperature. After 15 min, a solution of **6a** (45 mg, 0.214 mmol) in DMF (2 mL) and DIEA (63 μL, 0.374 mmol) were sequentially added to the above solution at room temperature. The mixture was stirred at the same temperature for 12 h. After the addition of 1.0 M HCl aq and dilution with ethyl acetate, the organic layer was washed with H_2O, saturated aq $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by FSPE. A short column was packed with fluorous silica gel (7.2 g) using 50% aq THF as the solvent. The crude reaction mixture was then loaded onto this column and eluted with 120.0 mL of 50% aq THF followed by 25.0 mL of THF. The evaporation of the THF fraction by vacuum centrifuge gave product **9bc-mix** as a colorless semisolid (202 mg, 85%). Fluorous analytical HPLC (flow rate; 1.0 mL/min; 0 to 7.5 min: 80% MeCN/H_2O to 100% MeCN; 7.5 to 30 min: 100% MeCN): t_R =10.8 min (**9b**), 23.8 min (**9c**).

Compound ***9ad-mix***. Compound **9ad-mix** was synthesized from **8a-mix** and **6b** in 80% yield as a colorless semisolid by following the procedure used for the synthesis of **9bc-mix**. Fluorous analytical HPLC (flow rate; 1.0 mL/min; 0 to 7.5 min: 80% MeCN/H_2O to 100% MeCN; 7.5 to 30 min: 100% MeCN): t_R = 14.9 min (**9a**), 23.8 min (**9d**).

Compound ***9ef-mix***. Compound **9ef-mix** was synthesized from **8b-mix** and **6a** in 87% yield as a colorless semisolid by following the procedure used for the synthesis of **9bc-mix**. Fluorous analytical HPLC (flow rate; 1.0 mL/min; 0 to 7.5 min: 80% MeCN/H_2O to 100% MeCN; 7.5 to 30 min: 100% MeCN): t_R = 15.5 min (**9e**), 23.1 min (**9f**).

Compound ***9gh-mix***. Compound **9gh-mix** was synthesized from **8b-mix** and **6b** in 82% yield as a colorless semisolid by following the procedure used for the synthesis of **9bc-mix**. Fluorous analytical HPLC (flow rate; 1.0 mL/min; 0 to 7.5 min: 80% MeCN/H_2O to 100% MeCN; 7.5 to 30 min: 100% MeCN): t_R = 15.1 min (**9g**), 23.1 min (**9h**).

Preparative Separation of ***9bc-mix***. Compound **9bc-mix** was dissolved in THF (1.5 mL) and filtered through a syringe filter (0.45 μm pore size) prior to injection. The separation was carried out on a Fluoro*Flash* HPLC column, 20 mm i.d., 250 mm length. The separation was achieved by gradient elution with 80% MeCN/H_2O up to 100% MeCN in 7.5 min, followed by isocratic elution with 100% MeCN over 60 min with a constant flow rate of 7.0 mL/min. A UV detector (254 nm) was used to manually identify the peaks. **9bc-mix** (78 mg) was injected for the chromatographic run. The yield of the demixing was quantitative yield and the following two compounds were isolated: **9b** (30 mg) and **9c** (48 mg).

Compound ***9b:*** colorless semisolid; $[\alpha]_D^{25}$ = −11.2 (c = 0.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.00 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 6.5 Hz, 2H), 7.32 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.6 Hz, 2H), 6.09−5.94 (m, 1H), 5.59 (quin, J = 7.2 Hz, 1H), 5.50 (quin, J = 7.3 Hz, 1H), 5.42−5.26 (m, 3H), 4.99 (quin, J = 5.9 Hz, 1H), 4.83 (d, J = 5.9 Hz, 2H), 4.45−4.43 (m, 2H), 4.18 (t, J = 6.5 Hz, 1H), 3.01−2.95 (m, 4H), 2.62 (s, 3H), 2.51−2.31 (m, 4H), 1.79 (d, J = 7.3 Hz, 3H), 1.70 (d, J = 6.8 Hz, 3H), 1.57 (d, J = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.0, 161.3, 161.2, 161.1, 160.9, 160.8, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 144.2, 139.6 (2C), 138.0 (2C), 131.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.1−110.4 (9C), 66.9, 65.9, 47.1 (2C), 46.7, 45.2, 26.5 (2C), 20.9 (3C), 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.85 (4F), −124.27 (4F), −114.61 (4F), −80.85 (6F); HRMS [FAB+] m/z calcd for $C_{49}H_{43}F_{18}N_6O_7S_2$ 1233.2347, found 1233.2366.

Compound ***9c:*** colorless semisolid; $[\alpha]_D^{25}$ = +3.63 (c = 0.2, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.00 (s, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 7.3 Hz, 2H), 7.32 (d, J = 8.6 Hz, 1H), 7.24 (d, J = 8.1 Hz, 2H), 6.09−5.94 (m, 1H), 5.59 (quin, J = 7.4 Hz, 1H), 5.50 (quin, J = 7.4 Hz, 1H), 5.42−5.26 (m, 3H), 4.99 (quin, J = 6.5 Hz, 1H), 4.83 (d, J = 5.9 Hz, 2H), 4.47−4.43 (m, 2H), 4.18 (t, J = 6.5 Hz, 1H), 3.01−2.95 (m, 4H), 2.62 (s, 3H), 2.50−2.31 (m, 4H), 1.79 (d, J = 7.3 Hz, 3H), 1.70 (d, J = 6.8 Hz, 3H), 1.57 (m, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.0, 161.4, 161.3, 161.1, 160.9, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 144.2, 139.7 (2C), 138.1 (2C), 131.8 (2C), 128.5 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.2−108.2 (13C), 67.1, 65.9, 47.1, 46.7, 46.6, 45.2, 26.6 (2C), 21.0 (2C), 20.9, 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.98 (4F), −123.31 (4F), −122.66 (4F), −121.68 (4F), −114.41 (4F), −80.61 (6F); HRMS [FAB+] m/z calcd for $C_{53}H_{43}F_{26}N_6O_7S_2$ 1433.2221, found 1433.2236.

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Preparative Separation of ***9ad-mix***. The preparative separation of **9ad-mix** was carried out in the same manner as **9bc-mix**. Compound **9ad-mix** (223 mg) was injected for the chromatographic run. The yield of the demixing was 96%, and the following two compounds were isolated: **9a** (102 mg) and **9d** (113 mg).

Compound ***9a:*** colorless semisolid; $[\alpha]_D^{25}$ = −14.4 (*c* = 0.088, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.01 (s, 1H), 7.90 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 7.35 (d, *J* = 7.8 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.10−5.94 (m, 1H), 5.59 (quin, *J* = 7.7 Hz, 1H), 5.50 (quin, *J* = 7.6 Hz, 1H), 5.43−5.26 (m, 3H), 6.07−5.97 (m, 1H), 4.83 (d, *J* = 9.5 Hz, 2H), 4.51−4.39 (m, 2H), 4.18 (t, *J* = 6.2 Hz, 1H), 3.00−2.94 (m, 4H), 2.61 (s, 3H), 2.50−2.31 (m, 4H), 1.78 (d, *J* = 7.3 Hz, 3H), 1.70 (d, *J* = 6.5 Hz, 3H), 1.58 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.1, 173.0, 161.3, 161.2, 161.1, 160.9, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 144.3, 139.7, 139.6, 138.1 (2C), 131.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.0−110.9 (9C), 66.9, 65.9, 47.0, 46.7, 46.6, 45.2, 26.6 (2C), 26.5, 20.9 (2C), 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.85 (4F), −124.24 (4F), −114.63 (4F), −80.89 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{49}H_{43}F_{18}N_6O_7S_2$ 1233.2347, found 1233.2344.

Compound ***9d:*** colorless semisolid; $[\alpha]_D^{25}$ = +6.92 (*c* = 0.095, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.01 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.33 (d, 8.4 Hz, 1H), 7.25 (d, *J* = 8.1 Hz, 2H), 6.10−5.96 (m, 1H), 5.59 (quin, *J* = 7.3 Hz, 1H), 5.50 (quin, *J* = 7.3 Hz, 1H), 5.44−5.27 (m, 3H), 5.00 (quin, *J* = 6.9 Hz, 1H), 4.85 (d, *J* = 5.9 Hz, 2H), 4.52−4.40 (m, 2H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.01−2.95 (m, 4H), 2.63 (s, 3H), 2.51−2.30 (m, 4H), 1.79 (d, *J* = 7.3 Hz, 3H), 1.71 (d, *J* = 7.3 Hz, 3H), 1.57 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.1, 173.0, 161.3, 161.2, 161.1, 160.9, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 144.3, 139.7 (2C), 138.1 (2C), 131.8, 131.7, 128.5 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.2−108.5 (13C), 66.9, 65.9, 47.1, 46.7, 46.6, 45.2, 26.6 (2C), 25.6, 20.9 (2C), 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.98 (4F), −123.30 (4F), −122.70 (4F), −121.72 (4F), −114.39 (4F), −80.64 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{53}H_{43}F_{26}N_6O_7S_2$ 1433.2221, found 1433.2207.

Preparative Separation of ***9ef-mix***. The preparative separation of **9ef-mix** was carried out in the same manner as for **9bc-mix**. Compound **9ef-mix** (90 mg) was injected for the chromatographic run. The yield of the demixing was 98%, and the following two compounds were isolated: **9e** (42 mg) and **9f** (46 mg).

Compound ***9e:*** colorless semisolid; $[\alpha]_D^{25}$ = −14.9 (*c* = 0.06, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.04 (s, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.43 (s, 2H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 6.08−5.97 (m, 1H), 5.59 (quin, *J* = 7.3 Hz, 1H), 5.50 (quin, *J* = 7.3 Hz, 1H), 5.43−5.26 (m, 3H), 4.99 (quin, *J* = 5.9 Hz, 1H), 4.84 (d, *J* = 4.6 Hz, 2H), 4.53−4.39 (m, 2H), 4.19 (t, *J* = 6.6 Hz, 1H), 3.00−2.95 (m, 4H), 2.62 (s, 3H), 2.50−2.34 (m, 4H), 1.78 (d, *J* = 6.5 Hz, 3H), 1.70 (d, *J* = 7.0 Hz, 3H), 1.56 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.1, 161.4, 161.2 (2C), 160.9, 160.4 (2C), 155.5, 154.3, 149.1, 146.9, 146.8, 144.6, 144.4, 139.7 (2C), 138.1 (2C), 131.9 (2C), 128.5 (2C), 128.0, 127.8 (2C), 125.0, 124.1, 120.2−110.4 (9C), 67.0, 66.0, 49.7, 46.8, 46.7, 45.2, 26.6 (2C), 21.0 (3C), 11.5; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.88 (4F), −124.23 (4F), −114.58 (4F), −80.86 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{49}H_{43}F_{18}N_6O_7S_2$ 1233.2347, found 1233.2397.

Compound ***9f:*** colorless semisolid; $[\alpha]_D^{25}$ = +13.1 (*c* = 0.12, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.12 (s, 1H), 8.01 (s, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.3 Hz, 2H), 6.10−5.94 (m, 1H), 5.59 (quin, *J* = 7.2 Hz, 1H), 5.50 (quin, *J* = 7.3 Hz, 1H), 5.44−5.27 (m, 3H), 5.00 (quin, *J* = 6.8 Hz, 1H), 4.84 (d, *J* = 5.1 Hz, 2H), 4.48−4.44 (m, 2H), 4.18 (t, *J* = 6.5 Hz, 1H), 3.01−2.95 (m, 4H), 2.62 (s, 3H), 2.51−2.32 (m, 4H), 1.79 (d, *J* = 6.5 Hz, 3H), 1.71 (d, *J* = 7.3 Hz, 3H), 1.58 (d, *J* = 8.1 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.1, 161.4, 161.1, 161.0 (2C), 160.4 (2C), 155.9, 155.3, 149.0, 146.7 (2C), 144.6, 144.3, 139.7, 139.6, 138.1 (2C), 131.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.0−108.4 (13C), 66.9, 65.9, 47.0, 46.7, 46.6, 45.1, 26.6 (2C), 21.0 (2C), 20.9, 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −126.09 (4F), −123.35 (4F), −122.77 (4F), −121.78 (4F), −114.42 (4F), −80.75 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{53}H_{43}F_{26}N_6O_7S_2$ 1433.2221, found 1433.2268.

Preparative Separation of ***9gh-mix***. The preparative separation of **9gh-mix** was carried out in the same manner as for **9bc-mix**. Compound **9gh-mix** (140 mg) was injected for the chromatographic run. The yield of the demixing was 97%, and the following two compounds were isolated: **9g** (64 mg) and **9h** (72 mg).

Compound ***9g:*** colorless semisolid; $[\alpha]_D^{25}$ = −1.57 (*c* = 0.05, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.04 (s, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 2H), 7.39−7.26 (m, 3H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.09−5.93 (m, 1H), 5.60 (quin, *J* = 7.6 Hz, 1H), 5.50 (quin, *J* = 7.3 Hz, 1H), 5.43−5.26 (m, 3H), 4.99 (quin, *J* = 7.1 Hz, 1H), 4.83 (d, *J* = 5.4 Hz, 2H), 4.52−4.39 (m, 2H), 4.19 (t, *J* = 6.2 Hz, 1H), 3.00−2.95 (m, 4H), 2.62 (s, 3H), 2.50−2.31 (m, 4H), 1.76 (d, *J* = 6.4 Hz, 3H), 1.70 (d, *J* = 7.0 Hz, 3H), 1.56 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.1, 161.3, 161.2, 161.0, 160.9, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 144.3, 139.7 (2C), 138.1 (2C), 131.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.2−110.0 (9C), 66.9, 65.9, 47.1 (2C), 46.7, 45.2, 26.6, 26.5, 20.9 (3C), 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.84 (4F), −124.24 (4F), −114.62 (4F), −80.86 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{49}H_{43}F_{18}N_6O_7S_2$ 1233.2347, found 1233.2377.

Compound ***9h:*** colorless semisolid; $[\alpha]_D^{25}$ = +12.4 (*c* = 0.087, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.00 (s, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 2H), 6.09−5.94 (m, 1H), 5.59 (quin, *J* = 7.3 Hz, 1H), 5.50 (quin, *J* = 7.3 Hz, 1H), 5.43−5.26 (m, 3H), 5.00 (quin, *J* = 7.4 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 2H), 4.46−4.44 (m, 2H), 4.18 (t, *J* = 6.6 Hz, 1H), 3.01−2.95 (m, 4H), 2.62 (s, 3H), 2.51−2.32 (m, 4H), 1.79 (d, *J* = 7.3 Hz, 3H), 1.70 (d, *J* = 6.8 Hz, 3H), 1.57 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 173.2, 173.1, 161.2 (2C), 161.1, 160.9, 160.4 (2C), 155.4, 154.2, 149.0, 146.7 (2C), 144.6, 1443, 139.7, 139.6, 138.1(2C), 131.8 (2C), 128.4 (2C), 127.9, 127.7 (2C), 124.9, 124.0, 120.2−107.1 (13C), 66.9, 65.9, 47.1, 46.7, 45.2, 43.4, 26.7 (2C), 21.0 (2C), 20.9, 11.6; ^{19}F NMR (466 MHz, $CDCl_3$) δ −125.97 (4F), −123.28 (4F), −122.71 (4F), −121.58 (4F), −114.45 (4F), −80.62 (6F); HRMS [FAB+] *m*/*z* calcd for $C_{53}H_{43}F_{26}N_6O_7S_2$ 1433.2221, found 1433.2218.

Procedure for Cyclization Using ***9a***. Diethylamine (2 mL) was added to a solution of **9a** (28 mg, 0.0230 mmol) in MeCN (2 mL), and the mixture was stirred at rt for 30 min. After concentration in vacuo, the reaction mixture was azeotroped to dryness with MeCN (3 × 3 mL). $Pd(OAc)_2$ (0.5 mg, 0.00230 mmol) and styrene polymer-bound triphenylphosphene (11 mg, 1.7 mol/g, 0.0184 mmol) were added to a flask containing dry CH_2Cl_2 (3 mL) under N_2. After the mixture was stirred for 15 min, a solution of the above residue in dry CH_2Cl_2 (2 mL) and $PhSiH_3$ (6 μL, 0.0461 mmol) were added separately. The reaction progress was monitored by TLC, and the reaction was complete in 30 min. The reaction mixture was passed through a pad of Celite and concentrated. The residue was used in the next step without further purification. The resulting amino acid derivative was dissolved in DMF (16 mL) solution. This solution was added to a flask containing fluorous tagged Mukaiyama reagent (373 mg, 0.461 mmol), TEA (192 μL, 1.38 mmol), and DMAP (23 mg, 0.184 mmol) in dry DMF (32 mL) at 50 °C over 8 h using a syringe pump. After the addition was complete, the mixture was stirred at the same temperature for 24 h. To the reaction mixture was added H_2O (12 mL) and then filtered. The filtrate was diluted with ethyl acetate and washed with 1.0 M HCl aq, H_2O, and brine. The organic layer was dried over Na_2SO_4 and concentrated. The crude residue was purified by short silica gel chromatography (EtOAc/hexane = 4/1) to obtain **1a** as a colorless semisolid (5.1 mg, 48%).

*Tenucyclamide A (***1a***):*[10a] colorless semisolid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.69−8.68 (m, 2H), 8.61 (d, *J* = 6.8 Hz, 1H), 8.24 (s, 1H), 8.17 (s, 1H), 5.60 (quin, *J* = 6.6 Hz, 1 H), 5.37 (quin, *J* = 6.4 Hz, 1H), 5.14 (quin, *J* = 6.3 Hz, 1H), 2.70 (s, 3H), 1.80 (d, *J* = 6.8 Hz, 3H), 1.71−1.69 (m, 6H).

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*Tenuecyclamide B (**1b**).*[10a] Compound **1b** was synthesized from **9b** in 71% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.70−8.66 (m, 2H), 8.60 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H), 8.14 (s, 1H), 5.68 (quin, J = 7.0 Hz, 1H), 5.44 (quin, J = 6.6 Hz, 1H), 5.24 (quin, J = 6.9 Hz, 1H), 2.69 (s, 3H), 1.73−1.71 (m, 9H).

*Compound **1c**.* Compound **1c** was synthesized from **9c** in 70% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; $[\alpha]_D^{25}$ = −24.0 (c = 0.21, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.70 (d, J = 6.5 Hz, 1H), 8.65−8.60 (m, 2H), 8.20 (s, 1H), 8.17 (s, 1H), 5.58 (quin, J = 6.6 Hz, 1H), 5.42 (quin, J = 6.6 Hz, 1H), 5.21 (quin, J = 6.6 Hz, 1H), 2.69 (s, 3H), 1.79 (d, J = 6.8 Hz, 3H), 1.70−1.65 (m, 6H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 171.7, 170.6, 161.3, 160.7, 159.7, 159.6, 154.2, 149.2, 148.3, 128.6, 124.6, 123.1, 48.0, 47.9, 44.2, 24.7, 24.5, 19.9, 11.7; HRMS [EI+] m/z calcd for $C_{19}H_{20}N_6O_4S_2$ 460.0987, found 460.0953.

*Compound **1d**.* Compound **1d** was synthesized from **9d** in 51% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; $[\alpha]_D^{25}$ = +40.3 (c = 0.29, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.68−8.66 (m, 2H), 8.56 (d, J = 6.8 Hz, 1H), 8.21 (s, 1H), 8.12 (s, 1H), 5.56 (quin, J = 6.5 Hz, 1H), 5.41 (quin, J = 6.6 Hz, 1H), 5.28 (quin, J = 6.8 Hz, 1H), 2.70 (s, 3H), 1.72−1.70 (m, 9H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 171.7, 170.6, 161.3, 160.7, 159.7, 159.6, 154.2, 149.2, 148.3, 128.6, 124.6, 123.1, 48.0, 47.9, 44.2, 24.7, 24.5, 19.9, 11.7; HRMS [EI+] m/z calcd for $C_{19}H_{20}N_6O_4S_2$ 460.0987, found 460.0953.

*Compound **1e**.*[10a] Compound **1e** was synthesized from **9e** in 41% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.68−8.66 (m, 2H), 8.57 (d, J = 5.9 Hz, 1H), 8.21 (s, 1H), 8.12 (s, 1H), 5.56 (quin, J = 6.8 Hz, 1H), 5.41 (quin, J = 6.4 Hz, 1H), 5.28 (quin, J = 6.9 Hz, 1H), 2.70 (s, 3H), 1.72−1.68 (m, 9H).

*Compound **1f**.* Compound **1f** was synthesized from **9f** in 49% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; $[\alpha]_D^{25}$ = +2.4 (c = 0.144, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.69−8.67 (m, 2H), 8.61 (d, J = 6.5 Hz, 1H), 8.24 (s, 1H), 8.17 (s, 1H), 5.60 (quin, J = 6.8 Hz, 1H), 5.36 (quin, J = 6.3 Hz, 1H), 5.14 (quin, J = 6.1 Hz, 1H), 2.70 (s, 3H), 1.79 (d, J = 6.8 Hz, 3H), 1.73−1.64 (m, 6H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 172.2, 171.4, 161.9, 160.7, 160.0, 159.6, 153.6, 148.8, 148.6, 128.6, 124.9, 123.9, 48.3, 48.0, 44.9, 24.9, 23.7, 20.8, 11.6; HRMS [EI+] m/z calcd for $C_{19}H_{20}N_6O_4S_2$ 460.0987, found 460.0980.

*Compound **1g**.*[10a] Compound **1g** was synthesized from **9g** in 43% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.70 (d, J = 5.9 Hz, 1H), 8.65−8.60 (m, 2H), 8.20 (s, 1H), 8.17 (s, 1H), 5.58 (quin, J = 6.6 Hz, 1H), 5.42 (quin, J = 6.6 Hz, 1H), 5.21 (quin, J = 6.6 Hz, 1H), 2.69 (s, 3H), 1.79 (d, J = 6.8 Hz, 3H), 1.70−1.65 (m, 6H).

*Compound **1h**.* Compound **1h** was synthesized from **9h** in 48% yield as a colorless semisolid by following the procedure used for the synthesis of **1a**: colorless semisolid; $[\alpha]_D^{25}$ = +4.14 (c = 0.98, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 8.70−8.66 (m, 2H), 8.59 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H), 8.13 (s, 1H), 5.67 (quin, J = 6.9 Hz, 1H), 5.44 (quin, J = 6.6 Hz, 1H), 5.24 (quin, J = 6.8 Hz, 1H), 2.69 (s, 3H), 1.73−1.68 (m, 9H); ^{13}C NMR (67.8 Hz, $CDCl_3$) δ 171.4, 170.9, 161.6, 160.5, 159.7, 159.4, 153.9, 148.9, 148.5, 128.4, 124.3, 123.5, 47.5, 47.3, 44.2, 25.0, 24.9, 20.8, 11.6; HRMS [EI+] m/z calcd for $C_{19}H_{20}N_6O_4S_2$ 460.0987, found 460.0941.

■ ASSOCIATED CONTENT

Supporting Information

Proton, carbon, and fluorine NMR data for all new compounds and fluorous HPLC chart of **5a**, **5b**, **9bc-mix**, **9ad-mix**, **9ef-mix**, and **9gh-mix**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

We dedicate this paper to Prof. Dennis P. Curran on the occasion of his 60th birthday.

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(11) Fluorous silica gel (Fluoro*Flash* silica gel, 40 μm), which is available from SIGMA-Aldrich, was used for all FSPE process.

(12) Preparative and analytical f-HPLC were conducted by Fluoro*Flash* columns (20 mm i.d., 250 mm length and 4.6 mm i.d., 150 mm length) purchased from Fluorous Technologies, Inc. The corporation is closing; however, fluorous column (Wakopak Fluofix-II 120E) having almost same separation ability is available from Wako Pure Chemical Industries, Ltd.

(13) Although other condensation reagents such as PyBOP ((benzotriazol-1-yloxy) tripyrrolidinophosphonium hexafluorophosphate) or DPPA (diphenyl phosphorazidate) or DEPC (diethoxyphosphoryl cyanide) or Yamaguchi reagent (2,4,6-trichlorobenzoyl chloride) were examined under high dilution conditions (0.5 mM), fluorous tagged Mukaiyama reagent **8** was the most effective for the lactamization in terms of the yield and handling.

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