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Total Synthesis of Siomycin A: Completion of the Total Synthesis

Tomonori Mori, Shuhei Higashibayashi, Taiji Goto, Mitsunori Kohno, Yukiko Satouchi, Kazuyuki Shinko, Kengo Suzuki, Shunya Suzuki, Hiraku Tohmiya, Kimiko Hashimoto,* and Masaya Nakata*[a]

Abstract: The total synthesis of siomycin A (**1**), a representative compound of the thiostrepton family of peptide antibiotics, was achieved by incorporating the five synthetic segments A (**2**), B (**3**), C (**4**), D (**5**), and E (**6**). The dehydropiperidine segment A (**2**) was esterified with the dihydroquinoline segment C (**4**), and the subsequent coupling with the β-phenylselenoalanine dipeptide segment D (**5**) at the segment C portion followed by lactamization between the segments A and D gave segment A-C-D (**27**). This was amidated with the pentapeptide segment B (**3**) at the segment A portion followed by one-pot cyclization (between segments A and B) and elongation (with the β-phenylselenoalanine dipeptide segment E (**6**) at the segment A portion), thus furnishing siomycin A (**1**).

Keywords: cyclization · natural products · epoxides · siomycin A · total synthesis

Introduction

In the preceding article,[1] we described, as the early stage of the total synthesis of siomycin A (**1**), the construction of the five practical synthetic segments: the tetrasubstituted dehydropiperidine segment A (**2**), the pentapeptide segment B (**3**), the tetrasubstituted dihydroquinoline segment C (**4**), and the β-phenylselenoalanine dipeptide segments D (**5**) and E (**6**; Figure 1). In this article, the segment couplings and the completion of the total synthesis of siomycin A (**1**) are described.

[a] Dr. T. Mori, Dr. S. Higashibayashi,[+] T. Goto, M. Kohno, Y. Satouchi, K. Shinko, K. Suzuki, S. Suzuki, H. Tohmiya, Prof. Dr. K. Hashimoto,[++] Prof. Dr. M. Nakata
Department of Applied Chemistry
Faculty of Science and Technology
Keio University
3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522 (Japan)
Fax: (+81) 45-566-1551
E-mail: msynktxa@applc.keio.ac.jp

[+] Current address:
Research Center for Molecular-Scale Nanoscience
Institute for Molecular Science
Okazaki 444-8787 (Japan)

[++] Current address:
Kyoto Pharmaceutical University
1 Shichono-cho, Misasagi, Yamashina-ku, Kyoto 607-8412 (Japan)
Fax: (+81) 75-595-4763
E-mail: kimikoh@mb.kyoto-phu.ac.jp

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Results and Discussion

Intramolecular Epoxide Opening for the A-Ring Construction[2]

As already described in the preceding article,[1] our strategy for the total synthesis of siomycin A (**1**) is as follows. After the A-ring construction from three segments (segments A (**2**), C (**4**), and D (**5**)), it is coupled with segment B (**3**) followed by cyclization (lactamization) of the resulting coupling product and elongation of the side-chain segment E (**6**) onto the cyclization product (Figure 1). We anticipated as the first plan that the cyclic core segment A-C-D (A ring) could be obtained by an intramolecular epoxide-opening reaction of several epoxy amines having the masked dehydroalanine structures (for example, the L- and/or D-β-phenylselenoalanine substructures) or the dehydroalanine structure ($R^1, R^2 = R^3$, $R^4 = \pi$ bond; Figure 2).

To this end, we prepared the cyclization precursor **13** by the route shown in Scheme 1. Segment D (**5**)[1] was condensed with Bpoc-L-Val-OH (**7**)[3] (Bpoc = 1-(4-biphenyl)-1-methylethoxycarbonyl) using 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP)[4] and 1-hydroxy-7-azabenzotriazole (HOAt) to afford tripeptide **8** in 77% yield from the NHBoc (Boc = *tert*-butoxycarbonyl) derivative of **5**.[1] Deprotection of the 9-fluorenylmethyl (Fm) ester in **8** was realized using diethylamine[5] in CH_2Cl_2 to give acid **9** in 95% yield. On the other hand, segment A (**2**)[1] was treated with dilute trifluoroacetic acid (TFA)[3] in CH_2Cl_2 at room temperature for 0.5 h to produce amine **10** in 91% yield.

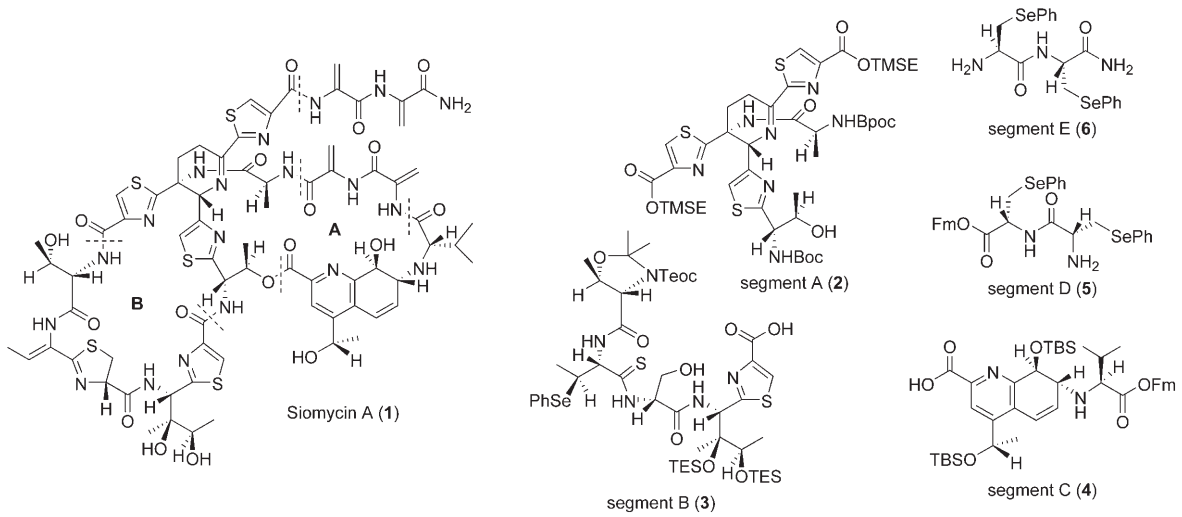

Figure 1. Siomycin A and its synthetic segments. Boc = *tert*-butoxycarbonyl, Bpoc = 1-(4-biphenyl)-1-methylethoxycarbonyl, TMSE = trimethylsilylethyl, TES = triethylsilyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl, TBS = *tert*-butyldimethylsilyl, Fm = 9-fluorenylmethyl.

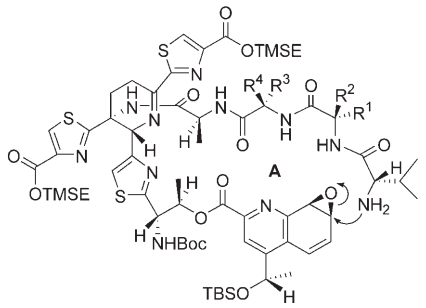

Figure 2. Intramolecular epoxide opening for the A-ring construction.

Condensation of acid **9** and amine **10** was conducted with 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[6] and *N*-methylmorpholine (NMM) in MeOH to afford **11** in 75% yield. The esterification of **11** with the epoxy–quinoline derivative **12**[1] was then examined. Using DCC–DMAP (DCC = 1,3-dicyclohexyl carbodiimide, DMAP = 4-(dimethylamino)pyridine), BOP-Cl–triethylamine–DMAP (BOP-Cl = *N*,*N*-bis(2-oxa-3-oxazolidinyl)phosphordiamidic chloride),[7] and BOP–triethylamine (BOP = benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate)[8] as the condensation reagents resulted in no reaction. In contrast, it was found that the CIP[4]–DMAP–*i*Pr$_2$NEt conditions were effective for this esterification, affording **13** in 84% yield.

Abstract in Japanese:

ペプチド性チオストレプトン系抗生物質シオマイシン A の全合成を、5 個のセグメント A ~ E の連結と 2 度の環化により達成した。すなわち、1) セグメント A、C の連結、2) D の連結、3) A–D 間でのラクタム環化、4) B の連結、5) one-pot による A–B 間でのラクタム環化と E の連結、によりシオマイシン A を全合成した。

Deprotection of the Bpoc group in **13** by Mg(ClO$_4$)$_2$[9] in acetonitrile at 40 °C for 1 h afforded the free amine, which was used for the intramolecular epoxide-opening reaction. Although extensive reaction conditions, for example, Lewis acid (LiClO$_4$,[10] Mg(ClO$_4$)$_2$,[10] LiOTf,[11] Yb(OTf)$_3$[12] (Tf = trifluoromethanesulfonyl)), solvent, and reaction temperature, were investigated, all efforts resulted in failure, either with no reaction or decomposition (probably aromatization after the epoxide opening) of **13**. Expecting a conformational change in the cyclization precursor, other substrates **14**,[13] **15**,[13] **16**,[13] and **17**[14] were prepared (Figure 3) and subjected to a variety of cyclization conditions after deprotection of the Bpoc group. Unfortunately, either no reaction or decomposition of the substrates occurred just as in the case of **13**.

Model Studies for Intermolecular Epoxide Opening with Amine[2]

Since the intramolecular epoxide opening for the A-ring construction was unsuccessful, we next investigated the intermolecular epoxide-opening reaction using the model quinoline epoxide **18**[15] (racemate) and L-Val-OBn **19** (Bn = benzyl) in the presence of several types of Lewis acids as an epoxide activator. The relevant experimental data are shown in Table 1. By our reported procedure[16] using LiClO$_4$,[10] a 1:1 mixture of the coupling product **20** (40% yield of isolated product as a 1:1 diastereomeric mixture) and the aromatized 8-hydroxyquinoline (**21**) were obtained (Table 1, entry 1). Other Lewis acids such as Ti(*i*PrO)$_4$,[17] Zn(OTf)$_2$,[10] Cu(OTf)$_2$,[18] and CeCl$_3$·7H$_2$O[19] were not effective for this coupling (Table 1, entries 2–5). In the case of Yb(OTf)$_3$, which had been used as a catalyst for the epoxide openings with amines by the Crotti[12a] and Yamamoto groups,[12b] the success depended on the solvent used. In CH$_2$Cl$_2$,[12] the reaction resulted in a decomposition (Table 1,

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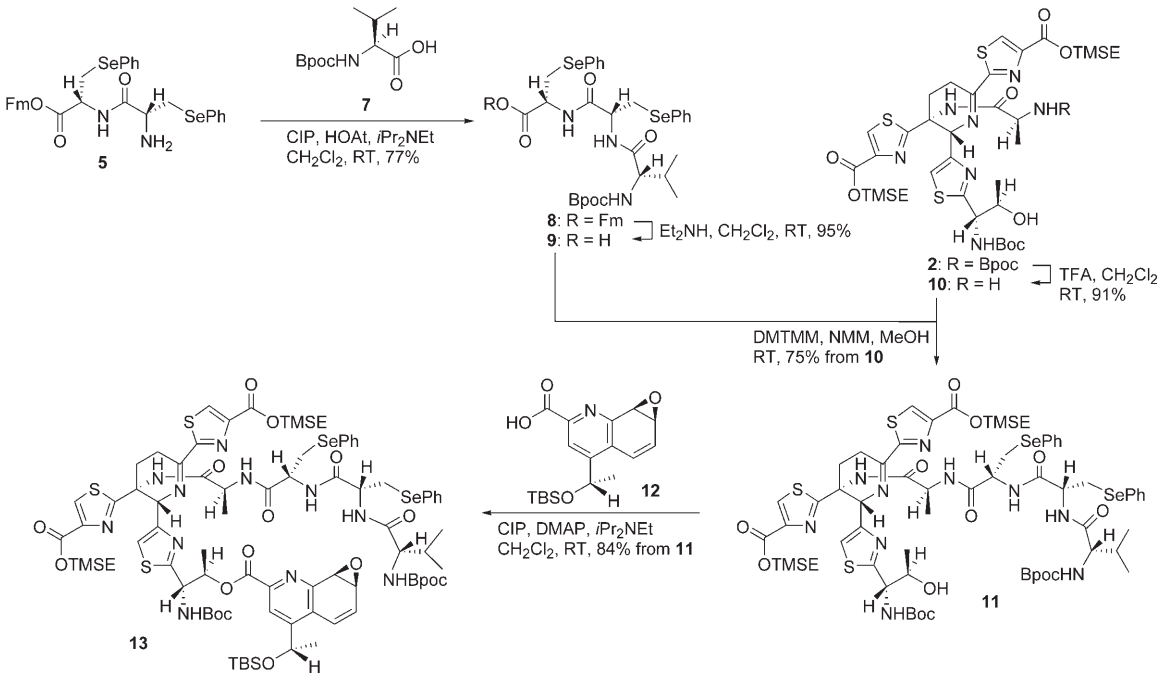
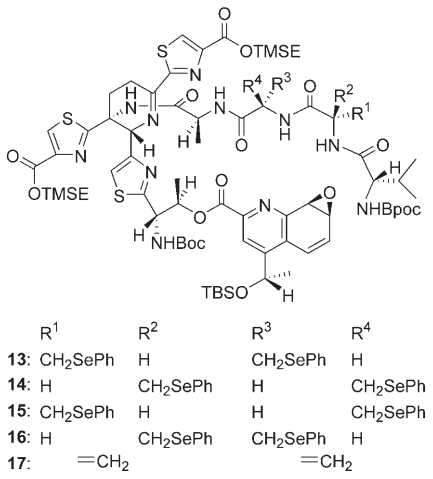


Scheme 1. Synthesis of precursor **13** for the A-ring cyclization. CIP = 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole, TFA = trifluoroacetic acid, DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, NMM = *N*-methylmorpholine, DMAP = 4-(dimethylamino)pyridine.

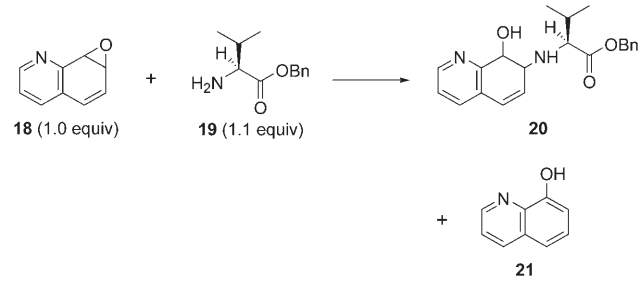


	R^1	R^2	R^3	R^4
13:	CH_2SePh	H	CH_2SePh	H
14:	H	CH_2SePh	H	CH_2SePh
15:	CH_2SePh	H	H	CH_2SePh
16:	H	CH_2SePh	CH_2SePh	H
17:	$=CH_2$		$=CH_2$	

Figure 3. Five precursors for the A-ring cyclization.

entry 6). In THF,[12b] compounds **20** and **21** were obtained in a 1:1 ratio (Table 1, entry 7). The best result so far obtained was when a 1:10 CH_2Cl_2–H_2O mixture was used as a biphasic solvent, affording **20** in 73% yield of isolated product without the formation of **21** (Table 1, entry 8). The presence of water seems to be crucial to this epoxide-opening reaction.[20] The substrates **18** and **19** dissolve in CH_2Cl_2, and Yb(OTf)$_3$ dissolves in water. This biphasic reaction medium seems to match our demand to softly activate epoxide **18**; the strong activation of **18** with a Lewis acid induces the formation of the aromatized **21**.

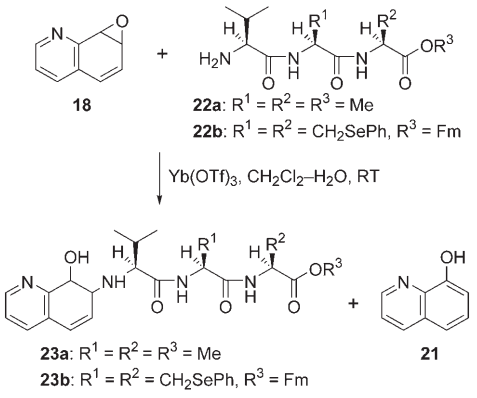
Table 1. Model studies for intermolecular epoxide opening.[a]



Entry	Lewis acid (equiv)	Solvent	*T* [°C]	*t* [h]	Ratio[b] of **20**/**21**/**18**
1	$LiClO_4$ (5.0)	CH_3CN	70	15	49:51:0[c]
2	Ti(*i*PrO)$_4$ (2.0)	THF	reflux	25	10:0:90
3	Zn(OTf)$_2$ (1.0)	CH_3CN	RT	22	decomp.
4	Cu(OTf)$_2$ (0.1)	CH_3CN	70	22	0:79:21
5	$CeCl_3 \cdot 7H_2O$ (0.5)	9:1 CH_3CN–H_2O	RT	22	no reaction
6	Yb(OTf)$_3$ (0.5)	CH_2Cl_2	RT	21	decomp.
7	Yb(OTf)$_3$ (0.1)	THF	reflux	30	30:30:40
8	Yb(OTf)$_3$ (0.2)	1:10 CH_2Cl_2–H_2O	RT	24	91:0:9[c]

[a] Bn = benzyl. [b] The ratio of **20**/**21**/**18** was based on ^{1}H NMR analysis of the crude products. [c] Yield of isolated **20** after silica-gel column chromatography was 40% (entry 1) and 73% (entry 8).

These results prompted us to investigate the coupling of **18** with tripeptide **22a**[21] (L-valine-L-alanine-L-alanine structure) and **22b**[21] (L-valine-L-β-phenylselenoalanine-L-β-phenylselenoalanine structure; Scheme 2). Quinoline epoxide

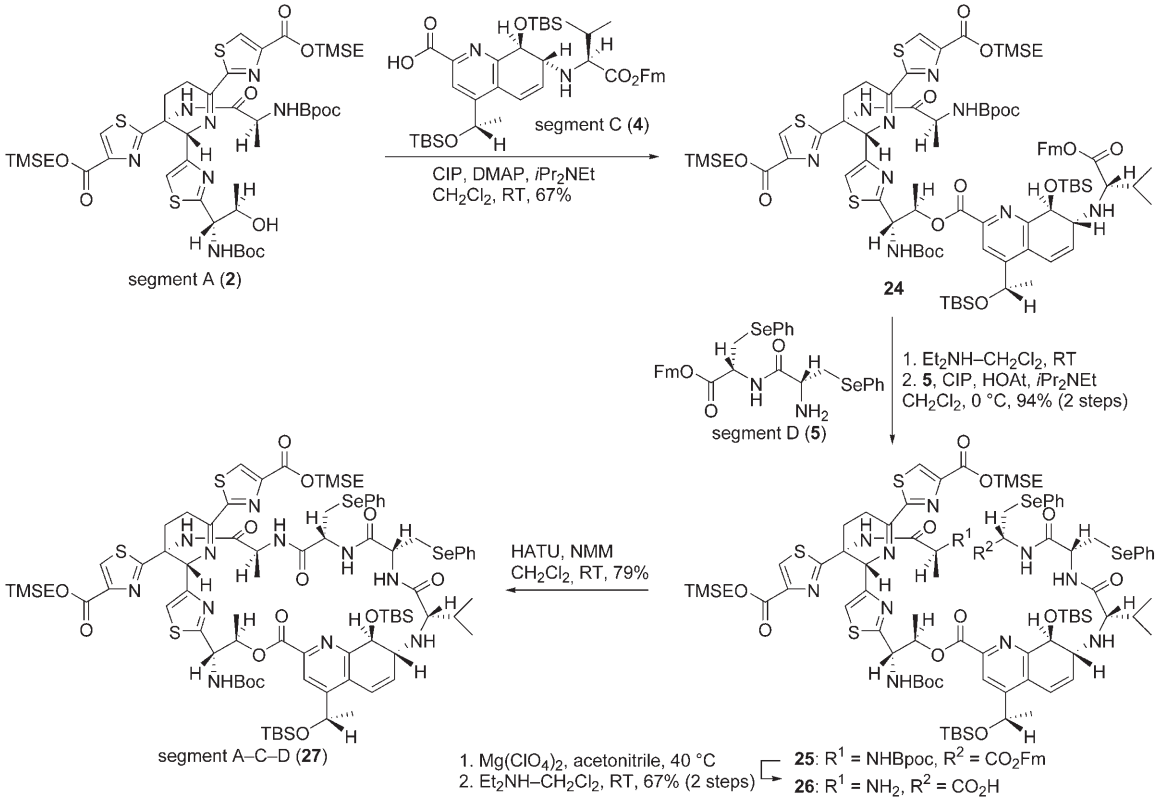


Scheme 2. Model studies for intermolecular epoxide opening with tripeptides.

18 (1.0 equiv) was treated with **22a** (1.1 equiv) in 1:10 CH_2Cl_2–H_2O in the presence of a catalytic amount (0.2 equiv) of $Yb(OTf)_3$ at room temperature for 48 h, giving a 76:9:15 mixture of **23a**, **21**, and **18**. In contrast, the coupling of **18** with **22b** under the same conditions afforded a 56:44 mixture of **21** and **18**; unfortunately, no **23b** was obtained. Therefore, we selected, as segment C, compound **4** (Figure 1), which was prepared by the epoxide opening with L-Val-OFm as already described in the preceding article.[1]

Synthesis of Segments A-C-D (27):[2] Successful A-Ring Construction

Condensation of 1.2 equiv of segment A (**2**)[1] and 1.0 equiv of segment C (**4**)[1] was realized with CIP,[4] DMAP, and iPr_2NEt in CH_2Cl_2 to give **24** in 67% yield (Scheme 3). After deprotection of the Fm ester in **24** with 1:1 diethylamine–CH_2Cl_2,[5] the resulting carboxylic acid (1.0 equiv) was coupled with 1.2 equiv of segment D (**5**)[1] with CIP,[4] HOAt, and iPr_2NEt in CH_2Cl_2 to give **25** in 94% yield from **24**. Deprotection of the Bpoc group in **25** with $Mg(ClO_4)_2$[9] in acetonitrile followed by deprotection of the Fm group[5] afforded the cyclization precursor **26** in 67% yield. The crucial cyclization into segment A-C-D (**27**) was carried out under a variety of condensation conditions, which are compiled in Table 2. Under the EDC–HOAt–NMM (EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) and PyBOP–iPr_2NEt[22] (PyBOP = benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate) conditions, the yield of isolated **27** was 49% in each case (Table 2, entries 1 and 2). The DPPA–iPr_2NEt[23] (DPPA = diphenylphosphoryl azide) conditions did not meet our demands, being accompanied by decomposition (19% yield of **27**, Table 2, entry 3). After investigating a variety of reaction conditions using 2-(1-oxy-7-azabenzotriazol-3-yl)-1,1,3,3-tetramethylguanidium hexafluorophosphate (HATU)[24] (i.e., base and solvent, Table 2, entries 4–8), we found that the best conditions were 5.0 equiv of HATU and 5.0 equiv of



Scheme 3. Synthesis of segment A-C-D (**27**). HATU = 2-(1-oxy-7-azabenzotriazol-3-yl)-1,1,3,3-tetramethylguanidium hexafluorophosphate.

Table 2. A-ring cyclization.[a]

26 → (RT) segment A–C–D (**27**)

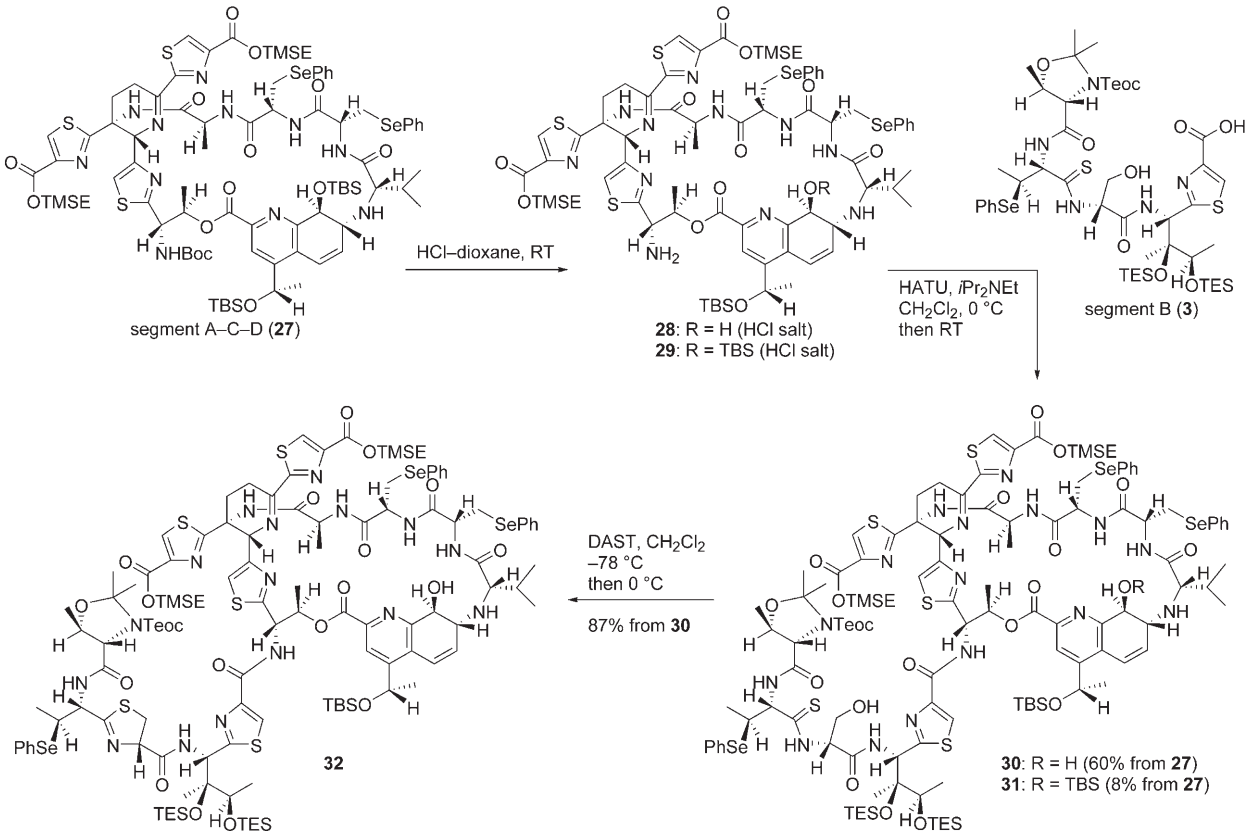
Entry	Reagents and solvent[b]	*t* [h]	Yield [%][c]
1	EDC, HOAt, NMM, DMF	25	49
2	PyBOP, *i*Pr$_2$NEt, CH_2Cl_2	45	49
3	DPPA, *i*Pr$_2$NEt, CH_2Cl_2	45	19[d]
4	HATU, 2,4,6-collidine, CH_2Cl_2	24	46
5	HATU, *i*Pr$_2$NEt, CH_2Cl_2	22	58
6	HATU, NMM, CH_2Cl_2	24	79
7	HATU, NMM, DMF	25	45
8	HATU, NMM, THF	45	14[d]

[a] EDC = 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride, PyBOP = benzotriazolyloxy-tris(pyrrolidino)-phosphonium hexafluorophosphate, DPPA = diphenylphosphoryl azide. [b] 5.0 equiv (for **26**) of each reagent and 1 mM (for **26**) solvent were used. [c] Yield of isolated product after silica-gel column chromatography. [d] Multispot on TLC.

NMM in CH_2Cl_2 at room temperature for 24 h, affording **27** in 79% yield (Table 2, entry 6). The structure of **27** was confirmed by the mass spectrum and the ^{1}H and ^{13}C NMR spectra, including H–H COSY, HMQC, and HMBC.

Completion of the Total Synthesis of Siomycin A (1)[25]

With segment A-C-D (**27**; A ring) in hand, we pursued the final goal. The Boc group in **27** was deprotected with 4 M HCl–dioxane to afford mono-*tert*-butyldimethylsilyl (TBS) ether **28** along with a small amount of di-TBS ether **29** (Scheme 4). It is noted that these compounds must be treated as the HCl salt because the corresponding free amines easily undergo O→N acyl-group migration at the segment A–C junction. This crude mixture was coupled with segment B (**3**)[1,26] using HATU[24] and *i*Pr$_2$NEt in CH_2Cl_2, giving **30** and its TBS ether **31** in 60% and 8% yields, respectively. We first attempted selectively deprotecting one of the two trimethylsilylethyl (TMSE) esters in **30**. It was anticipated that $ZnCl_2$, which had been used as a deprotection reagent for the 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group,[27] would be applicable to the deprotection of the TMSE ester, and additionally, the simultaneous deprotection of the Teoc and acetonide groups would occur. However, under the conditions of 100 equiv of $ZnCl_2$–ether in nitromethane at room temperature for 24 h, we could not realize this selective deprotection; the dicarboxylic acid and a mixture of the monocarboxylic acids were nonselectively obtained, although the Teoc and acetonide groups were smoothly cleaved.[26] In the total synthesis of thiostrepton, Nicolaou et al. also encountered the uncontrollable deprotection and B-ring cyclization sequence (Figure 4).[28] Bis-methyl ester **33** was treated with Me_3SnOH in 1,2-dichloroethane to afford an inseparable mixture (ca. 2:1) of monoacids (**34** + **35**) in 52% combined yield, accompanied by a 14% yield of diacid **36** and 28%



Scheme 4. Coupling of segment A-C-D (**27**) and segment B (**3**). DAST = diethylaminosulfur trifluoride.

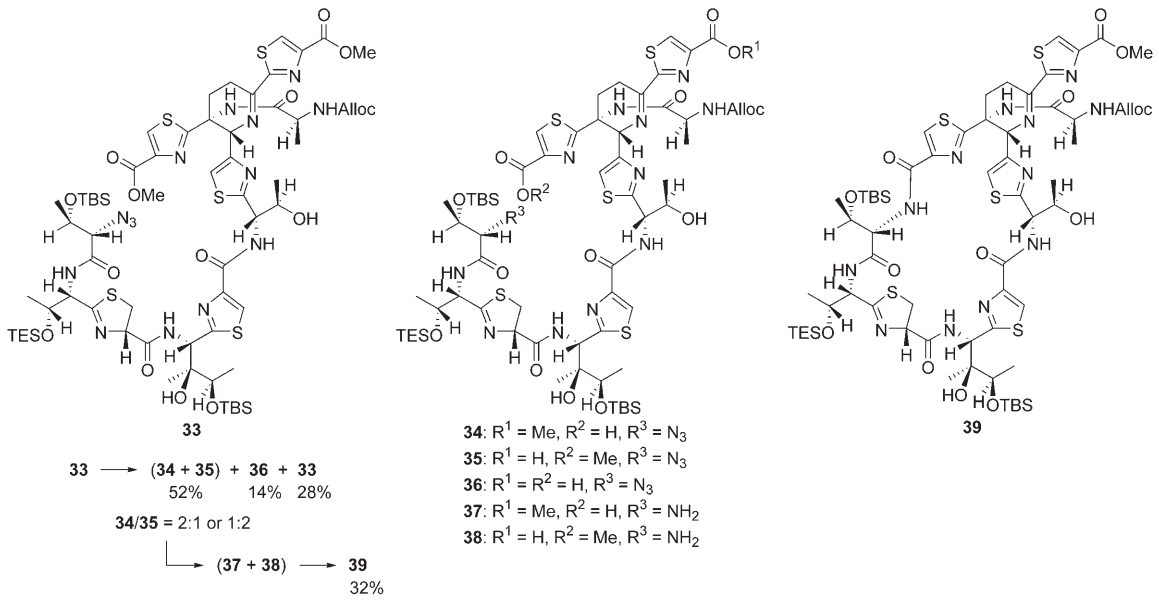
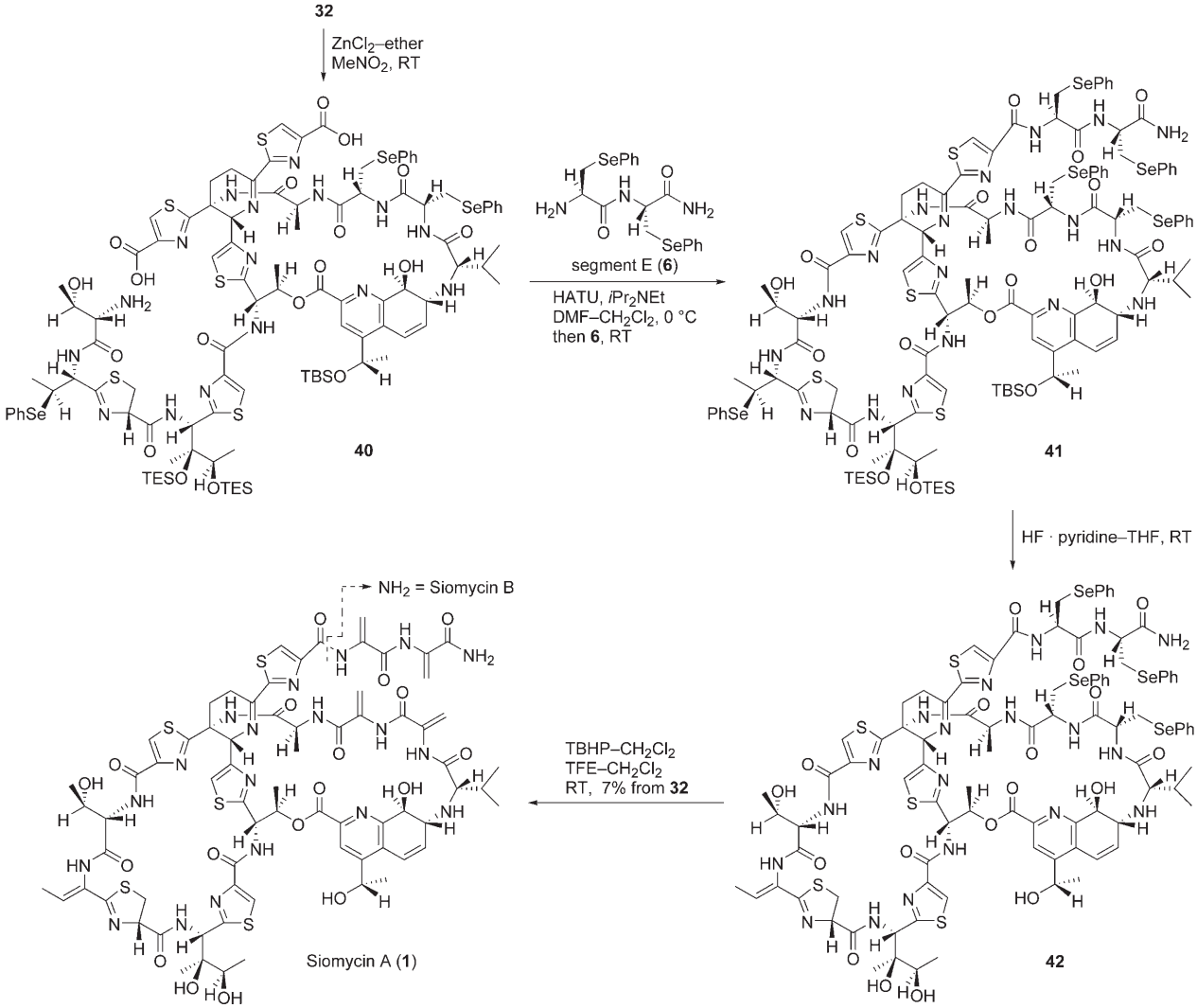


Figure 4. Uncontrollable deprotection and B-ring cyclization by the Nicolaou group. Alloc = allyloxycarbonyl.

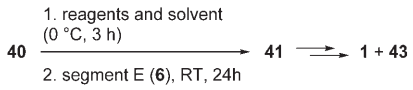
yield of the starting material **33**. Reduction of the azide group in this mixture (**34** + **35**) with PMe_3–H_2O led to the corresponding amino acids (**37** + **38**), which were cyclized by HATU–HOAt–iPr$_2$NEt to afford a single product **39** in 32% yield from acids **34** and **35**. They claimed that the undesired **38** was unable to cyclize upon activation, being instead consumed during the reaction through polymerization or decomposition pathway.

We then turned our attention to the regioselective cyclization–elongation of the dicarboxylic acid. Prior to this, **30** was first treated with diethylaminosulfur trifluoride (DAST)[1,26,29] in CH_2Cl_2 to give thiazoline **32** in 87% yield (Scheme 4). Deprotection of three kinds of protecting groups (Teoc, acetonide, and TMSE) in **32** was cleanly realized using 100 equiv of $ZnCl_2$–ether[27] in nitromethane at room temperature for 48 h, thus producing the cyclization–elongation precursor **40** (Scheme 5). The one-pot reaction was carried out under the conditions shown in Table 3. First (Table 3, entry 1), to a solution of 1.0 equiv of **40** in DMF (1 mM) were added at 0 °C EDC and HOAt. After 3 h at 0 °C, 5.0 equiv of segment E (**6**)[1] was added and the mixture was stirred at room temperature for 24 h, affording the crude products including **41** after removing the excess **6** by Sephadex LH-20 eluted with $CHCl_3$. Since the structure of **41** could not be confirmed at this stage, we further proceeded to the two-step transformation into siomycin A. These crude products were treated with HF·pyridine-THF (1:4)[28b,30] to afford the crude products including **42**, which were finally subjected to oxidative elimination with 4 M TBHP–CH_2Cl_2 (TBHP = *tert*-butyl hydroperoxide) in 1:5 TFE–CH_2Cl_2 (TFE = 2,2,2-trifluoroethanol) at room temperature for 1 h,[2,26,28b,30,31] giving siomycin A (**1**) in only 1% yield from **32**, along with 4% yield of the regioisomeric cyclization–elongation product **43** (Figure 5). The structure of **43** was tentatively assigned on the basis of the ^{1}H NMR and MS spectra. We next examined the HATU[24]–iPr$_2$NEt conditions in several solvents, that is, DMF (Table 3, entry 2), THF (Table 3, entry 3), dioxane (Table 3, entry 4), 1:4 DMF–CH_3CN (Table 3, entry 5), and 1:4 DMF–CH_2Cl_2 (Table 3, entry 6). The best conditions were entry 6, giving siomycin A (**1**) and its isomer **43** in 7% and 8% yields, respectively, from **32**. The synthetic siomycin A was identical to the natural siomycin A based on the ^{1}H NMR, ^{13}C NMR, IR, and MS spectra, TLC, and optical rotation. This four-step sequence (**32**→**1**) consists of 14 chemical transformations (deprotection of seven protecting groups, B-ring cyclization, elongation of segment E, *Z*-olefin formation, and oxidative dehydroselenation of four phenylselenoalanines); therefore, the 7% overall yield of **1** from **32** corresponds to an average of about 83% yield. It is noteworthy that the final two-step operation could not be reversed, in contrast to Nicolaou's thiostrepton synthesis,[28b,30] because it was found that siomycin A gradually changed into siomycin B,[32] which is the side-chain degradation product of siomycin A, under the HF·pyridine–THF (1:4) conditions (RT, during 24 h). In addition, when the model pentapeptide **44**[26] was subjected to the HF·pyridine–THF (1:4) conditions (RT, 4 h), the *Z* olefin **45** was obtained in 70% yield as the sole product (Scheme 6). The stereochemistry of **45** was confirmed by NOE analysis of the ^{1}H NMR spectrum, and additionally, by transformation with triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-lutidine into **46**, which was identical to the sample[26] derived from **44** by *syn* elimination using TBHP. These facts indicate that the dehydroselenation next to the thiazoline C2 position affords the thermodynamically stable *Z* olefin by equilibration that originated from the protonation of the nitrogen atom in the thiazoline ring, and therefore, account for the *Z* selectivity from **41** to **42**.



Scheme 5. Completion of the total synthesis of siomycin A (**1**). TBHP = *tert*-butyl hydroperoxide, TFE = 2,2,2-trifluoroethanol.

Table 3. One-pot cyclization–elongation of **40**.



Entry	Reagents[a]	Solvent[a]	Yield [%][b]	
			1	**43**
1	EDC, HOAt, iPr$_2$NEt	DMF	1	4
2	HATU, iPr$_2$NEt	DMF	2	18
3	HATU, iPr$_2$NEt	THF	0	3
4	HATU, iPr$_2$NEt	dioxane	3	0
5	HATU, iPr$_2$NEt	1:4 DMF–MeCN	4	8
6	HATU, iPr$_2$NEt	1:4 DMF–CH_2Cl_2	7	8

[a] 5.0 equiv (for **40**) of each reagent and 1 mM (for **40**) solvent were used. [b] Isolated yield (preparative TLC on silica gel) from **32** after conversion of the crude products including **41** to siomycin A (**1**) and its isomer **43** through further two steps.

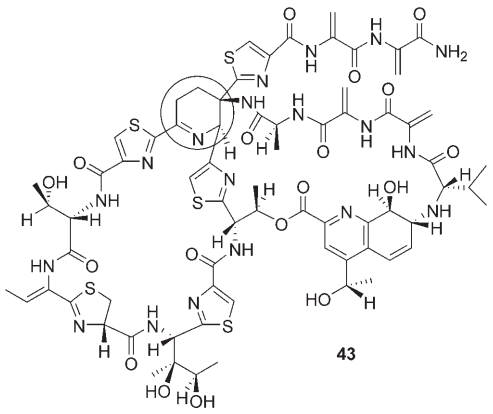
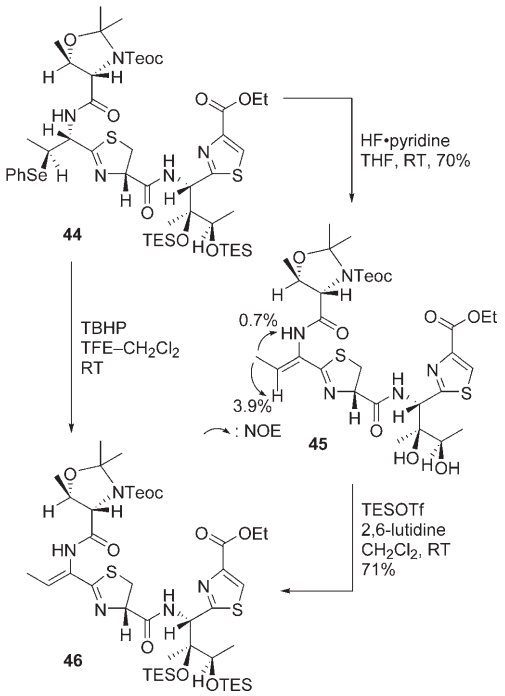


Figure 5. Structure of regioisomeric cyclization–elongation product **43**.



Scheme 6. Model studies for dehydroselenation.

Conclusions

We have succeeded in the total synthesis of siomycin A, a representative compound of the thiostrepton family of peptide antibiotics, by the coupling of the five practical synthetic segments: the tetrasubstituted dehydropiperidine segment A (**2**), the pentapeptide segment B (**3**), the tetrasubstituted dihydroquinoline segment C (**4**), and the β-phenylselenoalanine dipeptide segments D (**5**) and E (**6**). Because the intramolecular epoxide-opening reaction with the amino function for the synthesis of segment A-C-D (**27**) was a failure, segment A-C-D (**27**) was prepared by the condensation (esterification) of segment A (**2**) with segment C (**4**), which was derived from the epoxyquinoline derivative by the intermolecular epoxide opening with the L-valine derivative, followed by the coupling (amidation) with segment D (**5**) and cyclization (lactamization). The amidation of segment A-C-D (**27**) with segment B (**3**) and thiazoline formation afforded **32**. After deprotection of the Teoc, acetonide, and TMSE groups, the resulting diacid was subjected to a one-pot cyclization–elongation (with segment E (**6**)), deprotection, and oxidative elimination to furnish siomycin A (**1**).

Experimental Section

General

The melting points were determined on a micro-hot-stage Yanaco MP-S3 and were uncorrected. Optical rotations were measured on a JASCO DIP-360 polarimeter. IR spectra were recorded on a JASCO FT IR-200 spectrometer. ^{1}H and ^{13}C NMR spectra were measured on a JEOL GSX-270 spectrometer, a JEOL LAMBDA 300 spectrometer, a Varian MERCURY plus 300 spectrometer, or a Bruker AV-600 spectrometer. Chemical shifts of ^{1}H NMR spectra are expressed in ppm relative to TMS (0 ppm) in $CDCl_3$ or to the solvent residual signal $CDCl_3$ (7.26 ppm), CD_3CN (1.94 ppm), 4:1 $CDCl_3$–CD_3OD (7.38 ppm), or [D_8]THF (3.57 ppm) as an internal standard unless otherwise noted. Chemical shifts of ^{13}C NMR spectra are expressed in ppm relative to the solvent signal in $CDCl_3$ (77.00 ppm), CD_3CN (118.26 ppm), or [D_8]THF (24.55 ppm) as an internal standard unless otherwise noted. Low- and high-resolution mass spectra were recorded on a JEOL GCmate (EI and FAB) and JEOL Accu TOF JMS-T100 LCS (ESI). Silica-gel TLC and preparative TLC (PTLC) were performed on a Merck 60F-254. Silica-gel column chromatography was performed on a Fuji-Davison PSQ100B. Air- and/or moisture-sensitive reactions were carried out under an atmosphere of argon with oven-dried glassware. In general, the organic solvents were purified and dried by appropriate procedures, and evaporation and concentration were carried out under reduced pressure below 30 °C.

Tripeptide **8**: To a solution of amine **5** (416 mg, 6.41×10^{-1} mmol) in dry CH_2Cl_2 (6.4 mL) at 0 °C under Ar atmosphere were added *i*Pr_2NEt (0.274 mL, 1.57 mmol), Bpoc-L-Val-OH (**7**)[3] (251 mg, 7.06×10^{-1} mmol), HOAt (105 mg, 7.71×10^{-1} mmol), and CIP (215 mg, 7.71×10^{-1} mmol). After stirring at room temperature for 3 h, the reaction mixture was quenched with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (1 mL). The mixture was extracted with $CHCl_3$ (10 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (30% AcOEt/hexane) to afford tripeptide **8** (484 mg, 77% from the NHBoc derivative[1] of **5**) as a colorless foam: R_f=0.53 (40% AcOEt/hexane); $[\alpha]_D^{26}$ −17.5 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3295, 3060, 2965, 1700, 1650, 1505, 1485, 1200, 1145, 1100, 1020, 760, 740, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.81–7.68 (m, 2H, PhSe), 7.60–7.06 (m, 25H, Fm, biphenyl, and PhSe), 6.94 (br d, *J*=7.2 Hz, 1H, CONH), 6.64 (br d, *J*=7.0 Hz, 1H, CONH), 5.20 (br d, *J*=8.2 Hz, 1H, NHBpoc), 4.70 (m, 1H, PhSeAla H-α), 4.47 (m, 1H, PhSeAla H-α), 4.24 (dd, *J*=6.4, 9.8 Hz, 1H, Fm CH_2), 4.12–3.96 (m, 2H, Fm CH_2 and Fm H-9), 3.88 (m, 1H, Val H-α), 3.30–2.98 (m, 4H, PhSeAla H-β×4), 2.14 (m, 1H, Val H-β), 1.81 (s, 6H, Bpoc Me×2), 0.93 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.87 ppm (d, *J*=6.8 Hz, 3H, Val Me-β); ^{13}C NMR ($CDCl_3$): δ=171.21, 169.55, 169.25, 155.14, 145.10, 143.29, 143.21, 141.25, 141.19, 140.68, 139.76, 133.64, 132.85, 129.28, 129.13, 128.67, 127.86, 127.63, 127.47, 127.16, 127.12, 127.04, 124.98, 124.92, 124.65, 120.00, 81.31, 67.26, 59.91, 52.74, 52.54, 46.42, 30.66, 29.10, 28.95, 19.33, 17.47 ppm; HRMS (ESI): *m*/*z* $[M+Na]^+$ calcd for $C_{53}H_{53}N_3NaO_6{}^{80}Se_2$: 1010.2163; found: 1010.2155.

Model A-D (**11**): To a solution of **8** (83.3 mg, 8.45×10^{-2} mmol) in CH_2Cl_2 (0.42 mL) at 0 °C was added $HNEt_2$ (0.42 mL). The reaction mixture was stirred at room temperature for 1.5 h and then evaporated. The residue was chromatographed on silica gel (30%–50% acetone/hexane) to afford carboxylic acid **9** (64.7 mg, 95%) as a colorless foam. On the other hand, segment A (**2**; 21.3 mg, 1.90×10^{-2} mmol) was dissolved in 0.5% TFA–CH_2Cl_2 (0.190 mL) at 0 °C. After stirring at room temperature for 30 min, the reaction mixture was evaporated. To the residue was added H_2O (1 mL) and this was washed with hexane (1 mL×3). The aqueous layer was basified with saturated aqueous $NaHCO_3$ and the mixture was extracted with AcOEt (1 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (40% acetone/hexane) to afford amine **10** (15.2 mg, 91%) as a yellow foam. To a solution of amine **10** (17.9 mg, 2.03×10^{-2} mmol), carboxylic acid **9** (19.7 mg, 2.44×10^{-2} mmol), and NMM (0.0030 mL, 2.7×10^{-2} mmol) in MeOH (0.2 mL) at room temperature was added DMTMM (6.8 mg, 2.5×10^{-2} mmol). After stirring at room temperature for 2 h, the reaction mixture was quenched with H_2O (1 mL) and the mixture was extracted with AcOEt (2 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (50% AcOEt/hexane) to afford **11** (25.4 mg, 75% from **10**) as a yellow foam: R_f=0.87 (100% AcOEt); $[\alpha]_D^{25}$ −13.3 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3315, 2955, 1715, 1500, 1365, 1250, 1175, 1100, 1020, 935, 840, 765, 740, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=8.14 (s, 1H, thiazole H-5), 8.04 (br s, 1H, piperidine 5-NHCO), 7.85 (s, 1H, thiazole H-5), 7.60–7.11 (m, 20H, biphenyl, PhSe×2, and Ala CONH), 7.10–7.00 (m, 1H, PhSeAla CONH),

6.80–6.68 (m, 1H, PhSeAla CONH), 6.76 (s, 1H, thiazole H-5), 5.85 (brd, J=8.2 Hz, 1H, BocNH), 5.43 (brs, 1H, piperidine H-6), 5.27–5.06 (m, 1H, BpocNH), 4.88 (brd, J=8.8 Hz, 1H, Thr H-α), 4.67–4.55 (m, 1H, Thr H-β), 4.52–4.27 (m, 5H, PhSeAla H-α, $CH_2CH_2SiMe_3$×2), 4.27–4.09 (m, 2H, PhSeAla H-α and Ala H-α), 3.81–3.68 (m, 1H, Val H-α), 3.56–3.42 (m, 1H, piperidine H-4), 3.36–2.66 (m, 7H, piperidine H-4 and H-3×2, and PhSeAla H-β×4), 2.20–2.03 (m, 1H, Val H-β), 1.95 (brs, 1H, OH), 1.81 (s, 3H, Bpoc Me), 1.78 (s, 3H, Bpoc Me), 1.48 (s, 9H, Boc), 1.31–1.20 (m, 6H, Ala Me-α and Thr Me-β), 1.20–1.08 (m, 4H, $CH_2CH_2SiMe_3$×2), 0.93 (d, 3H, J=6.4 Hz, Val Me-β), 0.89 (d, 3H, J=6.4 Hz, Val Me-β), 0.08 (s, 9H, $CH_2CH_2SiMe_3$), 0.06 ppm (s, 9H, $CH_2CH_2SiMe_3$); ^{13}C NMR($CDCl_3$): δ=175.02, 172.01, 171.92, 170.12, 169.68, 169.32, 162.97, 161.45, 161.40, 155.76, 152.32, 148.00, 147.03, 144.66, 140.40, 139.97, 132.99, 132.73, 130.20, 129.52, 129.24, 128.73, 128.34, 127.86, 127.67, 127.37, 127.29, 127.07, 126.97, 124.64, 118.22, 82.05, 80.13, 68.33, 66.47, 63.76, 63.49, 60.80, 59.94, 57.79, 53.69, 53.13, 50.30, 49.89, 30.02, 29.25, 28.79, 28.34, 26.98, 24.67, 22.09, 20.10, 19.28, 18.27, 17.76, 17.39, −1.47 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{76}H_{98}N_{10}NaO_{13}S_3{}^{80}Se_2Si_2$: 1693.4244; found: 1693.4239.

Model A-C-D (**13**): To a solution of **11** (32.2 mg, 1.93×10^{-2} mmol), **12** (20.1 mg, 5.78×10^{-2} mmol), DMAP (14.1 mg, 1.15×10^{-1} mmol), and iPr$_2$NEt (0.0200 mL, 1.15×10^{-1} mmol) in CH_2Cl_2 (0.2 mL) at room temperature under Ar atmosphere was added CIP (16.1 mg, 5.78×10^{-2} mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with H_2O (1 mL). The mixture was extracted with $CHCl_3$ (1 mL×1) and AcOEt (1 mL×2). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (20% AcOEt/$CHCl_3$) to afford ester **13** (32.4 mg, 84% from **11**) as a yellow foam: R_f=0.57 (45% AcOEt/$CHCl_3$); $[\alpha]_D^{22}$ −11.6 (c 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 2855, 1720, 1500, 1365, 1300, 1255, 1160, 1100, 1040, 970, 935, 840, 780 cm^{-1}; ^{1}H NMR (CD_3CN, 50°C): δ=8.25 (s, 1H, quinoline H-3 or thiazole H-5), 8.15 (s, 1H, quinoline H-3 or thiazole H-5), 7.91 (brs, 1H, piperidine 5-NHCO), 7.70–7.03 (m, 24H, biphenyl, PhSe×2, quinoline H-5, CONH×3, and quinoline H-3 or thiazole H-5), 7.09 (s, 1H, thiazole H-5), 6.73 (dd, J=3.8, 10.0 Hz, 1H, quinoline H-6), 6.24 (brd, J=8.8 Hz, 1H, NHBoc), 5.87–5.67 (m, 1H, NHBpoc), 5.72 (dq, J=3.8, 6.2 Hz, 1H, Thr H-β), 5.56 (brs, 1H, piperidine H-6), 5.31 (q, J=6.2 Hz, 1H, CH_3CH(OTBS)), 5.25 (dd, J=3.8, 8.8 Hz, 1H, Thr H-α), 4.62 (d, J=3.8 Hz, 1H, quinoline H-8), 4.52–4.26 (m, 6H, PhSeAla H-α×2 and $Me_3SiCH_2CH_2$×2), 4.14 (ddd, J=1.6, 3.8, 3.8 Hz, 1H, quinoline H-7), 4.04 (dq, J=6.4, 6.4 Hz, 1H, Ala H-α), 3.84 (brs, 1H, Val H-α), 3.40–2.78 (m, 7H, PhSeAla H-β×2, piperidine H-3 and H-4), 2.57 (m, 1H, piperidine H-3 or H-4), 2.06 (m, 1H, Val H-β), 1.75 (s, 3H, Bpoc CH_3), 1.74 (s, 3H, Bpoc CH_3), 1.48–1.39 (m, 3H, Thr H-β), 1.43 (s, 9H, Boc), 1.36 (d, J=6.2 Hz, 3H, CH_3CH(OTBS)), 1.19 (d, J=6.4, 3H, Ala Me-α), 1.16–1.00 (m, 4H, $Me_3SiCH_2CH_2$×2), 0.98–0.86 (m, 6H, Val Me-β×2), 0.93 (s, 9H, tBu-Me_2Si), 0.09 and 0.05 (each s, 21H, $Me_3SiCH_2CH_2$×2 and tBuMe_2Si), −0.04 ppm (s, 3H, tBuMe_2Si); ^{13}C NMR (CD_3CN, 50°C): δ=176.62, 173.68, 173.43, 171.58, 171.26, 170.66, 164.48, 163.95, 162.19, 162.09, 156.74, 154.52, 154.39, 153.65, 149.15, 147.77, 147.13, 146.92, 141.60, 140.49, 133.70, 133.35, 131.58, 131.26, 131.14, 130.65, 130.51, 130.30, 129.97, 128.71, 128.46, 128.10, 127.98, 127.81, 127.57, 126.13, 126.08, 123.99, 120.00, 82.02, 81.11, 74.78, 68.40, 66.58, 64.37, 64.06, 61.78, 60.49, 59.28, 59.10, 58.33, 54.95, 54.33, 54.24, 52.19, 31.53, 30.44, 29.88, 29.54, 29.44, 29.17, 28.82, 28.62, 26.48, 26.44, 26.28, 25.81, 19.84, 18.93, 18.39, 18.17, 18.14, 18.05, 17.73, −1.22, −1.23, −4.35, −4.49 ppm; HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{94}H_{121}N_{11}NaO_{16}S_3{}^{80}Se_2Si_3$: 2022.5691; found: 2022.5674.

Compound A-C (**24**): To a solution of segment A (**2**; 25.0 mg, 2.24×10^{-2} mmol), segment C (**4**; 14.1 mg, 1.86×10^{-2} mmol), iPr$_2$NEt (0.0080 mL, 4.6×10^{-2} mmol), and DMAP (1.1 mg, 9.0×10^{-3} mmol) in dry CH_2Cl_2 (0.2 mL) at 0°C under Ar atmosphere was added CIP (6.2 mg, 2.2×10^{-2} mmol). After stirring at room temperature for 10 min, the reaction mixture was quenched with H_2O (1 mL) and the mixture was extracted with $CHCl_3$ (1 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (30% AcOEt/hexane) to afford **24** (23.2 mg, 67%) as a yellow foam: R_f=0.40 (30% AcOEt/hexane); $[\alpha]_D^{26}$ −15.1 (c 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 2860, 1725, 1490, 1365, 1250, 1100, 840, 780, 700 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 50°C): δ=8.51 (s, 1H, quinoline H-3 or thiazole H-5), 8.47 (s, 1H, piperidin 5-NHCO), 8.09 (s, 1H, quinoline H-3 or thiazole H-5), 7.83 (m, 2H, Ph), 7.70–7.20 (m, 19H, quinoline H-3 or thiazole H-5, thiazole H-5, Fm, biphenyl, NHBpoc, and NHBoc), 6.87 (d, J=9.8 Hz, 1H, quinoline H-5), 6.12 (dd, J=3.8, 9.8 Hz, 1H, quinoline H-6), 5.59 (m, 1H, Thr H-β), 5.47 (brs, 1H, piperidine H-6), 5.22 (q, J=6.4 Hz, 1H, CH(CH$_3$)OTBS), 5.13 (m, 1H, Thr-α), 4.67 (d, J=6.0 Hz, 1H, quinoline H-8), 4.56 (d, J=6.0 Hz, 2H, Fm CH_2), 4.46–4.18 (m, 5H, $Me_3SiCH_2CH_2$×2 and Fm H-9), 3.78 (m, 1H, Ala H-α), 3.37 (m, 1H, quinoline H-7), 3.32 (m, 1H, piperidine H-4), 3.10–2.76 (m, 2H, piperidine H-3), 3.02 (m, 1H, Val H-α), 2.55 (m, 1H, piperidine H-4), 1.68–1.45 (m, 1H, Val H-β), 1.54 and 1.52 (each s, 6H, Bpoc Me×2), 1.42–1.17 (m, 9H, Thr Me-β, Ala Me-α, and CH(CH$_3$)OTBS), 1.34 (brs, 9H, Boc), 1.14–0.96 (m, 4H, $Me_3SiCH_2CH_2$×2), 0.86 (s, 9H, $SiMe_2t$Bu), 0.79 (s, 9H, $SiMe_2t$Bu), 0.68 (d, J=6.4 Hz, 3H, Val Me-β), 0.62 (d, J=6.4 Hz, 3H, Val Me-β), 0.07 and 0.03 (each s, 24H, $Me_3SiCH_2CH_2$×2 and $SiMe_2t$Bu×2), −0.03 (s, 3H, $SiMe_2t$Bu), −0.08 ppm (s, 3H, $SiMe_2t$Bu); ^{13}C NMR ([D$_6$]DMSO, 50°C): δ=175.02, 173.70, 172.88, 168.77, 163.25, 162.09, 160.47, 160.36, 156.21, 151.99, 150.05, 146.84, 145.60, 145.56, 144.48, 143.47, 143.40, 140.64, 139.76, 138.27, 132.15, 131.19, 128.60, 127.92, 127.36, 127.02, 126.82, 126.74, 126.49, 126.31, 126.06, 124.60, 121.62, 121.49, 119.79, 119.76, 119.25, 79.84, 78.79, 73.98, 72.22, 66.38, 65.31, 64.89, 63.08, 62.65, 62.35, 58.85, 56.28, 55.67, 51.35, 46.38, 30.74, 30.39, 29.40, 27.84, 25.52, 25.44, 25.21, 18.65, 17.81, 17.76, 17.53, 16.97, 16.77, −1.65, −1.69, −4.42, −5.06, −5.26, −5.34 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{95}H_{129}{}^{13}CN_9O_{15}S_3Si_4$: 1879.7779; found: 1879.7780.

Compound A-C-D (**25**): To a solution of **24** (20.6 mg, 1.11×10^{-2} mmol) in CH_2Cl_2 (0.55 mL) at 0°C was added Et_2NH (0.55 mL). The reaction mixture was stirred at room temperature for 1 h and then evaporated. The residue was chromatographed on silica gel (30% acetone/hexane) to afford carboxylic acid (18.6 mg, quantitative yield) as a yellow foam. To a solution of this carboxylic acid (18.6 mg, 1.11×10^{-2} mmol), segment D (**5**; 8.6 mg, 1.33×10^{-2} mmol), iPr$_2$NEt (0.0050 mL, 2.9×10^{-2} mmol), and HOAt (1.8 mg, 1.3×10^{-2} mmol) in dry CH_2Cl_2 (0.11 mL) at 0°C under Ar atmosphere was added CIP (3.7 mg, 1.3×10^{-2} mmol). The reaction mixture was stirred at 0°C for 0.5 h and then at room temperature for 0.5 h. The mixture was quenched with H_2O (1 mL) and saturated aqueous $NaHCO_3$ (0.1 mL), and the mixture was extracted with $CHCl_3$ (1 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (40% AcOEt/hexane) to afford **25** (24.0 mg, 94%) as a yellow foam: R_f=0.69 (50% AcOEt/hexane); $[\alpha]_D^{24}$ −29.0 (c 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 2860, 1720, 1500, 1365, 1250, 1220, 1100, 930, 840, 780, 760, 740, 700 cm^{-1}; ^{1}H NMR ([D$_6$]DMSO, 50°C): δ=8.62 (d, J=7.4 Hz, 1H, PhSeAla CONH), 8.52 (s, 1H, quinoline H-3 or thiazole H-5), 8.48 (brs, 1H, piperidine 5-NHCO), 8.32 (d, J=8.4 Hz, 1H, PhSeAla CONH), 8.28 (s, 1H, quinoline H-3 or thiazole H-5), 8.10 (s, 1H, quinoline H-3 or thiazole H-5), 7.91–7.80 (m, 3H, PhSe), 7.68–7.12 (m, 27H, NHBpoc, NHBoc, biphenyl, Fm, PhSe×2 and thiazole H-5), 6.91 (d, J=10.2 Hz, 1H, quinoline H-5), 6.40 (dd, J=4.0, 10.2 Hz, 1H, quinoline H-6), 5.60 (m, 1H, Thr H-β), 5.47 (brs, 1H, piperidine H-6), 5.22 (q, J=6.2 Hz, 1H, CH(CH$_3$)OTBS), 5.14 (m, 1H, Thr H-α), 4.77–4.63 (m, 1H, PhSeAla H-α), 4.68 (d, J=5.8 Hz, 1H, quinoline H-8), 4.50–4.25 (m, 7H, PhSeAla H-α, Fm CH_2, and $Me_3SiCH_2CH_2$×2), 4.20 (dd, J=6.2, 6.2 Hz, 1H, Fm H-9), 3.78 (m, 1H, Ala H-α), 3.57 (m, 1H, quinoline H-7), 3.31–3.16 (m, 1H, PhSeAla H-β), 3.14–2.78 (m, 6H, PhSeAla H-β×3, Val H-α, and (piperidine H-3 or H-4)×2), 2.57 (m, 1H, piperidine H-3 or H-4), 2.23 (m, 1H, piperidine H-3 or H-4), 1.62 (m, 1H, Val H-β), 1.54 (s, 3H, Bpoc Me), 1.52 (s, 3H, Bpoc Me), 1.40–1.21 (m, 9H, CH(CH$_3$)OTBS, Ala Me, and Thr Me-β), 1.34 (brs, 9H, Boc), 1.16–0.94 (m, 4H, $Me_3SiCH_2CH_2$×2), 0.84 (s, 9H, $SiMe_2t$Bu), 0.82–0.71 (m, 6H, Val Me-β×2), 0.77 (s, 9H, $SiMe_2t$Bu), 0.07 and 0.04 (each s, 24H, $Me_3SiCH_2CH_2$×2 and $SiMe_2t$Bu×2), −0.04 (s, 3H, $SiMe_2t$Bu), −0.11 ppm (s, 3H, $SiMe_2t$Bu); ^{13}C NMR ([D$_6$]DMSO, 50°C): δ=175.05, 173.22, 172.89, 170.03, 169.74, 168.77, 163.30, 162.10, 160.49, 160.34, 156.35, 151.97, 149.93, 146.84, 145.62, 144.50, 143.28, 143.17, 140.60, 140.55, 139.76, 138.28, 131.92, 131.85, 131.80, 131.19, 129.78, 129.02, 128.94, 128.83, 128.60, 127.49, 127.02, 126.88, 126.64, 126.56, 126.33, 126.08, 124.86, 124.80, 124.60, 121.59,

121.06, 119.86, 119.27, 79.82, 78.79, 74.39, 72.17, 66.35, 65.97, 63.60, 62.65, 62.35, 62.29, 58.86, 55.85, 52.19, 52.14, 51.74, 51.35, 46.15, 31.06, 29.62, 29.40, 27.86, 27.26, 26.57, 25.55, 25.44, 25.19, 24.16, 19.22, 18.51, 17.77, 17.53, 17.08, 16.98, 16.77, −1.64, −1.69, −4.40, −5.11, −5.24, −5.32 ppm; LRMS (MALDI): *m/z* $[M+Na]^+$ calcd for $C_{114}H_{147}N_{11}NaO_{17}S_3{}^{80}Se_2Si_4$: 2332.7; found: 2332.9; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{114}H_{147}N_{11}NaO_{17}S_3{}^{80}Se_2Si_4$: 2332.7444; found: 2332.7452.

Amino acid A-C-D (**26**): To a solution of **25** (221 mg, 9.57×10^{-2} mmol) in dry CH_3CN (1.5 mL) under Ar atmosphere was added $Mg(ClO_4)_2$ (107 mg, 4.49×10^{-1} mmol). After stirring at 40 °C for 5.5 h, the reaction mixture was quenched with H_2O (3.0 mL) and saturated aqueous $NaHCO_3$ (0.5 mL), and the mixture was extracted with AcOEt (4 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford the crude amine as a yellow foam. To a solution of this crude amine in CH_2Cl_2 (1.4 mL) at 0 °C was added Et_2NH (0.15 mL). The reaction mixture was stirred at room temperature for 2.5 h and then evaporated. The residue was chromatographed on silica gel (100% AcOEt, 5% MeOH/$CHCl_3$) to afford **26** (122 mg, 67%) as a yellow foam: R_f = 0.36 (5% MeOH/$CHCl_3$); $[\alpha]_D^{24}$ −33.8 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2955, 2860, 2360, 1720, 1500, 1370, 1250, 1220, 1100, 935, 840, 780, 740, 695 cm^{-1}; ^1H NMR ([D$_6$]DMSO, 80 °C): δ = 8.47 (s, 1H, quinoline H-3 or thiazole H-5), 8.22 (brd, *J* = 8.0 Hz, 1H, PhSeAla CONH), 8.16–8.10 (m, 2H, PhSeAla CONH and piperidine 5-NHCO), 8.09 (s, 1H, quinoline H-3 or thiazole H-5), 7.98 (s, 1H, quinoline H-3 or thiazole H-5), 7.54–7.39 (m, 4H, PhSe), 7.32–7.17 (m, 7H, thiazole H-5 and PhSe), 7.04 (brd, *J* = 8.0 Hz, 1H, NHBoc), 6.87 (d, *J* = 9.8 Hz, 1H, quinoline H-5), 6.41 (dd, *J* = 4.4, 9.8 Hz, 1H, quinoline H-6), 5.60 (m, 1H, Thr H-β), 5.53 (brs, 1H, piperidine H-6), 5.24 (q, *J* = 6.2 Hz, 1H, CH(CH$_3$)OTBS), 5.16 (dd, *J* = 6.0, 8.0 Hz, 1H, Thr H-α), 4.69 (d, *J* = 5.2 Hz, 1H, quinoline H-8), 4.76–4.58 (m, 1H, PhSeAla H-α), 4.48–4.27 (m, 5H, PhSeAla H-α and $Me_3SiCH_2CH_2$ × 2), 3.58 (m, 1H, quinoline H-7), 3.46 (q, *J* = 6.8 Hz, 1H, Ala H-α), 3.39–2.80 (m, 8H, PhSeAla H-β × 2, Val H-α, piperidine H-3 and H-4), 2.69–2.55 (m, 1H, piperidine H-3 or H-4), 1.69 (m, 1H, Val H-β), 1.42–1.23 (m, 6H, Thr H-γ and CH(CH$_3$)OTBS), 1.37 (brs, 9H, Boc), 1.20 (d, *J* = 6.8 Hz, 3H, Ala Me-β), 1.16–1.00 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 0.87 (s, 9H, SiMe$_2$*t*Bu), 0.84–0.72 (m, 6H, Val Me-β × 2), 0.78 (s, 9H, SiMe$_2$*t*Bu), 0.09 and 0.06 (each s, 24H, $Me_3SiCH_2CH_2$ × 2 and SiMe$_2$*t*Bu × 2), −0.05 (s, 3H, SiMe$_2$*t*Bu), −0.07 ppm (s, 3H, SiMe$_2$*t*Bu); ^{13}C NMR ([D$_6$]DMSO, 80 °C): δ = 174.92, 174.46, 173.10, 170.89, 169.49, 169.07, 168.65, 163.10, 162.03, 160.28, 156.05, 154.43, 151.93, 149.82, 146.79, 145.58, 144.46, 133.01, 131.74, 131.53, 130.85, 129.93, 129.71, 128.69, 128.64, 127.60, 126.37, 126.33, 121.25, 120.78, 118.78, 78.80, 74.22, 71.78, 65.99, 65.31, 63.67, 62.45, 62.15, 58.63, 55.78, 52.53, 52.08, 49.99, 30.86, 29.51, 28.63, 27.72, 26.41, 25.38, 25.33, 25.28, 24.98, 24.27, 19.76, 19.05, 18.13, 17.53, 17.35, 16.65, 16.32, −1.83, −1.86, −4.63, −5.25, −5.49 ppm; LRMS (MALDI): *m/z* $[M+Na]^+$ calcd for $C_{84}H_{123}N_{11}NaO_{15}S_3{}^{80}Se_2Si_4$: 1916.6; found: 1916.5; HRMS: (ESI) *m/z* $[M+Na]^+$ calcd for $C_{84}H_{123}N_{11}NaO_{15}S_3{}^{80}Se_2Si_4$: 1916.5667; found: 1916.5691.

Segment A-C-D (**27**): To a solution of **26** (122 mg, 6.44×10^{-2} mmol) and NMM (0.0354 mL, 3.22×10^{-1} mmol) in CH_2Cl_2 (64 mL) at 0 °C under Ar atmosphere was added HATU (122 mg, 3.21×10^{-1} mmol). After stirring at room temperature for 24 h, the reaction mixture was quenched with H_2O (30 mL) and the mixture was extracted with $CHCl_3$ (30 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (50% AcOEt/hexane) to afford segment A-C-D (**27**; 95.5 mg, 79%) as a yellow foam: R_f = 0.49 (50% AcOEt/hexane); $[\alpha]_D^{27}$ −85.2 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 2955, 2895, 2860, 2360, 1720, 1500, 1480, 1405, 1255, 1220, 1095, 840, 780, 695 cm^{-1}; ^1H NMR (CD_3OD, 40 °C): δ = 8.28 (s, 1H, quinoline H-3), 8.26 (s, 1H, thiazole H-5), 7.94 (s, 1H, thiazole H-5), 7.53–7.40 (m, 4H, PhSe), 7.30–7.12 (m, 6H, PhSe), 7.27 (s, 1H, thiazole H-5), 6.89 (d, *J* = 10.0 Hz, 1H, quinoline H-5), 6.40 (dd, *J* = 5.4, 10.0 Hz, 1H, quinoline H-6), 5.85 (m, 1H, Thr H-β), 5.52 (brs, 1H, piperidine H-6), 5.31 (q, *J* = 6.2 Hz, 1H, CH(CH$_3$)OTBS), 5.21 (m, 1H, Thr H-α), 4.94 (brs, 1H, quinoline H-8), 4.74–4.60 (m, 2H, PhSeAla H-α × 2), 4.52–4.33 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 4.20 (q, *J* = 7.0 Hz, 1H, Ala H-α), 3.52–2.68 (m, 9H, PhSeAla H-β, piperidine H-3, H-4, and Val H-α), 3.38 (dd, *J* = 1.2, 5.4 Hz, 1H, quinoline H-7), 2.01 (brs, 1H, Val H-β), 1.40 (d, *J* = 6.2 Hz, 3H, CH(CH$_3$)OTBS), 1.40 (d, *J* = 6.2 Hz, 3H, Thr Me-β), 1.33 (s, 9H, Boc), 1.30 (d, *J* = 7.0 Hz, 3H, Ala Me), 1.20–1.04 (m, 4H, $Me_3SiCH_2CH_2$), 0.98 (d, *J* = 7.0 Hz, 3H, Val Me-β), 0.95 (s, 9H, SiMe$_2$*t*Bu), 0.81 (d, *J* = 6.8 Hz, 3H, Val Me-β), 0.69 (s, 9H, SiMe$_2$*t*Bu), 0.10 and 0.08 (each s, 24H, $Me_3SiCH_2CH_2$ × 2 and SiMe$_2$*t*Bu × 2), −0.01 (s, 3H, SiMe$_2$*t*Bu), −0.30 ppm (s, 3H, SiMe$_2$*t*Bu); ^{13}C NMR (CD_3OD, 40 °C): δ = 176.55, 176.34, 175.14, 172.43, 171.13, 170.75, 165.85, 164.55, 162.84, 156.91, 156.85, 153.77, 152.49, 149.01, 148.05, 146.55, 134.21, 133.89, 132.36, 132.02, 131.60, 130.28, 130.20, 128.92, 128.44, 128.21, 128.09, 123.74, 122.94, 120.98, 81.55, 74.02, 73.08, 68.45, 67.77, 67.68, 67.29, 64.71, 64.59, 61.46, 61.29, 54.95, 52.63, 32.78, 30.40, 28.94, 28.85, 28.15, 26.44, 26.24, 25.95, 19.83, 19.10, 18.86, 18.29, 18.16, 17.98, −1.36, −1.41, −3.98, −4.15, −4.58, −4.65 ppm; LRMS (MALDI): *m/z* $[M+Na]^+$ calcd for $C_{84}H_{121}N_{11}O_{14}NaS_3{}^{80}Se_2Si_4$: 1898.6; found: 1898.5; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{84}H_{121}N_{11}NaO_{14}S_3{}^{80}Se_2Si_4$: 1898.5562; found: 1898.5578.

Compound A-B-C-D (**30**) and its TBS ether **31**: Segment A-C-D (**27**; 110 mg, 0.0587 mmol) was dissolved in 4.0 M HCl in dioxane (1.2 mL). After stirring at room temperature for 25 min, the reaction mixture was evaporated to afford a mixture of **28** and **29**. To a solution of this mixture in dry CH_2Cl_2 (1.8 mL) at 0 °C under Ar atmosphere were successively added *i*Pr$_2$NEt (0.0511 mL, 0.293 mmol), segment B (**3**; 64.7 mg, 0.0586 mmol), and HATU (22.3 mg, 0.0586 mmol). The reaction mixture was stirred at 0 °C for 0.5 h and at room temperature for 6 h. The reaction mixture was quenched with H_2O (3 mL) and extracted with $CHCl_3$ (4 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (50% AcOEt/hexane) to afford **30** (95.9 mg, 60%) as a pale yellow foam and **31** (13.2 mg, 8%) as a pale yellow foam. **30**: R_f = 0.27 (50% AcOEt/hexane); $[\alpha]_D^{26}$ −16.6 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$ = 3340, 2955, 2880, 1680, 1500, 1415, 1345, 1250, 1210, 1120, 1095, 940, 860, 840, 740, 695 cm^{-1}; ^1H NMR (CD_3CN, 50 °C): δ = 8.87 (brs, 1H), 8.25 (brd, *J* = 6.8 Hz, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 8.02 (s, 1H), 7.98 (brs, 1H), 7.89 (s, 1H), 7.73 (brd, *J* = 6.4 Hz, 1H), 7.65 (brd, *J* = 8.5 Hz, 1H), 7.60–7.37 (m, 7H), 7.33–7.02 (m, 11H), 7.16 (s, 1H), 6.77 (d, *J* = 9.8 Hz, 1H), 6.36 (dd, *J* = 6.0, 9.8 Hz, 1H), 5.89 (brs, 1H), 5.66–5.48 (m, 1H), 5.55 (brs, 1H), 5.32 (d, *J* = 8.5 Hz, 1H), 5.14 (dq, *J* = 4.4, 6.2 Hz, 1H), 5.06 (m, 1H), 4.89 (brs, 1H), 4.76 (m, 1H), 4.73 (brs, 1H), 4.51 (m, 1H), 4.46–4.26 (m, 4H), 4.24–3.96 (m, 6H), 3.96–3.76 (m, 3H), 3.76–3.64 (m, 2H), 3.40–3.13 (m, 3H), 3.28 (d, *J* = 6.0 Hz, 1H), 3.13–2.90 (m, 5H), 2.62–2.47 (m, 1H), 2.16–2.00 (m, 1H), 1.57 (s, 3H), 1.53 (s, 3H), 1.43 (d, *J* = 6.2 Hz, 3H), 1.38–1.24 (m, 9H), 1.21–1.00 (m, 15H), 0.98–0.78 (m, 21H), 0.76–0.50 (m, 15H), 0.66 (s, 9H), 0.07, 0.03, and −0.02 (each s, 30H), −0.27 ppm (s, 3H); ^{13}C NMR (CD_3CN, 50 °C): δ = 202.93, 176.32, 174.72, 173.89, 171.65, 171.37, 170.77, 170.55, 169.84, 165.67, 163.94, 162.22, 162.08, 156.34, 153.41, 152.50, 149.33, 149.21, 147.98, 146.78, 135.68, 133.72, 133.57, 132.28, 131.80, 130.85, 130.44, 130.39, 130.17, 129.13, 128.93, 128.32, 128.22, 127.93, 122.89, 122.65, 121.18, 95.98, 80.22, 75.54, 74.59, 73.44, 72.87, 68.87, 68.32, 67.14, 65.72, 64.40, 64.23, 62.14, 61.42, 60.85, 57.49, 54.53, 53.49, 51.81, 43.20, 32.51, 30.84, 29.77, 28.64, 27.85, 26.40, 25.71, 25.38, 20.50, 20.12, 18.89, 18.69, 18.56, 18.26, 18.21, 17.92, 7.83, 7.67, 6.25, −1.14, −1.17, −3.68, −3.97 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{120}H_{178}N_{16}NaO_{21}S_5{}^{80}Se_3Si_6$: 2769.7965; found: 2769.7969. **31**: R_f = 0.50 (50% AcOEt/hexane); ^1H NMR (CD_3CN, 50 °C): δ = 8.80 (m, 1H), 8.16 (brs, 2H), 8.05–7.93 (m, 1H), 8.00 (brs, 2H), 7.93–7.82 (m, 1H), 7.68–7.40 (m, 8H), 7.37–7.17 (m, 12H), 7.08 (brs, 1H), 6.84 (brd, *J* = 9.8 Hz, 1H), 6.42 (brdd, *J* = 5.4, 9.8 Hz, 1H), 5.76 (dd, *J* = 7.0, 7.5 Hz, 1H), 5.62 (brq, *J* = 7.0 Hz, 1H), 5.58 (m, 1H), 5.34 (brd, *J* = 8.4 Hz, 1H), 5.26 (q, *J* = 6.5 Hz, 1H), 5.05–4.91 (m, 1H), 4.91–4.73 (m, 4H), 4.55 (m, 1H), 4.48–4.30 (m, 5H), 4.22–3.67 (m, 7H), 3.66 (m, 1H), 2.96–2.38 (m, 9H), 2.64–2.46 (m, 1H), 2.10–1.84 (m, 1H), 1.59 (s, 3H), 1.56 (s, 3H), 1.43–0.82 (m, 48H), 0.92 (s, 9H), 0.79 (d, *J* = 6.8 Hz, 3H), 0.70–0.51 (m, 12H), 0.63 (s, 9H), 0.10, 0.06, and −0.01 (each s, 36H), −0.32 (s, 3H).

Thiazoline **32**: To a solution of **30** (16.3 mg, 0.00593 mmol) in dry CH_2Cl_2 (0.5 mL) at −78 °C under Ar atmosphere was added 0.076 M DAST in dry CH_2Cl_2 (0.125 mL, 0.00950 mmol). The reaction mixture was stirred at −78 °C for 1 h and then at 0 °C for 1 h. The mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the mixture was extracted with $CHCl_3$ (1 mL × 3). The combined extracts were dried over Na_2SO_4, fil-

tered through celite, and evaporated. The residue was chromatographed on silica gel (45% AcOEt/hexane) to afford thiazoline **32** (14.1 mg, 87%) as a yellow foam: R_f=0.27 (50% AcOEt/hexane); ^{1}H NMR ($CDCl_3$): δ=8.27 (brd, J=7.2 Hz, 1H), 8.15 (brs, 1H), 8.10 (s, 1H), 8.01 (brs, 1H), 7.91 (d, J=8.8 Hz, 1H), 7.76–7.65 (m, 2H), 7.64–7.10 (m, 19H), 6.97 (brs, 1H), 6.75 (d, J=10.0 Hz, 1H), 6.70 (m, 1H), 6.28 (dd, J=6.0, 10.0 Hz, 1H), 5.88 (m, 1H), 5.81–5.60 (m, 1H), 5.48 (d, J=8.8 Hz, 1H), 5.24–5.07 (m, 1H), 5.11 (brdd, J=5.4, 6.8 Hz, 1H), 5.02 (dd, J=10.2, 10.2 Hz, 1H), 4.71 (m, 1H), 4.63 (brs, 1H), 4.54–4.01 (m, 9H), 3.98–3.67 (m, 3H), 3.58–2.90 (m, 11H), 2.72 (m, 1H), 2.36 (brs, 1H, Val-β), 1.65 (brs, 3H, IP), 1.60 (brs, 3H, IP), 1.56 (d, J=6.0 Hz, 3H), 1.50 (d, J=7.0 Hz, 3H), 1.41 (d, J=6.0 Hz, 3H), 1.35 (m, 3H), 1.30–1.18 (m, 9H), 1.18–0.80 (m, 27H), 0.74–0.47 (m, 15H), 0.66 (s, 9H, *t*BuMe$_2$Si), 0.08, 0.04, and −0.01 (each s, 30H, Me$_3$SiCH$_2$CH$_2$×3 and *t*BuMe$_2$Si), −0.36 (s, 3H *t*BuMe$_2$Si).

Siomycin A: To a solution of thiazoline **32** (14.5 mg, 0.00531 mmol) in CH_3NO_2 (0.27 mL) at 0°C under Ar atmosphere was added 1.0 M $ZnCl_2$ in ether (0.54 mL, 0.54 mmol). After stirring at room temperature for 48 h, the reaction mixture was quenched with H_2O (2 mL) and the mixture was extracted with AcOEt (3 mL×3). The combined extracts were washed with 0.01 M aqueous HCl (5 mL×3). The organic layers were dried over Na_2SO_4, filtered through celite, and evaporated to afford the crude dicarboxylic acid **40** (12.7 mg). To a solution of this crude dicarboxylic acid **40** (12.7 mg) in DMF–CH_2Cl_2 (1:4, 5.4 mL) at 0°C under Ar atmosphere were added 0.57 M *i*Pr$_2$NEt in DMF (0.0475 mL, 0.0271 mmol) and HATU (10.3 mg, 0.0271 mmol). The reaction mixture was stirred at 0°C for 3 h and then segment E (**6**; 12.7 mg, 0.0271 mmol) was added at 0°C. After stirring at room temperature for 24 h, the reaction mixture was quenched with 0.01 M aqueous HCl (4 mL) and the mixture was extracted with AcOEt (4 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was separated by gel filtration (Sephadex LH-20, $CHCl_3$) to afford the crude products (16.4 mg) including the bicyclic peptide **41**. To a solution of these crude products (16.4 mg) in dry THF (1.4 mL) at 0°C under Ar atmosphere was added HF·pyridine (0.36 mL). After stirring at room temperature for 20 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the mixture was extracted with AcOEt (30 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford the crude products (11.5 mg) including pentaol **42**. To a solution of these crude products (11.5 mg) in TFE–CH_2Cl_2 (1:5, 1.7 mL) at 0°C was added 3.98 M TBHP in CH_2Cl_2 (0.76 mL, 3.02 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (2 mL). The resulting solution was stirred at 0°C for 0.5 h and extracted with AcOEt (4 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was washed with hexane (1 mL×3) and purified by PTLC on silica gel (10% MeOH/$CHCl_3$) to afford siomycin A (**1**; 0.6 mg, 7% from **32**) as pale yellow solids and the regioisomeric cyclization–elongation product **43** (0.7 mg, 8% from **32**) as pale yellow solids.

Siomycin A (natural): R_f=0.57 (10% MeOH/$CHCl_3$); $[\alpha]_D^{26}$ −88.8 (c 0.10, dioxane); IR (KBr): $\tilde{\nu}$=3375, 2975, 2930, 1650, 1520, 1490, 1210, 1120, 1095, 935, 895, 810, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$, ca. 0.5 mM): δ=9.98 (brs, 1H, Deala-S-1 CONH), 9.83 (brs, 1H, ThstA CONH), 9.20 (brs, 1H, Deala-2 CONH), 8.99 (brs, 1H, Deala-S-2 CONH), 8.60 (brs, 1H, Deala-1 CONH), 8.48 (brs, 1H, Debut CONH), 8.29 (s, 1H, Thstn Thz-4 H-5), 8.25 (s, 1H, ThstA Thz-1 H-5), 8.11 (s, 1H, ThstA Thz-2 H-5), 7.56 (brd, J=9.4 Hz, 1H, Thstn CONH), 7.44 (s, 1H, ThstA Thz-3 H-5), 7.40 (brs, 1H, Q H-3), 6.95 (d, J=10.0 Hz, 1H, Q H-5), 6.89 (brs, 1H, Thr-1 CONH), 6.80 (d, J=2.0 Hz, 1H, Deala-S-1 H-β(t)), 6.71 (d, J=1.8 Hz, 1H, Deala-S-2 H-β(t)), 6.44 (brs, 1H, Deala-2 H-β(t)), 6.41 (m, 1H, Thr-2 H-β), 6.40 (m, 1H, Q H-6), 6.39 (m, 1H, Ala-1 CONH), 6.20 (q, J=7.0 Hz, 1H, Debut H-β), 5.84 (d, J=9.2 Hz, 1H, Thr-2 H-α), 5.75 (d, J=9.4 Hz, 1H, Thstn H-α), 5.73 (brs, 1H, Deala-1 H-β(t)), 5.57 (brs, 1H, Deala-S-1 H-β(c)), 5.45 (brs, 1H, Deala-S-2 H-β(c)), 5.34 (bq, J=6.6 Hz, 1H, Q H-11), 5.18 (brs, 1H, Deala-2 H-β(c)), 5.18 (brs, 1H, ThstA piperidine H-6), 5.15 (brs, 1H, Deala-1 H-β(c)), 4.96 (dd, J=8.4, 13.2 Hz, 1H, (+)-Cys H-α), 4.77 (dq, J=6.2, 7.5 Hz, 1H, Ala-1 H-α), 4.47 (dd, J=3.0, 8.2 Hz, 1H, Thr-1 H-α), 4.11 (m, 1H, ThstA piperidine H-4e), 3.79 (brq, J=6.2 Hz, 1H, Thstn H-γ), 3.71 (dd, J=8.4, 11.4 Hz, 1H, (+)-Cys H-β′), 3.61 (d, J=4.8 Hz, 1H, Q H-7), 3.48 (m, 1H, ThstA piperidine H-3e), 3.12 (dd, J=11.4, 13.2 Hz, 1H, (+)-Cys H-β), 2.98 (m, 1H, ThstA piperidine H-3a), 2.96 (m, 1H, Val H-α), 2.27(m, 1H, ThstA piperidine H-4a), 2.22 (m, 1H, Val H-β), 1.69 (m, 3H, Thr-2 Me-β), 1.62 (d, J=7.0 Hz, 3H, Debut Me-β), 1.48 (d, J=6.2 Hz, 3H, Ala-1 Me), 1.37 (d, J=6.6 Hz, 3H, Q 11-Me), 1.34 (d, J=6.2 Hz, 3H, Thstn Me-γ), 1.25 (m, 1H, Thr-1 H-β), 1.20 (s, 3H, Thstn Me-β), 1.05 (d, J=6.6 Hz, 3H, Val Me-β), 1.09–0.99 (m, 3H, Thr-1 Me-β), 0.86 ppm (d, J=6.8 Hz, 3H, Val Me-β); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{71}H_{81}N_{19}NaO_{18}S_5$: 1670.4508; found: 1670.4493.

Siomycin A (synthetic): R_f=0.57 (10% MeOH/$CHCl_3$); $[\alpha]_D^{26}$ −90.5 (c 0.11, dioxane); IR (KBr): $\tilde{\nu}$=3380, 2960, 2925, 1650, 1530, 1495, 1210, 1120, 1095, 930, 895, 810, 760 cm^{-1}; ^{1}H NMR ($CDCl_3$, ca. 0.5 mM): δ=9.98 (brs, 1H, Deala-S-1 CONH), 9.83 (brs, 1H, ThstA CONH), 9.21 (brs, 1H, Deala-2 CONH), 8.99 (brs, 1H, Deala-S-2 CONH), 8.60 (brs, 1H, Deala-1 CONH), 8.49 (brs, 1H, Debut CONH), 8.29 (s, 1H, Thstn Thz-4 H-5), 8.25 (s, 1H, ThstA Thz-1 H-5), 8.10 (s, 1H, ThstA Thz-2 H-5), 7.56 (bd, J=9.4 Hz, 1H, Thstn CONH), 7.44 (s, 1H, ThstA Thz-3 H-5), 7.38 (brs, 1H, Q H-3), 6.95 (d, J=10.0 Hz, 1H, Q H-5), 6.89 (brs, 1H, Thr-1 CONH), 6.80 (d, J=2.0 Hz, 1H, Deala-S-1 H-β(t)), 6.71 (d, J=1.8 Hz, 1H, Deala-S-2 H-β(t)), 6.45 (brs, 1H, Deala-2 H-β(t)), 6.43 (m, 1H, Thr-2 H-β), 6.40 (m, 1H, Q H-6), 6.40 (m, 1H, Ala-1 CONH), 6.20 (q, J=7.0 Hz, 1H, Debut H-β), 5.84 (d, J=9.0 Hz, 1H, Thr-2 H-α), 5.75 (d, J=9.4 Hz, 1H, Thstn H-α), 5.73 (brs, 1H, Deala-1 H-β(t)), 5.57 (brs, 1H, Deala-S-1 H-β(c)), 5.45 (brs, 1H, Deala-S-2 H-β(c)), 5.34 (bq, J=6.5 Hz, 1H, Q H-11), 5.18 (brs, 1H, Deala-2 H-β(c)), 5.18 (brs, 1H, ThstA piperidine H-6), 5.16 (brs, 1H, Deala-1 H-β(c)), 4.96 (dd, J=9.4, 13.5 Hz, 1H, (+)-Cys H-α), 4.77 (dq, J=6.4, 7.2 Hz, 1H, Ala-1 H-α), 4.47 (dd, J=3.0, 8.8 Hz, 1H, Thr-1 H-α), 4.11 (m, 1H, ThstA piperidine H-4e), 3.79 (bq, J=6.2 Hz, 1H, Thstn H-γ), 3.71 (dd, J=9.4, 11.4 Hz, 1H, (+)-Cys H-β′), 3.61 (d, J=4.8 Hz, 1H, Q H-7), 3.48 (m, 1H, ThstA piperidine H-3e), 3.12 (dd, J=11.4, 13.5 Hz, 1H, (+)-Cys H-β), 2.97 (m, 1H, ThstA piperidine H-3a), 2.96 (m, 1H, Val H-α), 2.28 (m, 1H, ThstA piperidine H-4a), 2.22 (m, 1H, Val H-β), 1.69 (m, 3H, Thr-2 Me-β), 1.63 (d, J=7.0 Hz, 3H, Debut Me-β), 1.48 (d, J=6.4 Hz, 3H, Ala-1 Me), 1.36 (d, J=6.5 Hz, 3H, Q 11-Me), 1.34 (d, J=6.2 Hz, 3H, Thstn Me-γ), 1.25 (m, 1H, Thr-1 H-β), 1.20 (s, 3H, Thstn Me-β), 1.05 (d, J=6.8 Hz, 3H, Val Me-β), 1.08–0.98 (m, 3H, Thr-1 Me-β), 0.87 ppm (d, J=6.8 Hz, 3H, Val Me-β); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{71}H_{81}N_{19}NaO_{18}S_5$: 1670.4508; found: 1670.4508.

^{13}C NMR spectrum of siomycin A (natural and synthetic): Owing to a scarcity of the synthetic siomycin A, the identity of ^{13}C NMR spectra of the natural and synthetic siomycin A was established by comparison of their HSQC and HMBC spectra: ^{13}C NMR ([D$_8$]THF, ca. 6 mM, 600 MHz): δ=174.1, 173.4, 171.7, 171.1, 170.2, 168.2, 166.3, 166.0, 164.2, 162.3, 162.0, 161.8, 161.2, 159.7, 159.0, 155.6, 152.0, 151.7, 150.5, 148.0, 135.7, 134.6, 133.9, 131.0, 130.6, 128.3, 127.9, 125.1, 123.8, 123.2, 118.3, 102.3, 101.9, 101.4, 100.0, 80.5, 78.5, 73.3, 69.3, 68.4, 68.0, 67.5, 65.3, 64.9, 61.4, 58.6, 57.0, 56.5, 54.0, 52.6, 35.7, 32.5, 30.3, 25.7, 25.4, 23.9, 23.6, 20.6, 19.6, 19.2, 17.9, 17.6, 15.7 ppm.

Regioisomeric cyclization–elongation product **43**: R_f=0.11 (10% MeOH/$CHCl_3$); $[\alpha]_D^{26}$ −19.3 (c 0.10, dioxane); IR (KBr): $\tilde{\nu}$=3370, 2975, 2935, 1655, 1520, 1490, 1220, 1120, 1065, 935, 895, 805, 750 cm^{-1}; ^{1}H NMR (4:1 $CDCl_3$–CD_3OD, ca. 4.8 mM) δ=9.64 (brs, 1H), 9.07 (brs, 1H), 8.91 (brd, J=4.6 Hz, 1H, Thr-2 CONH), 8.66 (brs, 1H), 8.34 (brs, 1H), 8.22 (s, 1H), 8.15 (s, 1H), 8.10 (s, 1H), 8.09 (brd, J=9.5 Hz, 1H, Thr-1 CONH), 8.08 (brd, J=5.0 Hz, 1H, Thstn CONH), 7.84 (brd, J=9.0 Hz, 1H, Ala-1 CONH), 7.38 (s, 1H), 6.87 (d, J=2.0, 10.0 Hz, 1H, Q H-5), 6.52 (brs, 1H), 6.44 (brs, 1H, Deala H-β), 6.40 (q, J=7.2 Hz, 1H, Thr-2 H-β), 6.34 (d, J=1.2 Hz, 1H, Deala H-β), 6.23 (brs, 1H, Deala H-β), 6.18 (dd, J=2.5, 10.0 Hz, 1H, Q H-6), 6.04 (brs, 1H, Deala H-β), 5.80 (brs, 1H, Deala H-β), 5.78 (q, J=6.2 Hz, 1H, Debut H-β), 5.74 (d, J=0.8 Hz, 1H, Deala H-β), 5.71 (d, J=1.2 Hz, 1H, Deala H-β), 5.47 (d, J=5.0 Hz, 1H, Thstn H-α), 5.44 (m, 1H, (+)-Cys H-α), 5.42 (brd, J=4.6 Hz, 1H, Thr-2 H-α), 5.41 (brs, 1H, Deala H-β), 5.10 (bq, J=6.4 Hz, 1H, Q H-11), 4.73 (d, J=10.5 Hz, 1H, Q H-8), 4.54 (dd, J=1.2, 9.5 Hz, 1H, Thr-1 H-α), 4.48 (dq, J=7.0, 9.0 Hz, 1H, Ala-1 H-α), 4.34 (dq, J=1.2, 6.2 Hz, 1H,

Thr-1 H-β), 3.69 (q, $J=6.4$ Hz, 1H, Thstn H-γ), 3.60 (m, 2H, (+)-Cys H-β and H-β′), 3.60–3.48 (m, 2H, ThstA piperidine H-3e and H-4e), 3.50 (m, 1H, Q H-7), 3.23 (d, $J=4.0$ Hz, 1H, Val H-α), 3.02 (m, 1H, ThstA piperidine H-3a), 2.74 (m, 1H, ThstA piperidine H-4a), 2.27 (m, 1H, Val H-β), 1.84 (d, $J=7.2$ Hz, 3H, Thr-2 Me-β), 1.45 (d, $J=6.4$ Hz, 3H, Q 11-Me), 1.42 (d, $J=7.0$ Hz, 3H, Ala-1 Me), 1.25 (s, 3H, Thstn Me-β), 1.22 (d, $J=6.2$ Hz, 3H, Thstn Me-γ), 1.15 (d, $J=7.0$ Hz, 3H, Val Me-β), 1.01 (d, $J=7.0$ Hz, 3H, Val Me-β), 0.87 (d, $J=6.2$ Hz, 3H, Thr-1 Me-β), 0.69 (d, $J=6.2$ Hz, 3H, Debut Me-β); HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{71}H_{81}N_{19}NaO_{18}S_5$: 1670.4508; found: 1670.4500.

Compound **45**: To a solution of **44**[26] (7.8 mg, 0.00815 mmol) in dry THF (1.9 mL) at 0°C under Ar atmosphere was added HF·pyridine (0.47 mL). After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (45 mL) and the mixture was extracted with AcOEt (40 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was purified by PTLC on silica gel (40% acetone/hexane) to afford **45** (4.2 mg, 70%) as a colorless foam: $R_f=0.55$ (50% acetone/hexane); ^{1}H NMR ($CDCl_3$) $\delta=8.60$ (brs, 1H, Ile CONH), 8.07 (s, 1H, thiazole H-5), 7.74 (brs, 1H, ΔAbu CONH), 6.34 (q, $J=7.0$ Hz, 1H, ΔAbu H-β), 5.44 (d, $J=8.6$ Hz, 1H, Ile H-α), 5.20 (dd, $J=8.0$, 8.0 Hz, 1H, thiazoline H-4), 4.67 (brs, 1H, OH), 4.44–4.28 (m, 1H, oxazolidine H-5), 4.38 (q, $J=7.2$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.18 (m, 2H, $Me_3SiCH_2C\underline{H}_2$), 4.05 (d, $J=7.0$ Hz, 1H, oxazolidine H-4), 3.78–3.56 (m, 4H, thiazoline H-5×2, Ile H-γ, and OH), 1.83 (d, $J=7.0$ Hz, 3H, ΔAbu Me-β), 1.65 (s, 6H, oxazolidine 2-Me×2), 1.47 (d, $J=6.0$ Hz, 3H, oxazolidine 5-Me), 1.39 (t, $J=7.2$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.27 (s, 3H, Ile Me-β), 1.23 (d, $J=6.2$ Hz, 3H, Ile Me-γ), 1.00 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.02 (s, 9H, $\underline{Me}_3SiCH_2CH_2$) (irradiation at 1.83 ppm produced a 0.7% NOE enhancement at 7.74 ppm and a 3.9% NOE enhancement at 6.34 ppm).

Compound **46**: To a solution of **45** (3.1 mg, 0.00426 mmol) in dry CH_2Cl_2 (0.21 mL) at 0°C under Ar atmosphere were added 2,6-lutidine (0.005 mL, 0.043 mmol) and TESOTf (0.0049 mL, 0.022 mmol). After stirring at room temperature for 0.5 h, the reaction mixture was quenched with H_2O (2 mL) and the mixture was extracted with $CHCl_3$ (2 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was purified by PTLC on silica gel (30% AcOEt/hexane) to afford **46** (2.9 mg, 71%) as a colorless foam: $R_f=0.60$ (30% AcOEt/hexane); $[\alpha]_D^{26}$ −22.0 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3685$, 3620, 3405, 1706, 1520, 1478, 1420, 1338, 1118, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.09$ (s, 1H, thiazole H-5), 7.73 (brs, 1H, CONH), 7.55 (d, $J=8.6$ Hz, 1H, CONH), 6.48 (q, $J=7.0$ Hz, 1H, ΔAbu H-β), 5.45 (d, $J=8.6$ Hz, 1H, Ile H-α), 5.02 (dd, $J=9.2$, 11.0 Hz, 1H, thiazoline H-4), 4.42–4.24 (m, 1H, oxazolidine H-5), 4.35 (q, $J=7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.24–4.02 (m, 2H, $Me_3SiCH_2C\underline{H}_2$), 3.96 (d, $J=7.4$ Hz, 1H, oxazolidine H-4), 3.86–3.66 (m, 2H, thiazoline H-5, Ile H-γ), 3.57 (dd, $J=9.2$, 11.0 Hz, 1H, thiazoline H-5), 1.82 (d, $J=7.0$ Hz, 3H, ΔAbu Me-β), 1.67 (s, 3H, oxazolidine 2-Me), 1.64 (s, 3H, oxazolidine 2-Me), 1.46 (d, $J=5.6$ Hz, 3H, oxazolidine 5-Me), 1.36 (t, $J=7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.35 (s, 3H, Ile Me-β), 1.12 (d, $J=6.0$ Hz, 3H, Ile Me-γ), 1.06–0.87 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.94 (t, $J=7.6$ Hz, 9H, $(\underline{Me}CH_2)_3Si$), 0.87 (t, $J=7.6$ Hz, 9H, $(\underline{Me}CH_2)_3Si$), 0.72–0.42 (m, 12H, $Me\underline{CH}_2Si$×6), 0.20 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$); ^{13}C NMR ($CDCl_3$): $\delta=171.11$, 170.86, 168.74, 167.34, 161.37, 152.80 (br), 146.01, 131.99, 128.16, 95.29, 79.47, 79.14, 74.65 (br), 72.02, 67.76, 63.79, 61.11, 59.37, 36.16, 27.15 (br), 25.20, 19.26, 18.95, 17.95, 17.78, 15.08, 14.33, 7.20, 6.91, 6.76, 5.08, −1.60 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{43}H_{78}N_5O_9S_2Si_3$: 956.4519; found: 956.4548. This **46** was identical with the sample derived from **44** by *syn* elimination using TBHP.

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