DOI: 10.1002/asia.200800032

Total Synthesis of Siomycin A: Construction of Synthetic Segments

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 five practical segments for the total synthesis of siomycin A, that is, the dehydropiperidine segment A (**5**), the pentapeptide segment B (**3**), the dihydroquinoline segment C (**6**), and the β-phenylselenoalanine dipeptide segments D (**7**) and E (**4**), were synthesized. Segment A (**5**) was constructed by the coupling of the azomethine ylide and the chiral sulfinimine, followed by the stereoselective reduction of the six-membered imine function. Segment B (**3**) was synthesized by the phenylselenylation of the β-lactone, stereoselective vinylzinc addition to the chiral sulfinimine, and oxazoline–thioamide conversion. Segment C (**6**) was prepared by the one-pot olefination of the tetrahydroquinoline *N*-oxide using triflic anhydride and triethylamine, stereoselective reduction of the methyl ketone function, and regioselective Yb(OTf)$_3$-catalyzed epoxide opening by the amino group. Segments D (**7**) and E (**4**) were synthesized by coupling of the properly protected β-phenylselenoalanines.

Keywords: heterocycles · peptides · siomycin A · stereoselectivity · sulfinimines

Introduction

Thiostrepton was isolated in 1955 from the culture broth of *Streptomyces azureus* by the Squibb group as an antibiotic with high inhibition activities against Gram-positive bacteria.[1] Its structure assignment had been investigated for a long time by chemical degradation studies[2] until the complete structure was elucidated by an X-ray crystallographic analysis in 1970.[3] NMR spectral studies of thiostrepton, together with the siomycins and thiopeptins, have been carried out in detail.[4] In 1961, siomycin A (**1**) was isolated from the culture broth of *Streptomyces sioyaensis* by the Shionogi group.[5] In 1969, siomycin B was recognized as an artifact of siomycin A (**1**), and siomycin C was isolated from the same culture broth.[6] Siomycin D_1 was also isolated from the same culture broth in 1980 as a minor component of the siomycins.[7] The structures of the siomycins were elucidated by chemical degradation studies[8] and NMR spectral studies[4a–d,7,9] by comparison with that of thiostrepton. Other structurally related antibiotics, the thiopeptins,[10] Sch 18640,[11] and Sch 40832,[12] were also isolated. The characteristic structure of this thiostrepton family of peptide antibiotics is the bicyclic skeleton containing a tetrasubstituted dehydropiperidine and/or piperidine moiety, a tetrasubstituted dihydroquinoline moiety, four thiazole moieties, a thiazoline moiety, dehydroamino acid moieties, and a dihydroxyisoleucine moiety (Figure 1). Fascinated by their stunningly complex structural features, we[13] and the Nicolaou group[14] have aimed to synthesize these antibiotics. Recently, Nicolaou and his co-workers have succeeded in the fascinating total synthesis of thiostrepton.[15] We have also succeeded in the total synthesis of siomycin A (**1**).[16] Other efforts have focused on the syntheses of the structurally simpler thiopeptide antibiotics which have the pyridine-containing monocyclic skeleton, for example, the micrococcins,[17] promothiocin A,[18] amythiamicin D,[19] GE2270A,[20,21] and GE2270T[20]

[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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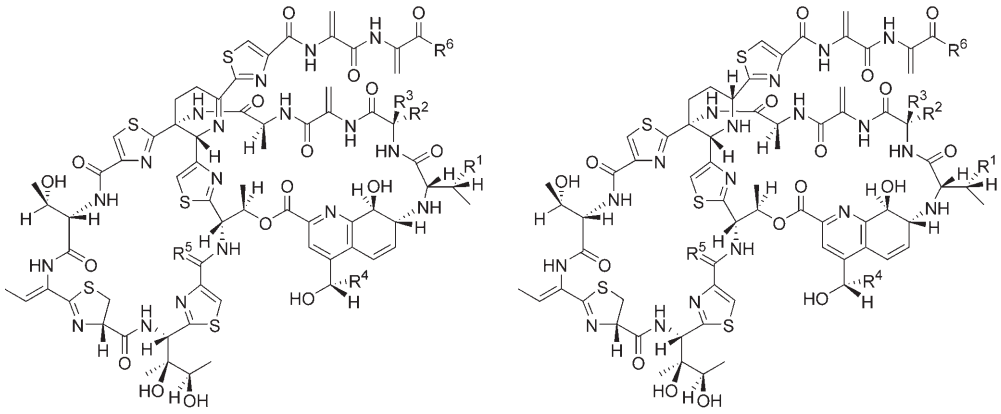
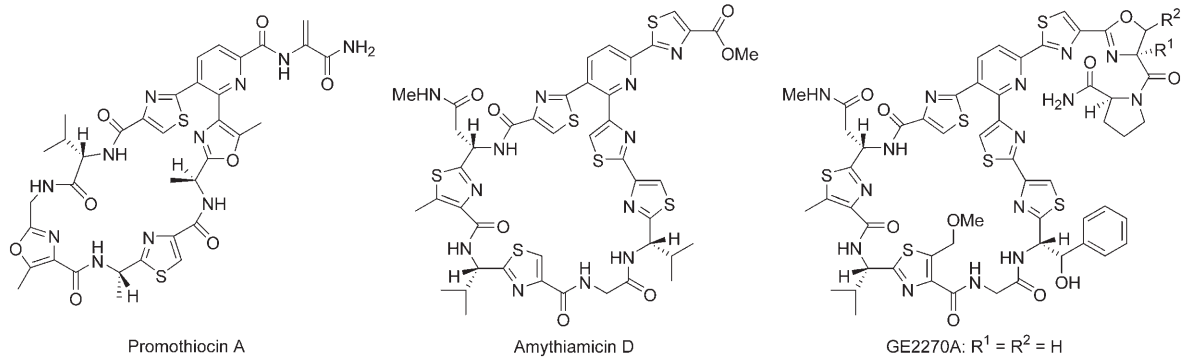


Thiostrepton (left): $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$
Siomycin A (**1**) (left): $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = NH_2$
Siomycin C (left): $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = CH_3$, $R^5 = O$, $R^6 = OMe$
Siomycin D_1 (left): $R^1 = CH_3$, $R^2 = R^3 = CH_2$ (dehydroalanine), $R^4 = H$, $R^5 = O$, $R^6 = NH_2$
Thiopeptin B_b (left): $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = S$, $R^6 = OH$
Thiopeptin B_a (right): $R^1 = CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = S$, $R^6 = OH$
Sch 18640 (right): $R^1 = CH_2CH_3$, $R^2 = CH_3$, $R^3 = H$, $R^4 = CH_3$, $R^5 = S$, $R^6 = NH_2$

Figure 1. Structures of thiostrepton antibiotics.



Promothiocin A

Amythiamicin D

GE2270A: $R^1 = R^2 = H$
GE2270T: $R^1 = R^2 = \pi$ bond

Figure 2. Structures of thiopeptide antibiotics.

(Figure 2). The chemical and biological properties of the thiostrepton and thiopeptide antibiotics have been recently reviewed (for example, the thiostrepton and thiopeptide antibiotics interfere with bacterial protein synthesis on the ribosome).[22] In this and the following[23] article, we report the construction of the five practical synthetic segments and the total synthesis of siomycin A (**1**).

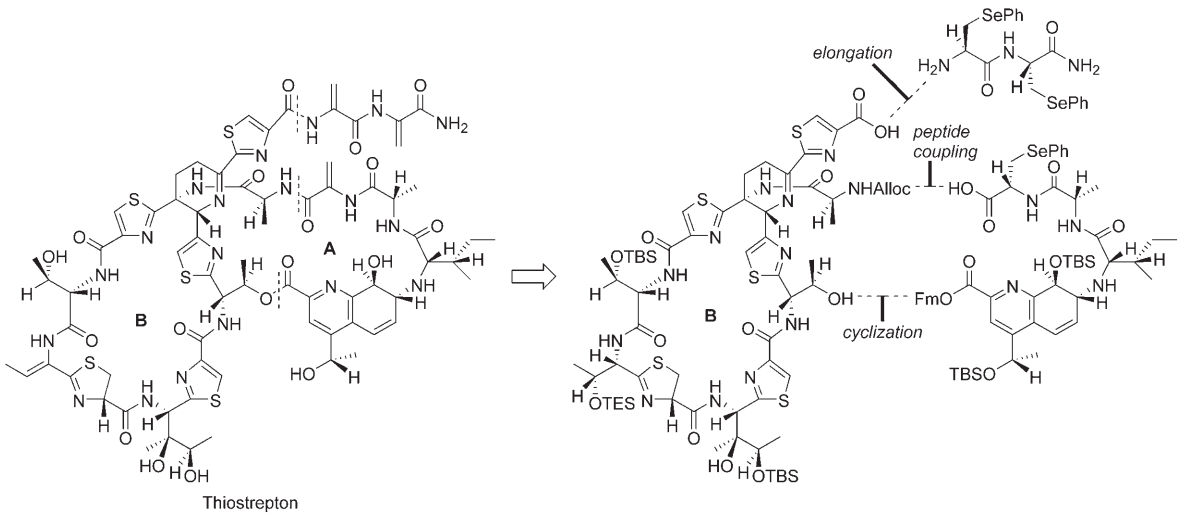
Abstract in Japanese:

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 の全合成のための重要な 5 個のセグメント、すなわち、デヒドロピペリジンセグメント A、ペンタペプチドセグメント B、ジヒドロキノリンセグメント C、β-フェニルセレノアラニンジペプチドセグメント D と E を合成した。

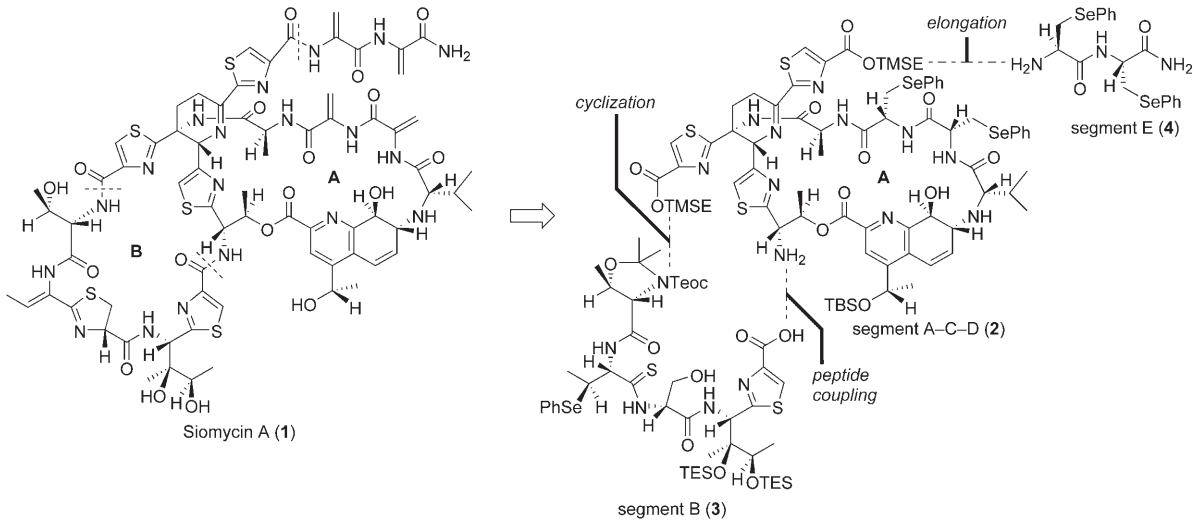
Results and Discussion

Strategy for Construction of the Bicyclic Skeleton

Aimed at the total synthesis of thiostrepton, Nicolaou and co-workers adopted the strategy of first constructing the B ring, followed by elongation of the side chain, A-ring precursor incorporation (peptide coupling), and the final A-ring cyclization (lactonization; Scheme 1).[15] Our strategy for the total synthesis of siomycin A (**1**), on the other hand, is different from the Nicolaou one; after the A-ring (segment A-C-D (**2**)) construction, it is coupled to segment B (**3**), followed by cyclization (lactamization) of the resulting coupling product and elongation of the side-chain segment E (**4**) onto the cyclization product (Scheme 2). We anticipated that this cyclization–elongation step would be realized in a stepwise manner after the selective deprotection of one of the two trimethylsilylethyl (TMSE) esters, or more conveniently, in a one-pot operation by the regioselective cycliza-



Scheme 1. Nicolaou's strategy for construction of the second ring and the side-chain elongation. Alloc = allyloxycarbonyl, Fm = 9-fluorenylmethyl, TES = triethylsilyl, TBS = *tert*-butyldimethylsilyl.



Scheme 2. Our strategy for construction of the second ring and the side-chain elongation. TMSE = trimethylsilylethyl, Teoc = 2-(trimethylsilyl)ethoxycarbonyl.

tion–elongation of the dicarboxylic acid secured by the simultaneous deprotection of the two TMSE esters. Other challenging tasks include the well-timed construction of the easily racemizing thiazoline ring and the tricky dehydroamino acid units (that is, four dehydroalanine groups and one trisubstituted *Z* olefin adjacent to the thiazoline ring), the latter of which would be obtained by the oxidative *syn* elimination of five phenylseleno groups[24] during the final stage of the total synthesis.

Retrosyntheses of Segments A-C-D (2) and A (5)

Scheme 3 shows the retrosynthetic analysis of segment A-C-D (**2**), which is divided into the tetrasubstituted dehydropiperidine segment A (**5**) (strategically including the L-threonine and L-alanine residues), the tetrasubstituted dihydroquinoline segment C (**6**) (having the L-valine residue), and the β-phenylselenoalanine dipeptide segment D (**7**). Segment A (**5**) would be derived from the tetrasubstituted piperidine **8** by the alanine coupling and dehydrogenation. It is expected that the latter dehydrogenation would regioselectively proceed because the C2 hydrogen atom in **8** seems to be more acidic than the C6 hydrogen atom.[25] Piperidine **8** is expected to be obtained from an equilibrium mixture of the six-membered imine derivative **9** and the five-membered imine derivative **10** by chemo- and stereoselective reduction. We anticipated that the six-membered imine **9** in this mixture would be preferentially reduced owing to steric hindrance around the imine function in the five-membered imine **10**. It is also expected that the stereoselectivity of this reduction would be controlled by the stereoelectronic effect as shown in Scheme 3. To synthesize the equilibrium mix-

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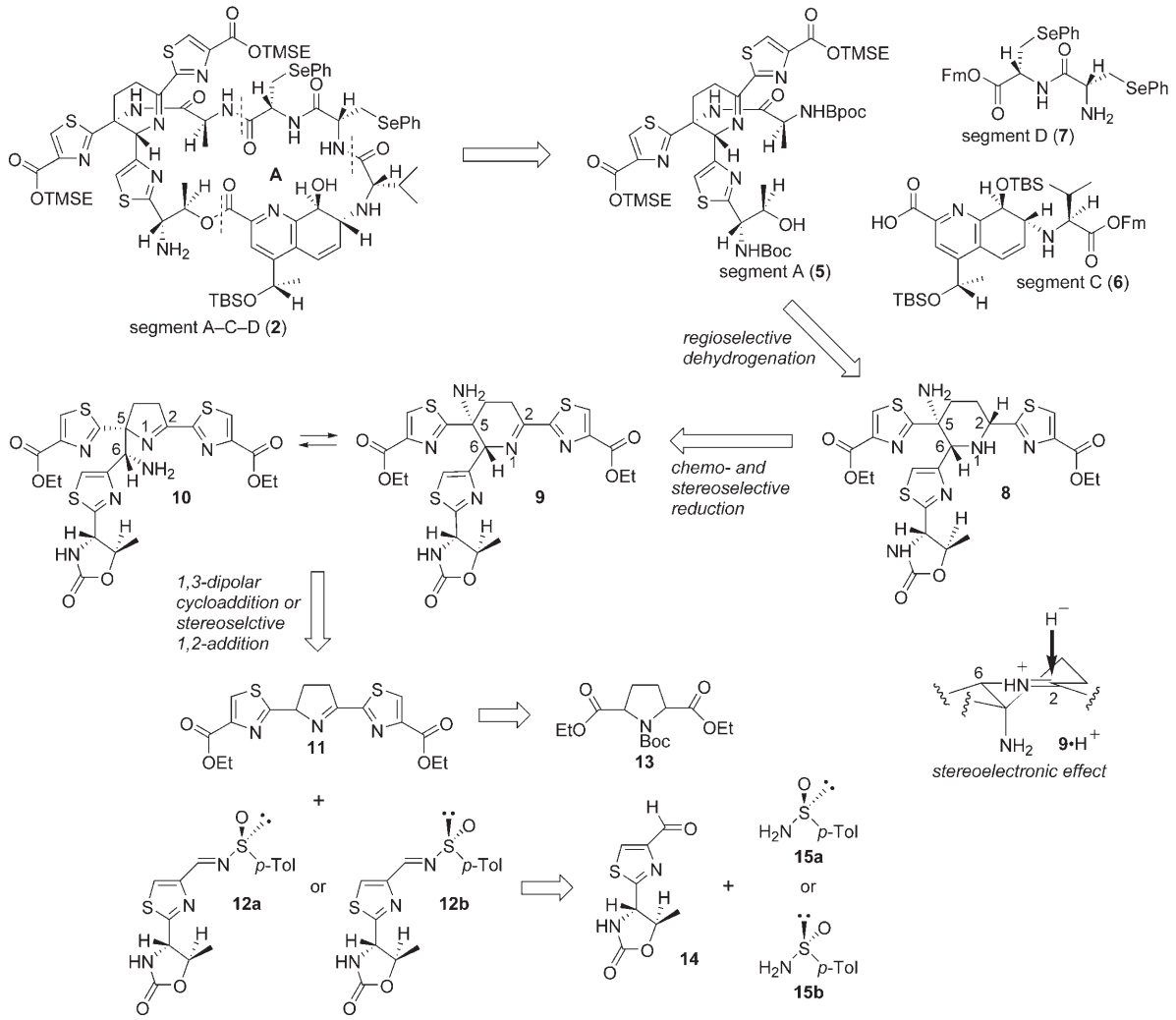
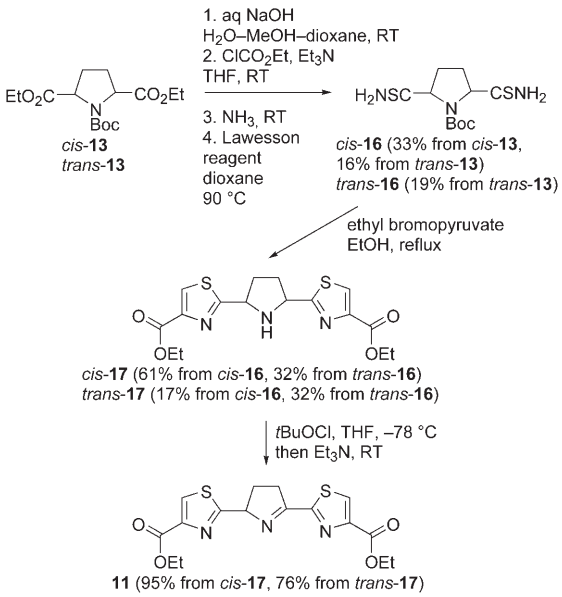


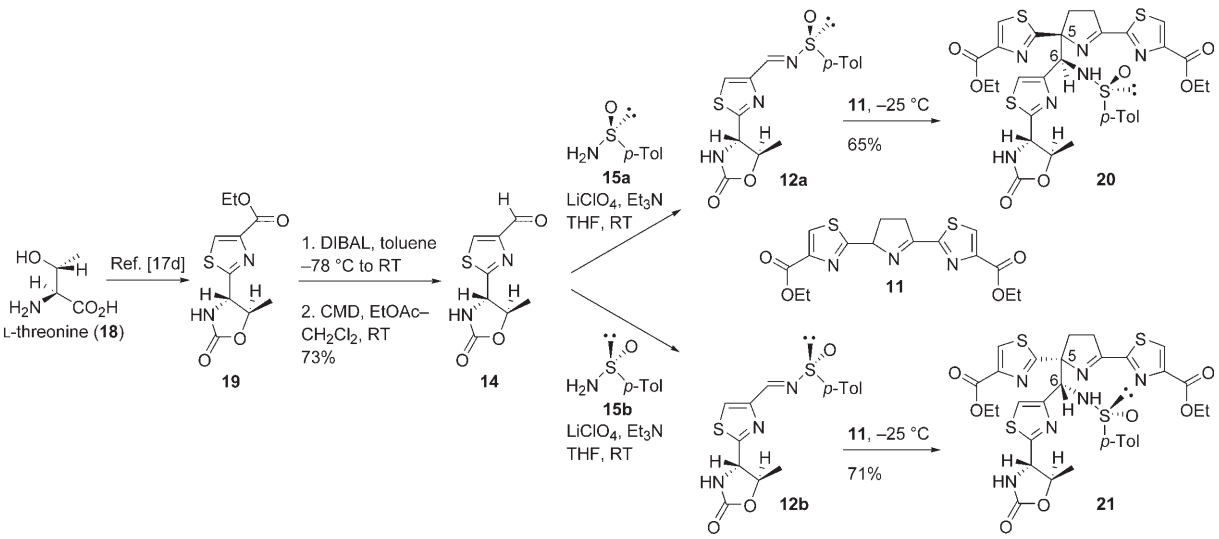
Scheme 3. Retrosynthetic analyses of segments A-C-D (**2**) and A (**5**). Boc = *tert*-butoxycarbonyl, Bpoc = 1-(4-biphenyl)-1-methylethoxycarbonyl, *p*-Tol = *p*-toluene.

ture of **9** and **10**, we selected the coupling reaction between the azomethine ylide derived from dehydropyrrolidine **11** and the chiral sulfinimine **12a** or its epimer **12b**, followed by desulfinylation. This coupling reaction may proceed by either 1,3-dipolar cycloaddition[26] or 1,2-addition. There is a precedent for the 1,3-dipolar cycloaddition between the azomethine ylides, derived from the *N*-benzylidene α-aminoesters, and the chiral sulfinimines.[27,28] The stereochemical outcome described in the literature[27a] matches our requirement when sulfinimine **12a** is used. On the other hand, when this reaction proceeds by 1,2-addition, it is possible to control the C6 stereochemistry by employing sulfinimine **12a** or **12b**; however, the C5 stereochemistry is unpredictable. Dehydropyrrolidine **11** was prepared from the known pyrrolidine **13**,[29] and the chiral sulfinimine **12a** (or **12b**) was prepared from aldehyde **14** and the chiral sulfinamide **15a** (or **15b**).[30]

Synthesis of dehydropyrrolidine 11:[13a] *cis*-1-Boc-2,5-dicarbethoxypyrrolidine (*cis*-**13**)[29] (Scheme 4), prepared with modification from diethyl 2,5-dibromoadipate, was hydro-



Scheme 4. Synthesis of dehydropyrrolidine **11**.



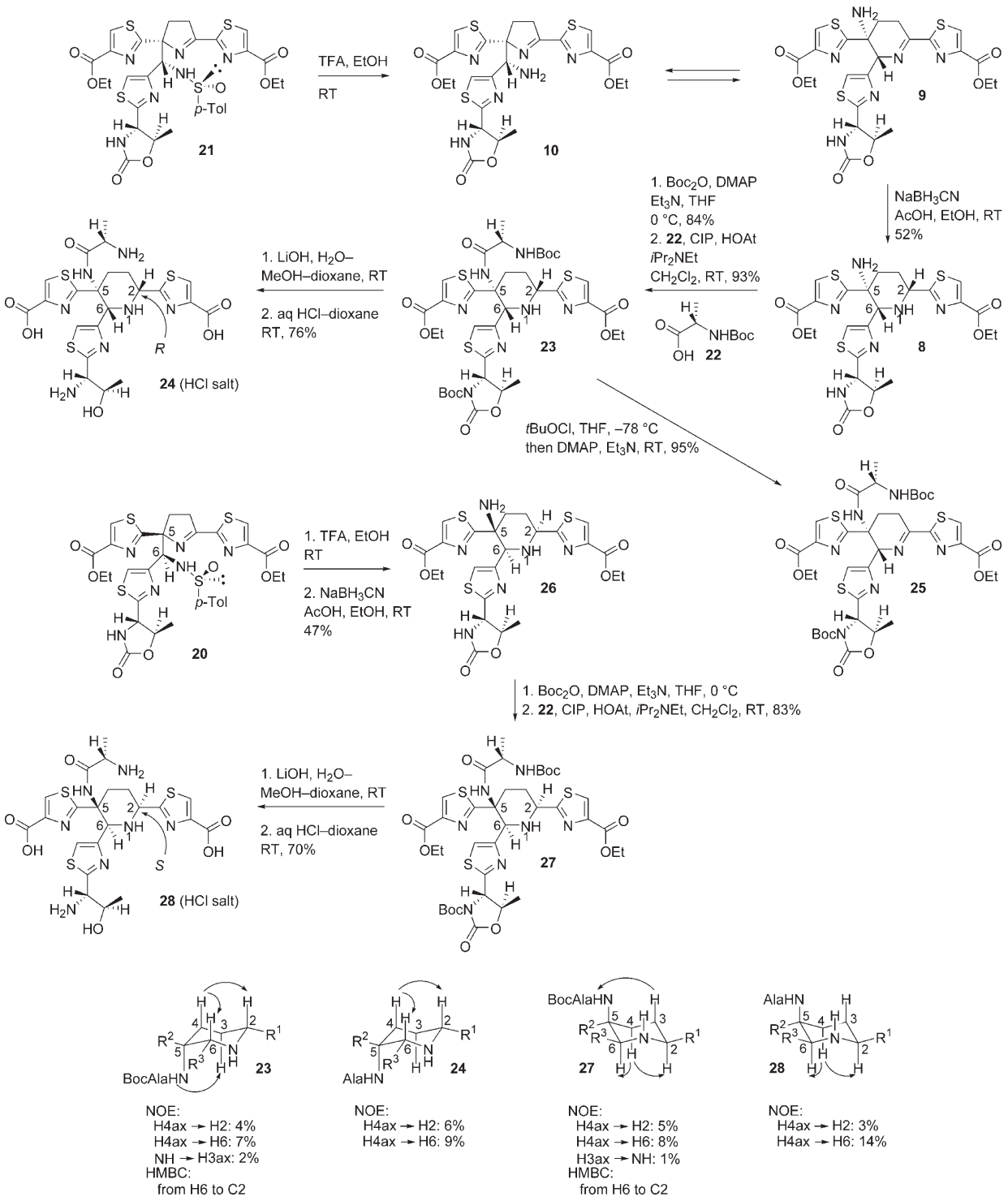
Scheme 5. Coupling between dehydropyrrolidine **11** and sulfinimine **12**. DIBAL = diisobutylaluminium hydride, CMD = chemical manganese dioxide.

lyzed to the acid, which was converted into the mixed anhydride with ethyl chloroformate; into this solution, gaseous NH_3 was then introduced. The resulting amide was treated with the Lawesson reagent,[31] giving thioamide *cis*-**16** in 33% overall yield. The treatment of *cis*-**16** with ethyl bromopyruvate[17d] in EtOH afforded *cis*-**17** and *trans*-**17** in 61 and 17% yield, respectively. The treatment of *cis*-**17** with *t*BuOCl[32] in THF followed by dehydrochlorination with triethylamine provided **11** in 95% yield. In addition, *trans*-1-Boc-2,5-dicarbethoxypyrrolidine (*trans*-**13**)[29] (Scheme 4) was also transformed into **11** by the same procedure as described in the *cis* series. From thioamide *trans*-**16**, obtained from *trans*-**13** in 19% yield together with the 16% yield of *cis*-**16**, a comparable yield (each 32%) of *cis*-**17** and *trans*-**17** was obtained, and then *trans*-**17** was converted into **11** in 76% yield.

Synthesis of chiral sulfinimines 12a and 12b, and their coupling with dehydropyrrolidine 11:[13a] The synthesis of the chiral sulfinimines **12a** and **12b** began with the known **19**,[17d] which was prepared from L-threonine (**18**; Scheme 5). Diisobutylaluminum hydride (DIBAL) reduction of **19** followed by oxidation with manganese dioxide[33] afforded aldehyde **14** in 73% yield. We postulated that a mixture of $LiClO_4$–Et_3N,[26] which seemed to be suitable for the subsequent key coupling between dehydropyrrolidines and sulfinimines, might be used for condensation of an aldehyde with a sulfinamide. Condensation of **14** in THF with the Davis sulfinamide[34] **15a** or **15b** in the presence of $LiClO_4$ and Et_3N provided sulfinimine **12a** or **12b**, respectively. Each solution of these sulfinimines was directly used in the subsequent coupling. First, based on the results described in the literature,[27a] dehydropyrrolidine **11** and sulfinimine **12a** were selected for the coupling partners. The coupling products turned out to be the 1,2-addition product **20** and its diastereomer[35] in 65 and 6% yield, respectively. The following transformation of the coupling product **20** led to **28**, which proved to be a diastereomer of the desired **24** and has the opposite configurations at the C2, C5, and C6 positions (see below). Therefore, sulfinimine **12b** was next chosen as the coupling partner. To the above-mentioned solution of **12b** in THF was added **11** at −25 °C. After one day, the addition product **21** and its diastereomer[35] were obtained in 71 and 17% yield, respectively. The ^{1}H NMR signal of NHSO (δ = 5.79, J = 8.7 Hz) in **21** supported the five-membered imine structure; however, the C5 and C6 configurations could not be determined at this stage.

Synthesis of segment A (5):[13a,e] After desulfinylation of **21** with TFA in EtOH, the obtained mixture of **9** and **10** was subjected to reduction with $NaBH_3CN$ in AcOH/EtOH to afford, as we expected, piperidine **8** in 52% yield as the sole reduction product (Scheme 6). In preference to the structurally congested primary amine at C5, the oxazolidinone amine in **8** was protected with Boc_2O, and the following condensation with Boc-Ala-OH (**22**) using 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate (CIP)[36] and 1-hydroxy-7-azabenzotriazole (HOAt), which are useful coupling reagents for structurally congested cases, afforded piperidine **23** in 78% yield (two steps). The HMBC spectrum of **23** (from H6 to C2) supported the piperidine skeleton and the NOE experiments supported the relative configuration of the piperidine ring (Scheme 6). The absolute structure of **23** (and hence **8**) was confirmed by its transformation (deprotection) to **24** and comparison of its optical rotation and ^{1}H and ^{13}C NMR spectra with those of a degradation product from the natural thiopeptin B_a.[10f,37] On the other hand, dehydropyrrolidine **20** was also transformed, through **26** and **27**, into **28**, which has the identical relative but opposite absolute configurations within the piperidine ring to those of **24**. As we expected, dehydrogenation of **23** with *t*BuOCl[32] and triethylamine gave only dehydropiperidine **25** in 95% yield.

It is interesting to note that the configuration of the piperidine ring in thiopeptin B_a (Figure 1) was confirmed by our synthesis of **24**. According to reference [10f], the authors



Scheme 6. Structure determination of piperidines **8** and **26**. TFA = trifluoroacetic acid, DMAP = 4-(dimethylamino)pyridine, CIP = 2-chloro-1,3-dimethylimidazolidium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.

have isolated two degradation products, **IIA** and its C2 epimer **IIB** (the compound numbers described in reference [10f]), from thiopeptin B_a as the piperidine residue. Compound **IIA** was formed from **IIB** as an artifact under the degradation conditions. Therefore, compound **IIB** was the intact piperidine residue. Unfortunately, the authors could not analyze the coupling constant $J_{2,3}$ of compound **IIB** because the C2 proton signal overlapped with the C6 proton signal using the 100 MHz NMR spectrometer.[37] Instead, judging from the coupling constant ($J_{2,3} = 3.5$ and 12.0 Hz) in the ^{1}H NMR spectrum of **IIA** together with the X-ray analysis of thiostrepton,[3] they proposed that **IIA** was **24** and

hence the C2 configuration of the piperidine ring in natural thiopeptin B_a was *S*. In contrast, according to reference [4f], the authors proposed the C2 configuration of the piperidine ring in thiopeptin B_a to be *R* based on the coupling constant ($J_{2,3}$ = 3.5 and 10.0 Hz) in the ^{1}H NMR spectrum of thiopeptin A_{1a} (thiopeptin A_{1a} is the methyl ester of thiopeptin B_a at the terminal position R^6 depicted in Figure 1). These two assignments disagree. Therefore, we did NOE experiments for both **23** and the synthetic **24** that are shown in Scheme 6 and unambiguously determined the C2, C5, and C6 relative configurations.

The stereoselectivity observed in the 1,2-addition manner of the coupling between the azomethine ylide derived from **11** and sulfinimine **12b** may be interpreted as follows (Figure 3). The metal species chelates with both the sulfinyl

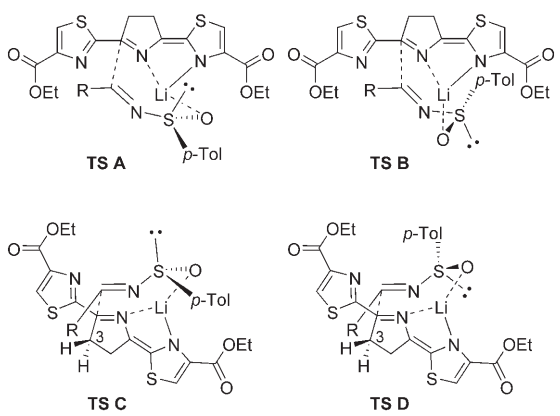
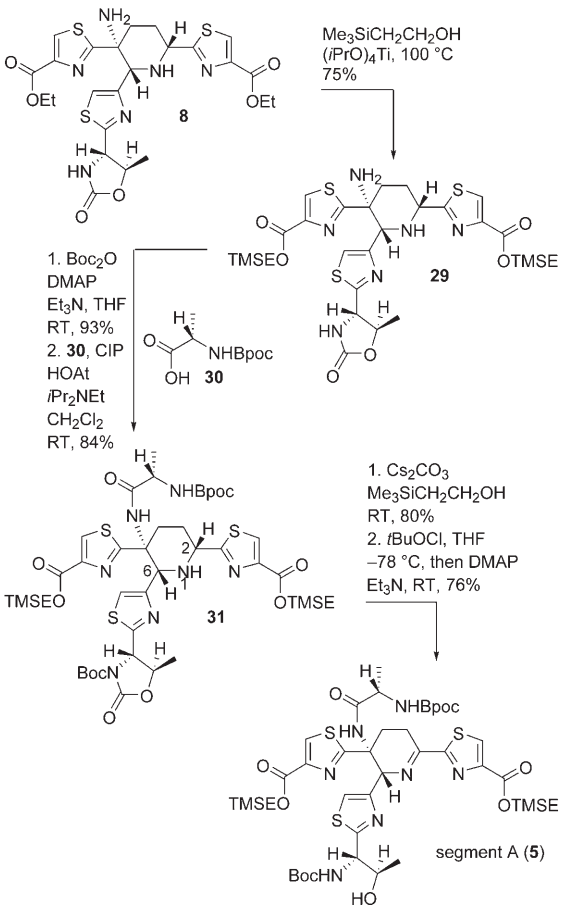


Figure 3. Transition-state models for coupling between azomethine ylide and sulfinimine.

oxygen atom and the azomethine ylide nitrogen atom in the transition state (TS). It seems likely that the azomethine ylide attacks the sulfinimine opposite to the *p*-Tol group. In this situation, **TS B** and **TS D** suffer from an electronic repulsion between the lone pairs on the sulfur and sulfimine nitrogen atom. Thus, **TS A** and **TS C** are lower in energy than **TS B** and **TS D**. In **TS C**, there is a steric repulsion between the R substituent of the sulfinimine and the hydrogen atom (H3) of the azomethine ylide. As a result **TS A** is the most likely, giving the coupling product **21** as the major product. In the case of **12a**, the same explanation is applicable.

Since it seems apparent that the ethyl esters in **25** (Scheme 6) cannot be hydrolyzed after the construction of segment A-C-D (**2**), which contains the lactone function, these ethyl groups were changed to the TMSE protecting groups (Scheme 7). The treatment of **8** with trimethylsilylethanol in the presence of Ti(*i*PrO)$_4$[38] gave TMSE ester **29** in 75% yield. The Boc protection (93% yield) of the oxazolidinone amine in **29** followed by condensation with Bpoc-Ala-OH (**30**)[39] using CIP,[36] HOAt, and *i*Pr$_2$NEt afforded **31** in 84% yield. The selective deprotection of the oxazolidinone in the presence of the TMSE esters was realized

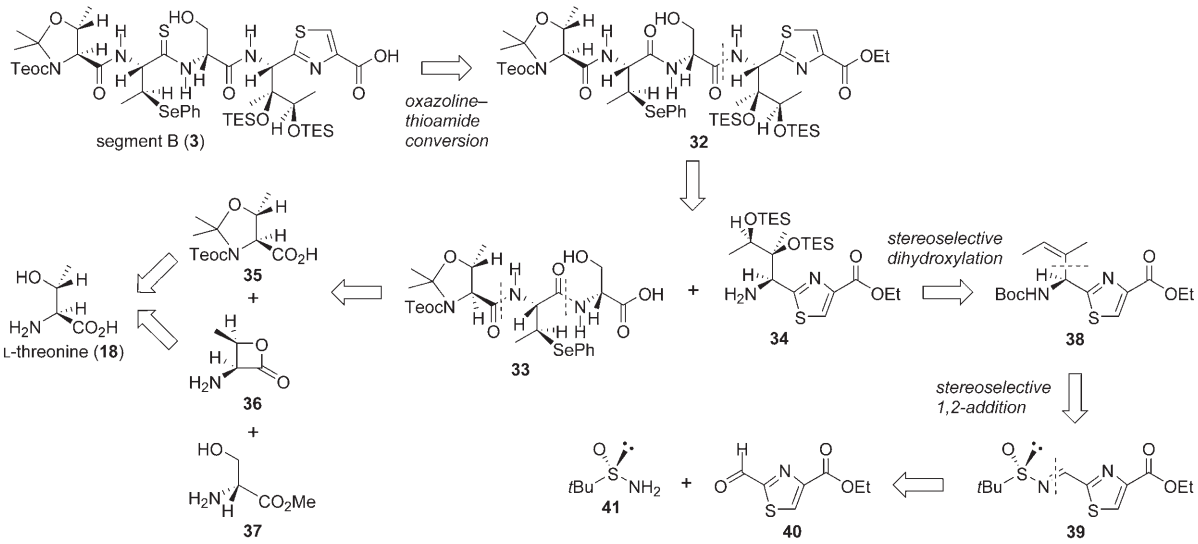


Scheme 7. Synthesis of segment A (**5**).

with Cs_2CO_3[40] in trimethylsilylethanol (80% yield) and the successive chlorination with *t*BuOCl[32], and dehydrochlorination with triethylamine and DMAP gave the dehydropiperidine segment A (**5**) in 76% yield.

Retrosynthesis of Segment B (3)

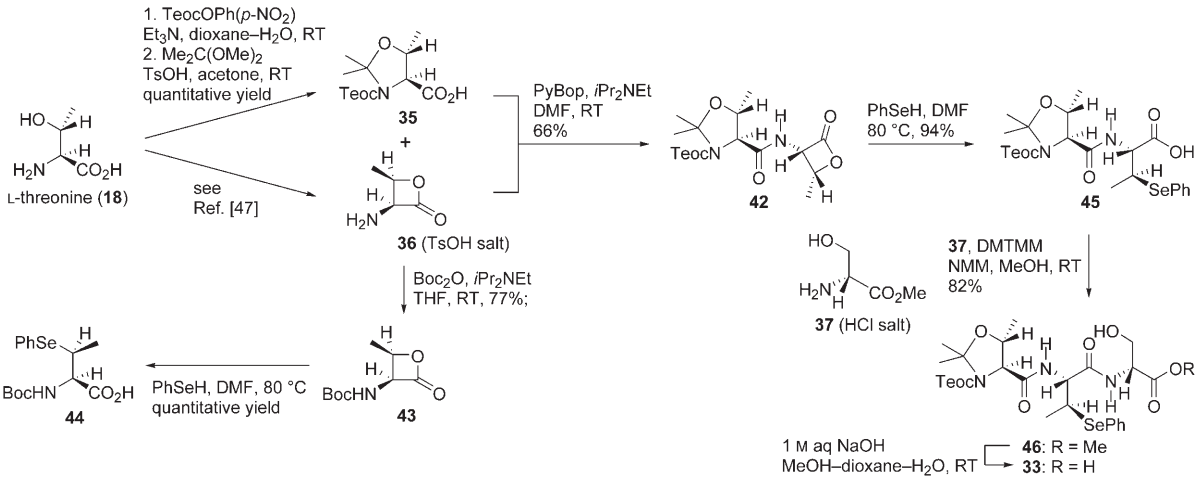
The retrosynthetic analysis of segment B (**3**) is illustrated in Scheme 8. In general, thiazolines are sensitive to epimerization;[41] therefore, it is desirable to construct the thiazoline ring in the later stage of the total synthesis. We anticipated that the β-hydroxythioamide function would be suitable as the thiazoline precursor. The β-hydroxythioamide portion would be constructed from β-hydroxyamide **32** by the Wipf oxazoline–thiazoline conversion method.[41d–f] On the other hand, the (*Z*)-dehydroamino acid portion would be obtained by the oxidative *syn* elimination of the phenylseleno group.[24,42] β-Hydroxyamide **32** is divided into carboxylic acid **33** and the dihydroxyisoleucine derivative **34**. Tripeptide **33** would be obtained from three amino acids **35**–**37** by consecutive condensations as well as phenylselenylation of the β-lactone part. The β-lactone function acts as not only the protecting group of the carboxylic acid group during the amide formation, but also the activating group of the hydroxy group for phenylselenylation. Two amino acids, **35**



Scheme 8. Retrosynthetic analysis of segment B (**3**).

and **36**, could be obtained from L-threonine (**18**). The dihydroxyisoleucine derivative **34** would be obtained from the trisubstituted olefin **38** by the stereoselective dihydroxylation. The chiral olefin **38** would be obtained from the chiral sulfinimine **39** by the stereoselective addition of an organometallic reagent.[30] If this reaction mainly affords the adduct having the undesired configuration, all we have to do is use the enantiomer of **39**. Sulfinimine **39** could be easily obtained by the condensation of the known thiazole aldehyde **40**[43] and the Ellman chiral sulfinamide **41**[44] using the Cs_2CO_3-mediated sulfinimine synthesis recently developed by our group.[45]

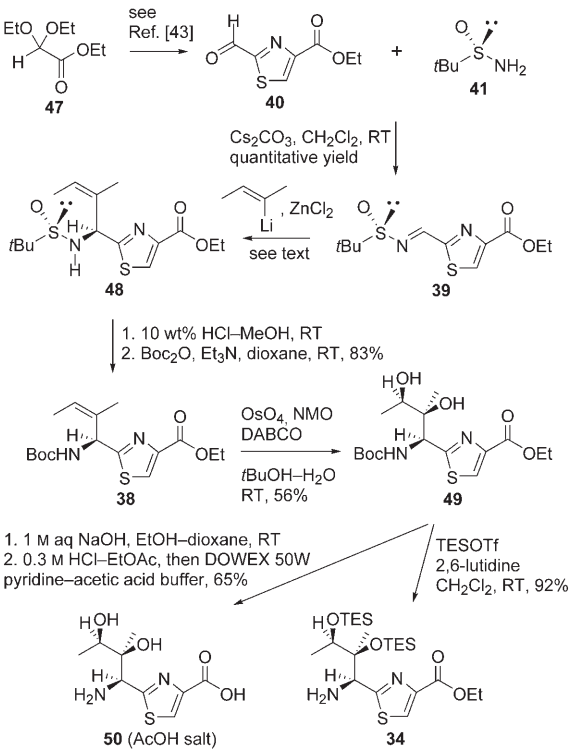
Synthesis of tripeptide 33:[13c] Tripeptide **33** was synthesized by the route shown in Scheme 9. L-Threonine (**18**) was treated with 2-(trimethylsilyl)ethyl 4-nitrophenyl carbonate[46] and triethylamine followed by acetonization with acetone dimethylacetal and TsOH to afford **35** quantitatively. β-Lactone **36** (TsOH salt) was prepared from **18** by the Vederas method.[47] After several screenings of condensation reagents, coupling of **35** with **36** was realized using benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP)[48] and iPr$_2$NEt in DMF to give **42** in 66% yield. The crucial step in the synthesis of **33** was the β-lactone opening by phenylselenylation. This phenylselenylation was tested using **43** (derived from **36** by the Boc protection) as the model compound. First, Shirahama's conditions[42a] (PhSeNa)[49] were applied to **43**, resulting in failure probably because attack of the nucleophiles at the β-position of the threonine β-lactone is disfavored in contrast to the facile ring opening at the methylene of the serine-derived β-lactones.[47] Other methods available for the nucleophilic phenylselenylation include $PhSeSiMe_3$+KF,[50] $PhSeSiMe_3$+ZnI_2,[51] both of which had been used for the lactone-opening reactions, and $PhSeSiMe_3$ and/or PhSeH used for



Scheme 9. Synthesis of tripeptide **33**. Ts = *p*-toluenesulfonyl, PyBop = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, DMTMM = 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride, NMM = *N*-methylmorpholine.

opening of the oxazoline and oxazine rings.[52] Among them, the PhSeH method[52] was the best choice in view of the easy experimental procedures (PhSeH, DMF, 80 °C, 2 h), quantitatively giving **44**.[53] To the best of our knowledge, this is the first example of the opening reaction of β-substituted β-lactones using PhSeH. β-Lactone **42** was then subjected to the same reaction conditions to afford the desired **45** in 94% yield. Condensation of **45** with **37** (HCl salt) using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM)[54], which is convenient for amide formation in the presence of an alcohol function, and *N*-methylmorpholine (NMM) in MeOH afforded tripeptide **46** in 82% yield. Hydrolysis of **46** with aqueous NaOH gave the desired tripeptide **33**, which was used in the next step without purification.

Synthesis of dihydroxyisoleucine derivative 34:[13c] The synthesis of the dihydroxyisoleucine derivative **34** started with the known thiazole aldehyde **40**,[43] which was prepared from ethyl diethoxyacetate (**47**; Scheme 10). Condensation



Scheme 10. Synthesis of dihydroxyisoleucine derivative **34**. NMO = *N*-methylmorpholine *N*-oxide, DABCO = 1,4-diazabicyclo[2.2.2]octane, Tf = trifluoromethanesulfonyl.

of **40** with the Ellman chiral sulfinamide **41**[44] in CH_2Cl_2 using our recently developed method with Cs_2CO_3 as an amine-activating and dehydrating reagent[45] quantitatively produced **39**. The first crucial step in the synthesis of **34** was the chemo- and stereoselective addition of the organometallic reagent to the sulfinimine group of **39** in the presence of the ethoxycarbonyl group. To the vinyllithium reagent, prepared from 1.1 equiv of (*Z*)-2-bromo-2-butene and 2.2 equiv of *t*BuLi in THF or Et_2O, was added at −78 °C a solution of 1.0 equiv of **39** in THF or Et_2O, resulting in the decomposition of **39**. In contrast, transmetalation of the above vinyllithium reagent (prepared in THF) to the vinylzinc reagent by the addition of 1.1 equiv of ethereal $ZnCl_2$ was realized at 0 °C; to this was added 1.0 equiv of **39** in THF at −78 °C. The mixture was stirred at −40 °C for 6 h, affording the desired adduct **48** in about 20% yield. Fortunately, using 5.0 equiv of the vinylzinc reagent afforded **48** in 87% yield as the sole adduct. When this addition reaction was conducted at 0 °C (3 h), the ratio of **48** and its diastereomer was 3:1 and the yield of isolated **48** was reduced to 55%. The stereochemistry of **48** was confirmed in the later stage (see below). To the best of our knowledge, this is the first example of the addition of the vinylzinc reagent to the chiral sulfinimine.[55]

The next crucial step was the dihydroxylation of the trisubstituted double bond. We expected that the sulfoxide-mediated intramolecular-like dihydroxylation of olefins using OsO_4[56] was applicable to allylic sulfinamides; however, only the oxidation of the sulfinamide to the sulfonamide occurred. Sulfinamide **48** was then transformed into carbamate **38** by acid treatment followed by Boc protection in 83% yield. Dihydroxylation of **38** was conducted under a variety of conditions, including the Sharpless asymmetric dihydroxylation;[57] the best result was obtained using 0.1 equiv of OsO_4, 3 equiv of *N*-methylmorpholine *N*-oxide (NMO), and 0.2 equiv of 1,4-diazabicyclo[2.2.2]octane (DABCO)[58] in 85:15 *t*BuOH–H_2O at room temperature for 12 h, affording a 2:1 mixture of **49** and its diastereoisomer, from which the desired **49** was easily separated by silica-gel column chromatography in 56% yield. The structure determination of **49** (and hence **48**) was realized by its transformation into the naturally derived degradation product, thiostreptine (**50**),[2c,8a,10d] by deprotection and comparing the optical rotation and ^{1}H NMR spectrum. Disilylation of **49** with triethylsilyl trifluoromethanesulfonate (TESOTf) and 2,6-lutidine afforded, concomitant with cleavage of the Boc group,[59] **34** in 92% yield.

The high selectivity of the addition of the vinylzinc reagent to sulfinimine **39** might be rationalized by the open transition-state model (**TS E**)[30,55b,60] shown in Figure 4, in which the addition occurs from the *Si* face of the imine. On the basis of the Davis statement,[55b] we speculate that the existence of heteroatoms in the thiazole ester disrupts and prevents formation of the chelated transition state (**TS F** in

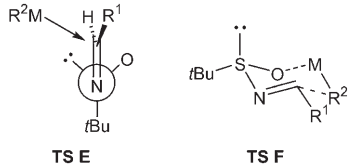
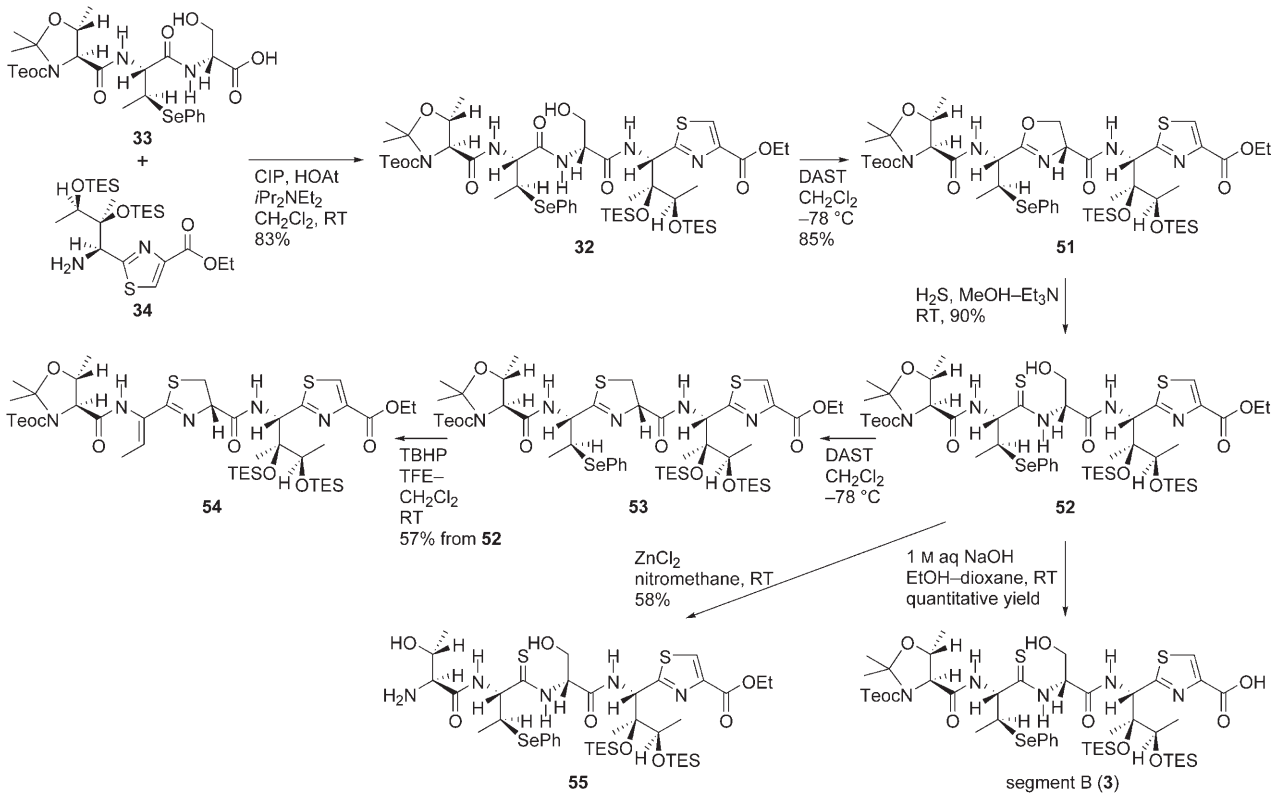


Figure 4. Transition-state models for addition of an organometallic reagent to sulfinimine.



Scheme 11. Synthesis of segment B (**3**). DAST = diethylaminosulfur trifluoride, TBHP = *tert*-butylhydroperoxide, TFE = 2,2,2-trifluoroethanol.

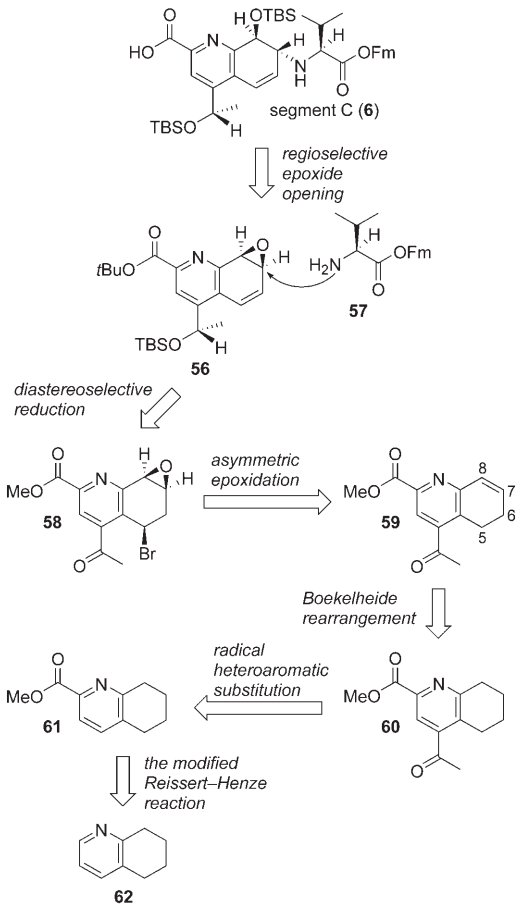
Figure 4, *Re* face attack). On the other hand, the selectivity of the dihydroxylation of **38**, though it was only 2:1, might be explained by considering that the carbamate group serves to deliver the oxidant to the desired face of the double bond.[61]

Synthesis of segment B (3):[13c] Condensation of carboxylic acid **33** with the dihydroxyisoleucine derivative **34** was conducted with CIP,[36] HOAt, and *i*Pr_2NEt in CH_2Cl_2 to give pentapeptide **32** in 83% yield (Scheme 11). Now the crucial Wipf oxazoline–thiazoline conversion method was realized as follows.[41,62] Treatment of **32** with diethylaminosulfur trifluoride (DAST)[63] in CH_2Cl_2 gave oxazoline **51** in 85% yield, which was subjected to H_2S in 1:1 MeOH–triethylamine to afford thioamide **52** in 90% yield. Thioamide **52** was again treated with DAST[63] to give thiazoline **53**, which was subsequently subjected to the oxidative *syn* elimination using *tert*-butylhydroperoxide (TBHP) in 2,2,2-trifluoroethanol (TFE)–CH_2Cl_2 (1:1) to afford pentapeptide **54** in 57% yield from **52**. The structure of **54** was confirmed by its ^{1}H and ^{13}C NMR spectra, including H–H COSY, HMQC, and HMBC. At this stage, we tried hydrolysis of the ethyl ester of **54** under a variety of conditions (for example, aqueous NaOH in 2:1 EtOH–dioxane, aqueous $Ba(OH)_2$ in MeOH,[64] Me_3SiOK in THF[65]); however, but not unexpectedly, the complete epimerization occurred.[66] Furthermore, the treatment of **54** with trimethyltin hydroxide, which could be used for hydrolysis of methyl phenylacetate,[67] afforded the carboxylic acid contaminated with about 20% of the epimerization product.[66] On the other hand, deprotection of the 2-(trimethylsilyl)ethoxycarbonyl (Teoc) group of **54** with $ZnCl_2$[68] in nitromethane at 50 °C resulted in approximately 20% epimerization.[66] Therefore, we considered that carboxylic acid **3** or amine **55** would be the more suitable intermediate for elaboration of the pentapeptide portion usable for the total synthesis of the thiostrepton family of peptide antibiotics. To this end, thioamide **52** was treated with aqueous NaOH in 2:1 EtOH–dioxane to afford segment B (**3**) quantitatively. Moreover, the treatment of thioamide **52** with $ZnCl_2$[68] in nitromethane afforded amine **55** in 58% yield.

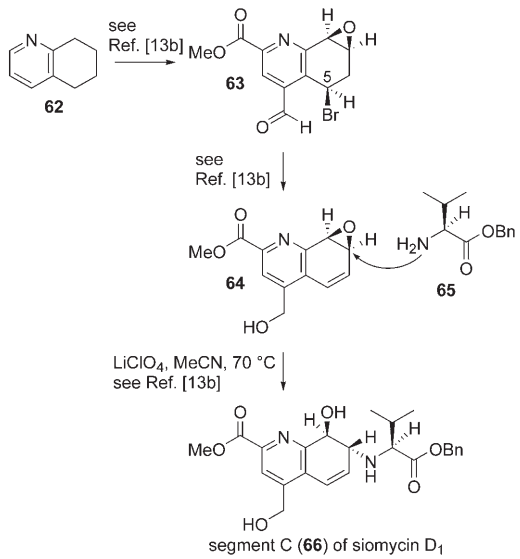
Retrosynthesis of Segment C (6)

It has been proposed by Floss and co-workers[69] that the 4-(1-hydroxyethyl)quinoline-2-carboxylic acid was an intermediate in the biosynthesis of thiostrepton. We were interested in their chemical synthesis from quinoline-2-carboxylic acid.[69] This synthetic process was applied to the early stage of our synthesis of segment C (**6**), but with slight modifications.

The retrosynthetic analysis of segment C (**6**) is shown in Scheme 12. The regioselective opening of epoxide **56** with the L-valine derivative **57**, like the biosynthetic pathway of the quinaldic acid portion,[69] would afford segment C (**6**). Epoxide **56** would be obtained by the chemo- and diastereoselective reduction of methyl ketone **58**, which would be de-

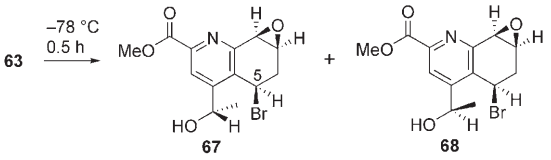


Scheme 12. Retrosynthetic analysis of segment C (**6**).



Scheme 13. Previous synthesis of segment C (**66**) of siomycin D_1. Bn = benzyl.

Table 1. Diastereoselective addition of methyl group to aldehyde **63**.[a]



Entry	Reagent	Additive	Solvent	Ratio[b] of **67**/**68**/**63**
1	MeMgBr	–	Et_2O	30:14:56
2	MeMgBr	–	toluene	56:28:16
3	MeMgBr	HMPA	toluene	68:18:14
4	MeMgBr	DMPU	toluene	21:14:65
5	MeMgBr	TMEDA	toluene	–[c]
6	MeLi	–	THF	41:13:46
7	MeLi	HMPA	THF	35:8:57

[a] 1.1 equiv of methylating reagent was added at −78 °C to a solution of 1.0 equiv of **63** in solvent in the presence or absence of 1.1 equiv of additive. [b] The ratio was based on ^{1}H NMR analysis of the crude products. [c] Multispot on TLC.

rived from 5,6-dihydroquinoline **59** by the asymmetric epoxidation and bromination. The 7,8-double bond in **59** would be constructed through the Boekelheide rearrangement from the 5,6,7,8-tetrahydroquinoline derivative **60**, of which the acetyl group would be introduced by the radical heteroaromatic substitution reaction of **61**. The modified Reissert–Henze reaction of the 5,6,7,8-tetrahydroquinoline (**62**) gave **61**.

Construction of the hydroxyethyl portion: the first route:[13d] We have previously synthesized the dihydroquinoline segment C (**66**) of siomycin D_1, with the hydroxymethyl group instead of the hydroxyethyl group (Scheme 13).[13b] Aldehyde **63** derived from 5,6,7,8-tetrahydroquinoline (**62**) was transformed into alcohol **64**, which was subjected to the regioselective epoxide-opening reaction[70] with the L-valine derivative **65** in the presence of $LiClO_4$[71] to afford **66**. The intermediate aldehyde **63** (91% *ee*) was the starting substance for our first route. The diastereoselective methylation of aldehyde **63** was examined under a variety of conditions and the relevant results are shown in Table 1. In the case of the methylation using MeMgBr, toluene was a better solvent than ether (Table 1, entries 1 and 2). As an additive, hexamethylphosphoramide (HMPA) was better than 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA; Table 1, entries 3–5). MeLi was less effective than MeMgBr (Table 1, entries 2, 3, 6, and 7). The best conditions to introduce the methyl group to aldehyde **63** on a 100-mg scale were as follows (Table 1, entry 3): 1.1 equiv of 3 M MeMgBr in Et_2O was added at −78 °C to a solution of 1.0 equiv **63** and 1.1 equiv HMPA in toluene. After 0.5 h at −78 °C, the desired addition product **67** was obtained in 48% yield together with the undesired diastereomer **68** (15%) and the recovered **63** (20%). The configuration of the newly formed chiral center in **67** was determined by the transformation of **67** into the quinoline derivative **69** by dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), aromatization under acidic conditions, and methyl ether formation with CH_2N_2 (Scheme 14). The obtained **69** was identical to the degradation product derived from thiostrepton[2c] and siomycin A.[8a] The configuration at the C5 position in **63**

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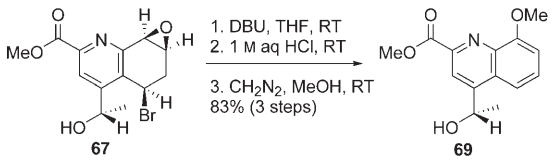
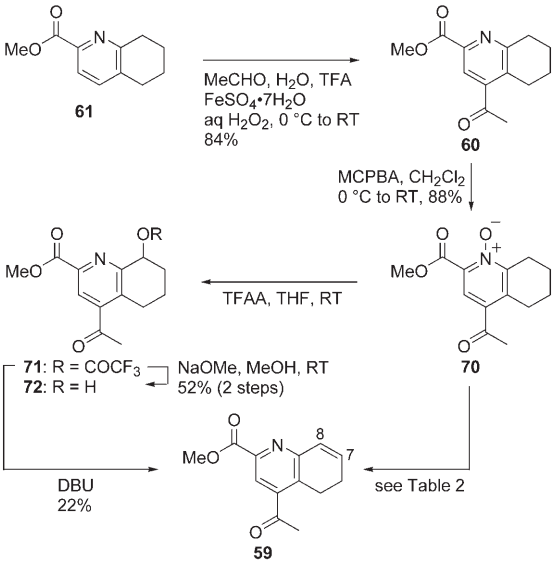


Scheme 14. Structure determination of **67**. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.

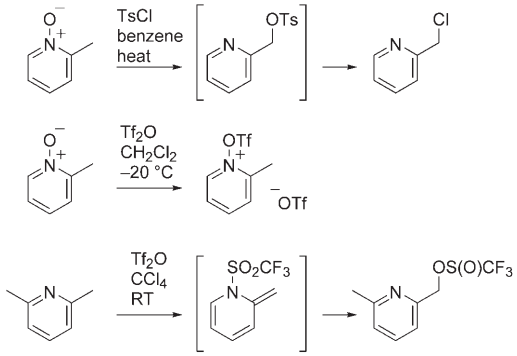
plays a key role in the diastereoselectivity of this reaction, the details of which will be discussed later. Although the hydroxyethyl-bearing dihydroquinoline substructure was secured at this stage, the synthetic route to **67** from **62** was lengthy and the total yield was not satisfactory. Therefore, we investigated a new route including the diastereoselective reduction of a methyl ketone function.

Construction of the hydroxyethyl portion: the second route including a new olefination at the C7–C8 position of 5,6,7,8-tetrahydroquinoline:[13d] Methyl ester **61**[13b] was acetylated under the radical heteroaromatic substitution conditions[69b] to afford **60** in 84% yield (Scheme 15), which was



Scheme 15. Synthesis of **59**. MCPBA = 3-chloroperoxybenzoic acid, TFAA = trifluoroacetic anhydride.

oxidized to *N*-oxide **70** with 3-chloroperoxybenzoic acid (MCPBA) in 88% yield. According to our reported procedure,[13b] *N*-oxide **70** was next subjected to the Boekelheide rearrangement[72] with trifluoroacetic anhydride (TFAA) followed by hydrolysis of the resulting trifluoroacetate **71** with sodium methoxide in one pot to afford **72** in 52% yield. In our previous synthesis of the siomycin D_1 segment C (**66**),[13b] the olefin function at the C7–C8 position was introduced in a moderate yield by treatment of the alcohol corresponding to **72** with the Burgess reagent. We expected that the C7–C8 double bond could be directly obtained from **71** under nonprotic conditions. It was found that the one-pot treatment of **71** with three equivalents of DBU at room temperature for 20 min afforded the elimination product **59**, albeit in low yield (22%). Furthermore, the following three experimental results have been reported (Scheme 16):

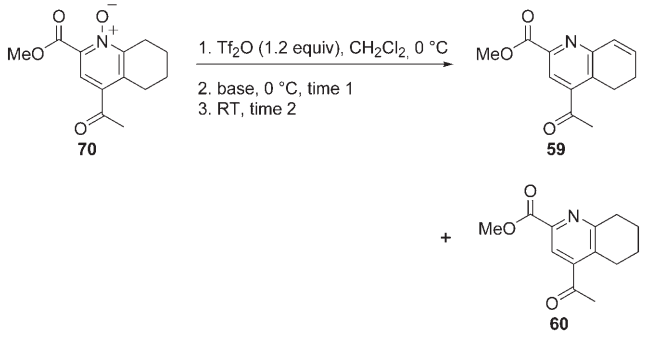


Scheme 16. Precedent reactions of pyridine or pyridine *N*-oxide with sulfonic acid derivatives.

1) Matsumura reported that 2-picoline *N*-oxide was transformed with tosyl chloride into 2-chloromethylpyridine via 2-tosyloxymethylpyridine;[73] 2) picoline *N*-oxides reacted with Tf_2O at −20 °C to give the stable *N*-sulfonyloxy triflate salts;[74] and 3) 2,6-dimethylpyridine reacted with Tf_2O to afford the compound in which a methyl hydrogen atom was replaced by a [(trifluoromethyl)sulfinyl]oxy group.[75] Encouraged by these results, we anticipated that using Tf_2O instead of TFAA in the Matsumura–Boekelheide rearrangement would more efficiently afford the elimination product **59**. The relevant experimental data along this line are shown in Table 2. The treatment of **70** in CH_2Cl_2 with Tf_2O and the consecutive addition of 2,6-lutidine or iPr$_2$NEt expectedly afforded the elimination product **59** (Table 2, entries 1 and 2). Interestingly, but unexpectedly, deoxygenation of *N*-oxide **70** to **60** accompanied this reaction. Fortunately, we found that dilution of iPr$_2$NEt in CH_2Cl_2 raised the ratio of **59**/**60** from 3.8:1 to 5.6:1 (Table 2, entries 2 and 3). Triethylamine was found to be a more suitable base; the ratio was improved to 10:1 (Table 2, entry 4). Finally, the best result was obtained by the slow addition of a 0.45 M CH_2Cl_2 solution of triethylamine to a solution of **70** and Tf_2O in CH_2Cl_2, producing only **59** in 98% yield (Table 2, entry 6). To the best of our knowledge, this is the first example of using Tf_2O in the Matsumura–Boekelheide rearrangement.

Although the reaction mechanism for the accompanied deoxygenation remains to be solved,[76] that for the olefination using Tf_2O and a base by the Matsumura–Boekelheide rearrangement seems to be probable, as depicted in Scheme 17. In the case of the Boekelheide rearrangement using TFAA,[72] the first step is the trifluoroacetylation of *N*-oxide **70** to give **73**. The trifluoroacetate anion abstracts the proton to give the unstable intermediate **74**, which undergoes rearrangement to give **71**; then the basic hydrolysis of **71** finally affords alcohol **72**. For the Tf_2O case, *N*-oxide **70** is sulfonylated to give **75**, which is a stable trifluoromethane-

Table 2. One-pot olefination of **70** via the Matsumura–Boekelheide rearrangement.



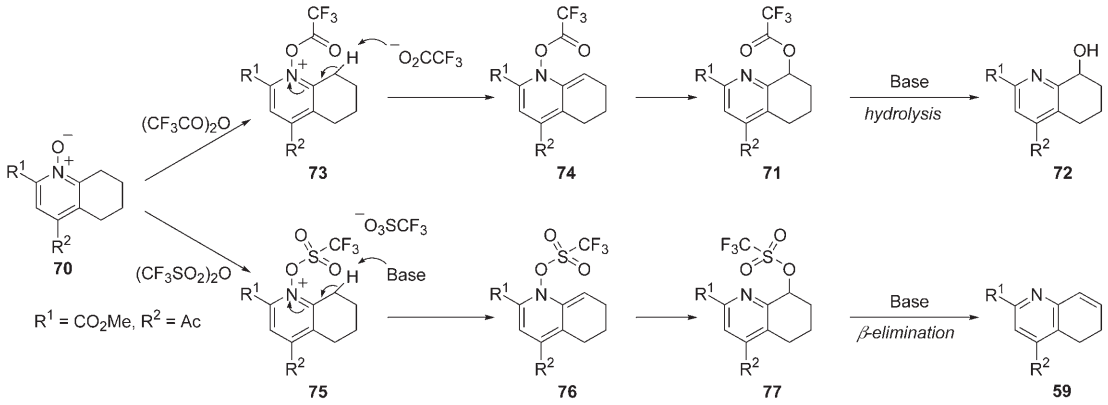
Entry	Base	Time 1 [min][a]	Time 2 [h][a]	Yield of **59**+**60** [%][b]	Ratio[c] of **59**/**60**
1	2,6-lutidine	–[d]	4	63	2.8:1
2	iPr$_2$NEt	–[d]	4	54	3.8:1
3	2.0 M iPr$_2$NEt/ CH_2Cl_2	10	5	66	5.6:1
4	2.0 M Et_3N/ CH_2Cl_2	10	5	58	10:1
5	0.45 M Et_3N/ CH_2Cl_2	30	5	74	**59** only
6	0.45 M Et_3N/ CH_2Cl_2	60	5	98	**59** only

[a] To a solution of **70** (1.0 equiv) in CH_2Cl_2 was added Tf_2O (1.2 equiv) at 0 °C, then a base (5.0 equiv) was added at 0 °C over time 1, and then the mixture was stirred at room temperature for time 2. [b] Yield of isolated product (**59**+**60**) after silica-gel column chromatography. [c] The ratio was based on ^{1}H NMR analysis of the isolated products. [d] Less than one minute.

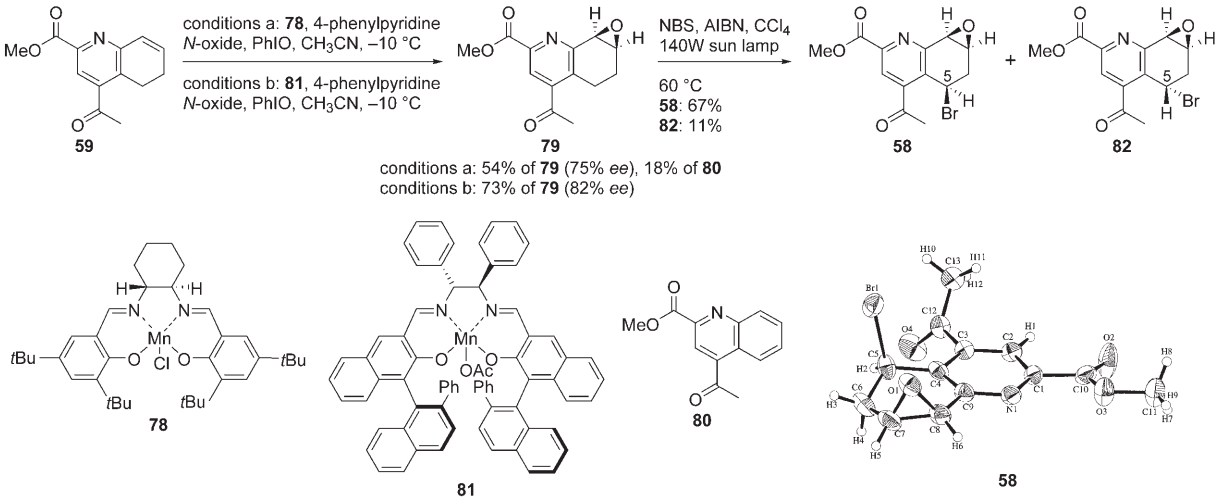
sulfonyloxy salt.[74] The purposely added base abstracts the proton to give the unstable intermediate **76**, which would undergo rearrangement to give **77**; finally, β-elimination of **77** affords olefin **59**.

Next, we turned our attention to an asymmetric epoxidation. Olefin **59** was treated with Jacobsen's reagent **78**[13b,77] in the presence of sodium hypochlorite as the oxidant, resulting in decomposition. In this reaction, by using iodosobenzene instead of sodium hypochlorite, epoxide **79** was obtained in 54% yield together with an 18% yield of the quinoline derivative **80** (Scheme 18). The enantiomeric excess of **79** was determined to be 75% by chiral HPLC analysis. In contrast, using Katsuki's reagent **81**[78] raised both the yield of isolated **79** and its enantiomeric excess to 73% and 82%, respectively, without the formation of **80**. The absolute configuration of **79** was determined in the next stage. Bromination of **79** with *N*-bromosuccinimide (NBS) in CCl_4 afforded **58** in 67% yield together with an 11% yield of its diastereomer **82**. The absolute configuration of **58** (and hence **79**) was confirmed by an X-ray crystallographic analysis (Scheme 18).[79] The crucial selective reduction of the methyl ketone function in **58** was conducted under a variety of conditions and the results are compiled in Table 3. DIBAL and LiBH(sBu)$_3$ preferentially reduced the ester function (Table 3, entries 1 and 2) to give **83** and **84**. Treatment of **58** with $NaBH_4$ in MeOH at −78 °C for 19 h afforded a 96:4 mixture of the desired reduction product **67** and its stereoisomer **68**, from which **67** was isolated in 95% yield (Table 3, entry 3). Other reducing reagents, BH_3·THF, 9-BBN, $Zn(BH_4)_2$, and $Me_4NHB(OAc)_3$, provided no better selectivity and yield (Table 3, entries 4–7). The fact that the compound **67** derived from aldehyde **63** (Table 1) was identical to that derived from methyl ketone **58** confirmed the structure of **63**, which had not previously been determined.[13b]

The diastereoselectivity observed in the addition reactions to aldehyde **63** and methyl ketone **58** may be interpreted as follows (Figure 5). Aldehyde **63**, coordinated with the metal species under the stated reaction conditions, seems to prefer the conformation depicted as **A** rather than conformation **B** because of steric crowding. The attack of a methyl anion seems to occur from the *Si* face of the aldehyde plane to avoid the bromine atom, affording the major isomer **67**. In contrast, the carbonyl and pyridine planes of methyl ketone **58** seem to be twisted to avoid the steric repulsion found in conformations **C** and **D**. Among the two conformations **E** and **F**, the former would be preferable to the latter from the viewpoint of the dipole–dipole interaction. This argument is supported by an X-ray crystallographic analysis of **58** (Scheme 18). The hydride attack seems to occur from the *Re* face of the carbonyl plane, affording the major isomer **67**.

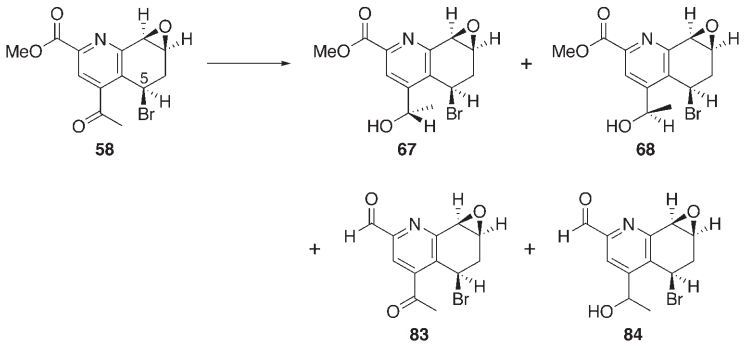


Scheme 17. Mechanisms for the Boekelheide rearrangement and for one-pot olefination via the Matsumura-Boekelheide rearrangement.



Scheme 18. Synthesis and structure determination of **58**. NBS = *N*-bromosuccinimide, AIBN = 2,2′-azobisisobutyronitrile.

Table 3. Diastereoselective Reduction of **58**.



Entry	Reagents (equiv)	Solvent	Temp [°C]	Time [h]	Ratio[a] of **67**/**68**/**83**/**84**/**58**	Yield [%][b] of **67**
1	DIBAL (1.1)	CH_2Cl_2	−78	2	–:–:13:6:81	–
2	LiBH(*s*Bu)$_3$ (1.1)	THF	−78	2	11:–:56:–:33	–
3	$NaBH_4$ (4.5)	MeOH	−78	19	96:4:–:–:–	95
4	BH_3·THF (1.0)	THF	RT	6.5	80:10:–:–:10	60
5	9-BBN[c] (2.0)	THF	−20 to RT	3	–	no reaction
6	$Zn(BH_4)_2$ (1.5)	Et_2O	0	22	42:17:–:–:41	36
7	$Me_4NHB(OAc)_3$ (1.7)	MeCN	RT	20	71:6:–:–:23	49

[a] The ratio was based on ^{1}H NMR analysis of the crude products. [b] Yield of isolated **67** after silica-gel column chromatography. [c] 9-BBN = 9-borabicyclo[3.3.1]nonane.

Comparing these two routes aimed at the preparation of **67**, the first one consists of 15 steps from **62** to **67** in 1.8% overall yield, and the second one consists of 10 steps in 14% overall yield. Therefore, through the second route, we could obtain sufficient amounts of the hydroxyethyl-bearing dihydroquinoline substructure.

Synthesis of segment C (6):[13d] After silylation of **67** with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and 2,6-lutidine (82% yield), the resulting silyl ether was subjected to dehydrobromination with DBU to afford **85** in 95% yield (Scheme 19). Methyl ester **85** was treated with potassium trimethylsilanolate[80] to afford carboxylic acid **86**, which was re-esterified with Boc_2O[81] to afford **56** in 86% yield. In the synthesis of the siomycin D_1 segment C (**66**; Scheme 13), we used $LiClO_4$ for the epoxide-opening reaction. After investigating a variety of reaction conditions that will be precisely discussed in the accompanying article,[23] it was found that $Yb(OTf)_3$ was more suitable for this coupling reaction; 1.0 equiv of dihydroquinoline **56** (75% *ee*) was coupled with 2.0 equiv of L-valine 9-fluorenylmethyl (Fm) ester **57**[82] in the presence of a catalytic amount (0.2 equiv) of $Yb(OTf)_3$ in 1:2 CH_2Cl_2–H_2O at room temperature to give **87** in 48% yield together with a 7% yield of the diastereomer of **87** arising from the enantiomer of **56**, a 6% yield of the regioisomer of **87**, and a 13% yield of the recovered **56**. After silylation of **87** with TBSOTf (96% yield), the *tert*-butyl ester was deprotected with *B*-bromocatecholborane[83] to give segment C (**6**) in 79% yield.

Syntheses of Segments D (7) and E (4)[13e,f]

The preparation of the β-phenylselenoalanine dipeptide segments D (**7**) and E (**4**), the masked precursors to the labile dehydroalanine portions, started with the known Boc-L-serine β-lactone **88**[84] (Scheme 20). Phenylselenylation[42] of **88** using the procedure reported by us[13c] (PhSeH, DMF, RT, 2 h) gave **89**,[15c] which was treated with 9-fluorenylmethanol[85] and 1,3-dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of DMAP to give Fm ester **90** in 82% yield from **88**. TFA treatment of **90** followed by condensation with **89** using CIP,[36] HOAt, and *i*Pr_2NEt in CH_2Cl_2 afforded **91** in 88% yield. Treatment of **91** with 3 M

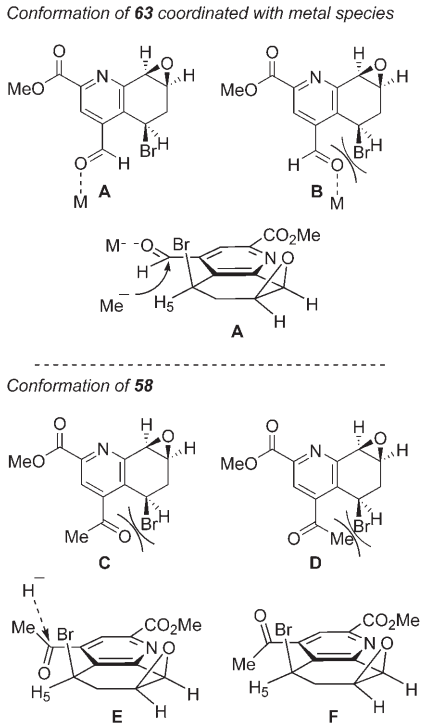
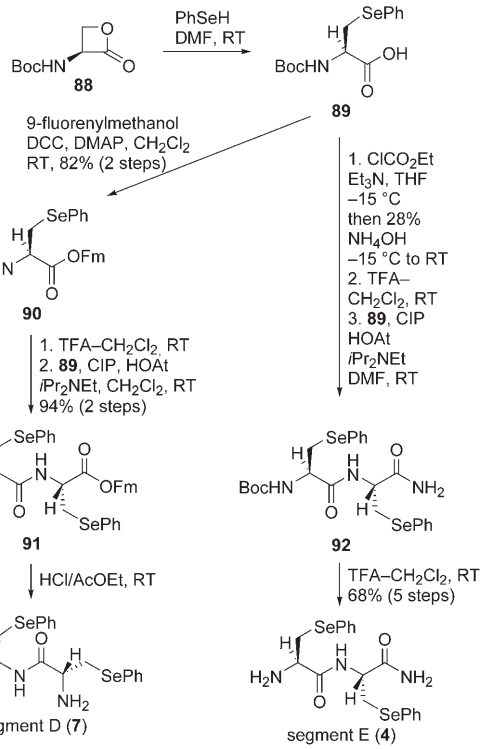
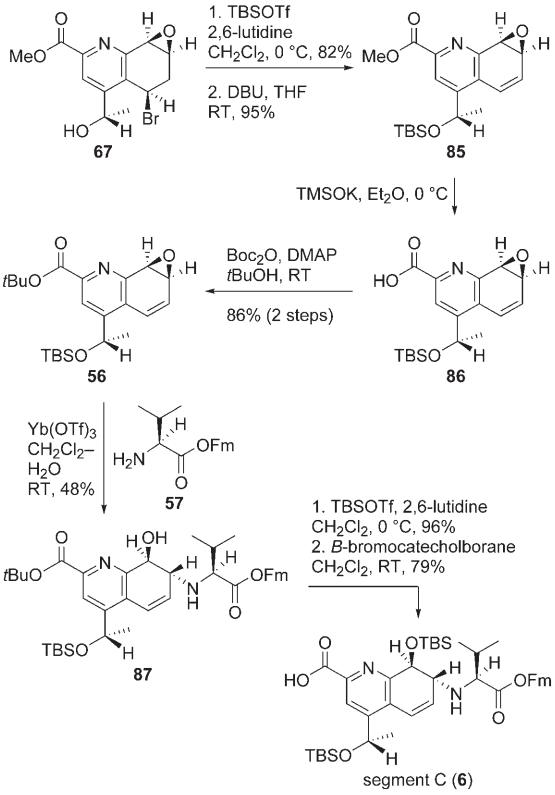


Figure 5. Plausible explanation for diastereoselectivity in addition reactions to **63** and **58**.



Scheme 20. Syntheses of segments D (**7**) and E (**4**). DCC = 1,3-dicyclohexylcarbodiimide.



Scheme 19. Synthesis of segment C (**6**). TMS = trimethylsilyl.

HCl/AcOEt provided segment D (**7**), which was used in the next step without purification.

On the other hand, **89** was converted into the mixed anhydride with $ClCO_2Et$, which was treated with aqueous ammonia to afford the amide. Deprotection of the Boc group with TFA followed by condensation with **89** using CIP,[36] HOAt, and iPr_2NEt in CH_2Cl_2 afforded **92**, which was again treated with TFA to give the side-chain segment E (**4**)[15c] in 68% overall yield from **88**.

Conclusions

We have synthesized the five practical segments for the total synthesis of siomycin A, that is, the tetrasubstituted dehydropiperidine segment A (**5**), the pentapeptide segment B (**3**), the tetrasubstituted dihydroquinoline segment C (**6**), and the β-phenylselenoalanine dipeptide segments D (**7**) and E (**4**). Segment A (**5**) was constructed by the coupling of the azomethine ylide derived from **11** and the chiral sulfinimine **12b**, followed by the stereoselective reduction of the six-membered imine function. Synthesis of piperidine **24** confirmed the configuration of the piperidine ring in thiopeptin B_a. Segment B (**3**) was synthesized by phenylselenylation of β-lactone **42**, stereoselective vinylzinc addition to the chiral sulfinimine **39**, and oxazoline–thioamide conversion method (**32**→**51**→**52**. Segment C (**6**) was prepared by the one-pot olefination of **70** by Matsumura–Boekelheide rear-

rangement using Tf_2O and triethylamine to give **59**, stereoselective reduction of the methyl ketone function in **58** controlled by the stereocenter of the *peri* position, and regioselective epoxide opening of **56** by amine **57** in the presence of $Yb(OTf)_3$. Segments D (**7**) and E (**4**) were synthesized by the coupling of the properly protected β-phenylselenoalanines. With all the important synthetic segments in hand, we set about the total synthesis of siomycin A, which will be reported in the following article.[23]

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. ^1H and ^{13}C NMR spectra were measured on a JEOL GSX-270 spectrometer, a JEOL LAMBDA 300 spectrometer, or a Varian MERCURY plus 300 spectrometer. Chemical shifts of ^1H NMR spectra are expressed in ppm relative to TMS (0 ppm) in $CDCl_3$ or to the solvent residual signal in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), $(CD_3)_2SO$ (2.50 ppm), $(CD_3)_2CO$ (2.05 ppm), CD_3CN (1.94 ppm), or 4:1 $CDCl_3$–CD_3OD (7.38 ppm) as an internal standard unless otherwise noted. Chemical shifts of ^{13}C NMR spectra are expressed in ppm relative to solvent signal in $CDCl_3$ (77.00 ppm), CD_3OD (49.00 ppm), $(CD_3)_2SO$ (206.26 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), JEOL Accu TOF JMS-T100 LCS (ESI), or Bruker Ultraflex (MALDI). 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.

Thioamide *cis*-**16**: To a solution of *cis*-**13** (5.00 g, 15.9 mmol) in MeOH (40 mL), 1,4-dioxane (40 mL), and H_2O (80 mL) at 0 °C was added dropwise 1 M aqueous NaOH (47.7 mL). The reaction mixture was stirred at room temperature for 2 h. AcOEt (200 mL) and 1 M aqueous HCl (60 mL) were added to the solution and the mixture was extracted with AcOEt (200 mL × 3). The combined extracts were evaporated. The residue was once again dissolved in AcOEt and the mixture was filtered through celite. The filtrate was evaporated to afford the dicarboxylic acid (3.57 g) as colorless solids. IR ($CHCl_3$): $\tilde{\nu}$ = 1760, 1705, 1045, 1390 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 10.05 (br s, 2H, CO_2H), 4.59 (m, 1H, pyrrolidine H-2), 4.43 (m, 1H, pyrrolidine H-5), 2.55–1.95 (m, 4H, pyrrolidine H-3, H-4), 1.45 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ = 177.3, 175.5, 153.6, 82.9, 60.8, 59.8, 29.1, 28.8, 28.0 ppm; HRMS (EI): *m*/*z* $[M-H_2O]^+$ calcd for $C_{11}H_{15}NO_5$: 241.0950; found: 241.0932. To a solution of this dicarboxylic acid (6.70 g, 25.8 mmol) and NEt_3 (8.64 mL, 62.0 mmol) in dry THF (260 mL) at 0 °C under Ar atmosphere was slowly added $ClCO_2Et$ (5.44 mL, 56.9 mmol). The solution was stirred at room temperature for 1 h. To the reaction mixture was introduced dry NH_3 gas for 10 min. Then the solvent was evaporated and the residue was chromatographed on silica gel (30–50 % EtOH/hexane) to afford the dicarboxamide (3.77 g) as solids. These solids contain ammonium chloride but can be used for the next reaction without further purification. ^1H NMR (CD_3OD): δ = 4.45–4.16 (m, 2H, pyrrolidine H-2, H-5), 2.46–2.19 (m, 2H, pyrrolidine H-3, H-4), 2.13–1.90 (m, 2H, pyrrolidine H-3, H-4), 1.44 ppm (s, 9H, Boc). To a solution of this dicarboxamide (3.77 g) in dry 1,4-dioxane (70 mL) under Ar atmosphere was added Lawesson's reagent (6.52 g, 16.1 mmol). The mixture was stirred at 90 °C for 1.5 h. The solvent was evaporated and then saturated aqueous $NaHCO_3$ (100 mL) was added to the residue. The mixture was extracted with AcOEt (150 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (50–80 % AcOEt/hexane) to afford *cis*-**16** (2.84 g, 33 % from *cis*-**13**) as solids: R_f = 0.54 (90 % AcOEt/hexane); m.p. 114–115 °C; IR (KBr): $\tilde{\nu}$ = 3300, 3130, 1685, 1630, 1440, 1390, 1365, 1245, 1160 cm^{-1}; ^1H NMR ($(CD_3)_2CO$): δ = 9.94 (br s, 1H, NH_2), 9.70 (br s, 1H, NH_2), 9.03 (br s, 2H, NH_2), 4.75–4.60 (m, 2H, pyrrolidine H-2, H-5), 2.46–2.25 (m, 2H, pyrrolidine H-3, H-4), 2.20–1.98 (m, 2H, pyrrolidine H-3, H-4), 1.39 ppm (s, 9H, Boc); ^{13}C NMR ($(CD_3)_2CO$): δ = 210.9, 209.9, 154.5, 81.0, 69.4, 33.5, 33.1, 28.2 ppm; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{19}N_3O_2S_2$: 289.0919; found: 289.0926.

Thioamides *trans*-**16** and *cis*-**16**: To a solution of *trans*-**13** (7.31 g, 23.2 mmol) in MeOH (60 mL), 1,4-dioxane (80 mL), and H_2O (120 mL) at 0 °C was added dropwise 1 M aqueous NaOH (69.6 mL, 69.6 mmol). The reaction mixture was stirred at room temperature for 3 h. AcOEt (50 mL) and 1 M aqueous HCl (100 mL) were added to the solution and the mixture was extracted with AcOEt (200 mL × 3). The combined extracts were evaporated. The residue was once again dissolved in AcOEt and the mixture was filtered through celite. The filtrate was evaporated to afford the dicarboxylic acid (5.87 g) as colorless solids. IR ($CHCl_3$): $\tilde{\nu}$ = 1725, 1700, 1420, 1045 cm^{-1}; ^1H NMR (CD_3OD): δ = 4.46–4.32 (m, 2H, pyrrolidine H-2, H-5), 2.42–2.22 (m, 2H, pyrrolidine H-3, H-4), 2.13–1.95 (m, 2H, pyrrolidine H-3, H-4), 1.43 ppm (s, 9H, Boc); ^{13}C NMR (CD_3OD): δ = 176.2, 175.9, 155.6, 82.0, 61.0, 60.6, 30.0, 29.2, 28.5 ppm; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{17}NO_6$: 259.1056; found: 259.1077. To a solution of this dicarboxylic acid (5.87 g, 22.6 mmol) and NEt_3 (7.56 mL, 54.2 mmol) in dry THF (226 mL) at 0 °C under Ar atmosphere was slowly added $ClCO_2Et$ (4.75 mL, 49.7 mmol). The solution was stirred at room temperature for 1.5 h. To the reaction mixture was introduced dry NH_3 gas for 10 min. The solvent was evaporated and the residue was chromatographed on silica gel (50 % EtOH/hexane) to afford the dicarboxamide (4.26 g) as solids. These solids contain ammonium chloride but can be used for the next reaction without further purification. ^1H NMR (CD_3OD): δ = 4.48–4.32 (m, 2H, pyrrolidine H-2, H-5), 2.43–2.23 (m, 2H, pyrrolidine H-3, H-4), 2.26–1.84 (m, 2H, pyrrolidine H-3, H-4), 1.44 ppm (s, 9H, Boc). To a solution of this dicarboxamide (4.26 g) in dry 1,4-dioxane (83 mL) was added Lawesson's reagent (7.37 g, 18.2 mmol) under Ar atmosphere. The mixture was stirred at 90 °C for 1.5 h. The solvent was evaporated and then saturated aqueous $NaHCO_3$ (100 mL) was added to the residue. The mixture was extracted with AcOEt (200 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (60–70 % AcOEt/hexane) to afford *cis*-**16** (1.22 g, 16 % from *trans*-**13**) as solids and *trans*-**16** (1.04 g, 19 % from *trans*-**13**) as solids. *trans*-**16**: R_f = 0.43 (90 % AcOEt/hexane); m.p. 257–258 °C; IR (KBr): $\tilde{\nu}$ = 3370, 3320, 3200, 3150, 1705, 1675, 1640, 1620, 1430, 1380, 1365, 1255, 1160 cm^{-1}; ^1H NMR ($(CD_3)_2CO$): δ = 8.88–8.52 (br m, 4H, NH_2 × 2), 4.96–4.86 (m, 2H, pyrrolidine H-2, H-5), 2.72–2.50 (m, 2H, pyrrolidine H-3, H-4), 1.98–1.81 (m, 2H, pyrrolidine H-3, H-4), 1.38 ppm (s, 9H, Boc); ^{13}C NMR (CD_3COCD_3): δ = 211.4, 210.6, 154.3, 80.3, 69.0, 68.7, 32.7, 31.8, 28.5 ppm; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{19}N_3O_2S_2$: 289.0919; found: 289.0919.

Pyrrolidines *cis*-**17** and *trans*-**17** from *cis*-**16**: To a solution of *cis*-**16** (1.22 g, 4.22 mmol) in dry EtOH (42 mL) in Ar atmosphere was added 85 % ethyl bromopyruvate (1.25 mL, 8.44 mmol). The mixture was heated at reflux for 2 h. The solvent was evaporated and then saturated aqueous $NaHCO_3$ (50 mL) was added to the residue. The mixture was extracted with AcOEt (50 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (5–10 % acetone/hexane) to afford *cis*-**17** (983 mg, 61 %) as solids and *trans*-**17** (268 mg, 17 %) as solids. *cis*-**17**: R_f = 0.26 (10 % acetone/$CHCl_3$); m.p. 112–113 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 1720, 1490, 1320, 1290, 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.12 (s, 2H, thiazole H-5), 4.90 (m, 2H, pyrrolidine H-2, H-5), 4.43 (q, 4H, J = 7.1 Hz, $CO_2C\underline{H}_2CH_3$ × 2), 3.46 (br s, 1H, NH), 2.58–2.38 (m, 2H, pyrrolidine H-3, H-4), 2.16–1.98 (m, 2H, pyrrolidine H-3, H-4), 1.41 ppm (t, 6H, J = 7.1 Hz, $CO_2CH_2C\underline{H}_3$ × 2); ^{13}C NMR ($CDCl_3$): δ = 179.3, 161.5, 147.5, 127.3, 61.3, 59.9, 34.1, 14.3 ppm; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{19}N_3O_4S_2$: 381.0817; found: 381.0801; elemental analysis (%) calcd

for $C_{16}H_{19}N_3O_4S_2$: C 50.38, H 5.02, N 11.02, S 16.81; found: C 50.24, H 4.99, N 11.03, S 16.89. *trans*-**17**: R_f=0.47 (10% acetone/$CHCl_3$); m.p. 149–150°C; IR ($CHCl_3$): $\tilde{\nu}$=1720, 1485, 1375, 1320, 1100 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.11 (s, 2H, thiazole H-5), 4.96–4.88 (m, 2H, pyrrolidine H-2, H-5), 4.42 (q, 4H, J=7.2 Hz, $CO_2C\underline{H}_2CH_3\times2$), 3.06 (brs, 1H, NH), 2.56–2.37 (m, 2H, pyrrolidine H-3, H-4), 2.22–2.04 (m, 2H, pyrrolidine H-3, H-4), 1.41 ppm (t, 6H, J=7.2 Hz, $CO_2CH_2C\underline{H}_3\times2$); ^{13}C NMR ($CDCl_3$): δ=177.5, 161.4, 147.2, 127.4, 61.4, 59.5, 33.1, 14.3 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{19}N_3O_4S_2$: 381.0817; found: 381.0844, elemental analysis (%) calcd for $C_{16}H_{19}N_3O_4S_2$: C 50.38, H 5.02, N 11.02, S 16.81; found: C 50.65, H 5.28, N 10.80, S 16.76.

Pyrrolidines *trans*-**17** and *cis*-**17** from *trans*-**16**: To a solution of *trans*-**16** (1.04 g, 3.60 mmol) in dry EtOH (36 mL) in Ar atmosphere was added 85% ethyl bromopyruvate (1.06 mL, 7.20 mmol). The mixture was heated at reflux for 2 h. The solvent was evaporated and then saturated aqueous $NaHCO_3$ (50 mL) was added to the residue. The mixture was extracted with AcOEt (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (5–10% acetone/hexane) to afford *trans*-**17** (441 mg, 32%) as solids and *cis*-**17** (443 mg, 32%) as solids.

Dehydropyrrolidine **11** from *cis*-**17**: To a solution of *cis*-**17** (741 mg, 1.94 mmol) in dry THF (20 mL) at −78°C under Ar atmosphere was added dropwise *tert*-butyl hypochlorite (0.231 mL, 2.04 mmol). The solution was stirred for 20 min and then NEt_3 (1.08 mL, 7.77 mmol) was added. The temperature was raised to room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with AcOEt (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (60% AcOEt/hexane) to afford **11** (701 mg, 95%) as colorless solids: m.p. 144–146°C; IR ($CHCl_3$): $\tilde{\nu}$= 1725, 1045 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.33 (s, 1H, thiazole H-5), 8.14 (s, 1H, thiazole H-5), 5.72 (dd, J=7.5, 7.5 Hz, 1H, pyrrolidine H-5), 4.46 (q, J=7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.44 (q, J=7.1 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.55–3.37 (m, 1H, pyrrolidine H-3), 3.37–3.19 (m, 1H, pyrrolidine H-3), 2.95–2.75 (m, 1H, pyrrolidine H-4), 2.44–2.23 (m, 1H, pyrrolidine H-4), 1.43 (t, J=7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.42 ppm (t, J=7.1 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$): δ=173.3, 171.8, 163.4, 161.3, 160.9, 148.4, 147.2, 130.7, 127.4, 74.4, 61.6, 61.4, 36.0, 30.4, 14.3, 14.2 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_{16}H_{17}N_3O_4S_2$: 379.0660; found: 379.0661; elemental analysis (%) calcd for $C_{16}H_{17}N_3O_4S_2$: C 50.65, H 4.52, N 11.07, S 16.90; found: C 50.63, H 4.34, N 11.10, S 16.84.

Dehydropyrrolidine **11** from *trans*-**17**: To a solution of *trans*-**17** (426 mg, 1.12 mmol) in dry THF (11 mL) at −78°C under Ar atmosphere was added *tert*-butyl hypochlorite (0.132 mL, 1.17 mmol). The solution was stirred for 20 min and then NEt_3 (0.624 mL, 4.48 mmol) was added. The temperature was raised to room temperature and the reaction mixture was stirred for 4 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with AcOEt (20 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (60% AcOEt/hexane) to afford **11** (321 mg, 76%) as colorless solids.

Thiazole aldehyde **14**: To a solution of **19** (800 mg, 3.12 mmol) in dry toluene (21 mL) at −78°C under Ar atmosphere was added DIBAL (1.0 M in toluene, 10.0 mL, 10.0 mmol). The reaction mixture was stirred at room temperature for 1.5 h. The reaction was quenched with H_2O (50 mL), followed by addition of pottasium sodium tartrate tetrahydrate (8.81 g, 31.2 mmol). The mixture was stirred until the emulsion disappeared. The mixture was extracted with AcOEt (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (50–70% acetone/hexane) to afford the alcohol (578 mg, 86%) as a syrup $[\alpha]_D^{28}$ −22.0 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=3280, 1750, 1385, 1300, 1235, 1205, 1110, 1060, 980 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.29 (brs, 1H, NH), 7.23 (s, 1H, thiazole H-5), 4.83 (dd, 1H, J=1.2, 6.3 Hz, oxazolidine H-4), 4.70 (brs, 2H, $C\underline{H}_2OH$), 4.62 (dq, 1H, J=6.3, 6.3 Hz, oxazolidine H-5), 3.87 (brs, 1H, OH), 1.57 ppm (d, 1H, J=6.3 Hz, oxazolidine 5-Me); ^{13}C NMR ($CDCl_3$): δ=170.4, 158.8, 157.1, 116.0, 80.0, 61.0, 60.3, 19.8 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_8H_{10}N_2O_3S$: 214.0412; found: 214.0411. This alcohol (402 mg, 1.88 mmol) and CMD (2.45 g) in AcOEt (9 mL) and CH_2Cl_2 (9 mL) were stirred at room temperature for 20 h. The suspension was filtered through celite and the filter cake was washed with AcOEt. The filtrate and washings were concentrated. The residue was chromatographed on silica gel (50% acetone/hexane) to afford **14** (340 mg, 85%) as a pale yellow syrup: $[\alpha]_D^{27}$ −54.0 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=1750, 1695, 1490, 1390, 1300, 1230, 1130, 1110, 1065 cm^{-1}; ^1H NMR ($CDCl_3$): δ=9.96 (s, 1H, CHO), 8.25 (s, 1H, thiazole H-5), 7.48 (brs, 1H, NH), 4.99 (dd, J=1.1, 6.1 Hz, 1H, oxazolidinone H-4), 4.69 (dt, J=6.1, 6.1 Hz, 1H, oxazolidinone H-5), 1.64 ppm (d, J=6.1 Hz, 3H, oxazolidinone 5-Me); ^{13}C NMR ($CDCl_3$): δ=184.1, 172.2, 158.8, 155.3, 129.2, 79.8, 60.9, 19.9 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_8H_8N_2O_3S$: 212.0256; found: 212.0254.

Adduct **21**: A solution of **14** (336 mg, 1.58 mmol), **15b** (245 mg, 1.58 mmol), $LiClO_4$ (1.40 g, 13.2 mmol), and NEt_3 (1.84 mL, 13.2 mmol) in dry THF (13 mL) was stirred at room temperature for 5 h under Ar atmosphere to form **12b**. The temperature was cooled to −40°C and then **11** (500 mg, 1.32 mmol) was added to the above solution. The mixture was stirred at −25°C for 1 day. The reaction mixture was quenched with H_2O (20 mL) and extracted with AcOEt (20 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (85–100% AcOEt/hexane) to afford **21** (678 mg, 71%) as colorless solids and its diastereomer (166 mg, 17%) as colorless solids. **21**: m.p. 110–111°C; $[\alpha]_D^{30}$ −134.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=1765, 1730, 1480, 1420, 1340, 1100, 1050 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.32 (s, 1H, thiazole H-5), 7.95 (s, 1H, thiazole H-5), 7.45 (d, J=8.4 Hz, 2H, toluene), 7.28 (d, J=8.4 Hz, 2H, toluene), 6.79 (s, 1H, thiazole H-5), 6.70 (d, J=1.2 Hz, 1H, oxazolidinone NH), 5.79 (d, J=8.7 Hz, 1H, NHSO), 4.94 (d, J=8.7 Hz, 1H, C$\underline{H}$NHSO), 4.77 (dd, J=1.2, 6.6 Hz, 1H, oxazolidinone H-4), 4.51 (dq, J=6.6, 6.6 Hz, 1H, oxazolidinone H-5), 4.43 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.39 (q, J=7.2 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.22–3.06 (m, 2H, pyrrolidine H-3×2), 2.66–2.46 (m, 2H, pyrrolidine H-4×2), 2.43 (s, 3H, toluene), 1.62 (d, J=6.6 Hz, 3H, oxazolidinone 5-Me), 1.42 (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.39 ppm (t, J=7.2 Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$): δ= 174.4, 172.0, 168.7, 163.0, 161.2, 160.8, 158.2, 154.7, 148.5, 146.7, 141.6, 140.6, 130.9, 129.6, 128.0, 125.5, 116.5, 86.2, 79.7, 61.7, 61.4, 61.2, 59.3, 36.8, 31.8, 21.3, 19.7, 14.2 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{31}H_{33}N_6O_7S_4$: 729.1293; found: 729.1302. Diastereomer of **21**: ^1H NMR ($CDCl_3$): δ=8.35 (s, 1H, thiazole H-5), 8.09 (s, 1H, thiazole H-5), 7.17–7.08 (m, 4H, toluene), 7.07 (s, 1H, thiazole H-5), 6.31 (brs, 1H, oxazolidinone NH), 5.97 (d, J=10.4 Hz, 1H, NHSO), 4.75 (d, J= 10.4 Hz, 1H, C$\underline{H}$NHSO), 4.60 (dd, J=6.0, 1.4 Hz, 1H oxazolidinone H-4), 4.56–4.37 (m, 4H, $CO_2C\underline{H}_2CH_3\times2$), 4.32 (dq, J=6.0, 6.0 Hz, 1H, oxazolidinone H-5), 3.09–2.95 (m, 1H, pyrrolidine H-3), 2.62–2.48 (m, 1H, pyrrolidine H-3), 2.46–2.14 (m, 2H, pyrrolidine H-4×2), 2.39 (s, 3H, toluene), 1.44 (t, J=7.0 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.40 (t, J=7.0 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.22 ppm (d, J=6.0 Hz, 3H, oxazolidinone 5-Me).

Aminopiperidine **8**: To a solution of **21** (500 mg, 6.86×10^{-1} mmol) in dry EtOH (7 mL) at 0°C under Ar atmosphere was added TFA (0.264 mL, 3.43 mmol). The solution was stirred at room temperature for 1 h. The reaction was quenched with aqueous $NaHCO_3$ (5 mL) at 0°C. The mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford a mixture of **9** and **10**. This mixture and AcOH (0.393 mL, 6.86 mmol) were dissolved in dry EtOH (4 mL). To the mixture at 0°C was added $NaBH_3CN$ (129 mg, 2.06 mmol) in dry EtOH (3 mL). The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with aqueous $NaHCO_3$ (7 mL) at 0°C. The mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (90–100% AcOEt/hexane) to afford **8** (213 mg, 52%) as colorless solids: m.p. 86–87°C; $[\alpha]_D^{30}$ +94.3 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$= 1760, 1720, 1480, 1390, 1365, 1340, 1320, 1300, 1100, 1050, 1025 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.14 (s, 1H, thiazole H-5), 7.95 (s, 1H, thiazole H-5), 6.98 (s, 1H, thiazole H-5), 6.92 (brs, 1H, oxazolidinone NH), 4.85 (s, 1H, piperidine H-6), 4.76 (dd, J=1.2, 6.3 Hz, 1H, oxazolidinone H-4),

4.52–4.34 (m, 2H, piperidine H-2, oxazolidinone H-5), 4.40 (q, $J=7.2$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.39 (q, $J=7.2$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 2.78–2.40 (m, 1H, piperidine H-4β), 2.38–2.22 (m, 1H, piperidine H-3), 2.19–1.96 (m, 2H, piperidine H-4α, H-3), 1.53 (d, $J=6.3$ Hz, 3H, oxazolidinone 5-Me), 1.39 ppm (t, $J=7.2$ Hz, 6H, $CO_2CH_2C\underline{H}_3\times2$); ^{13}C NMR ($CDCl_3$): $\delta=$ 181.6, 173.7, 169.3, 161.6, 161.3, 158.3, 154.2, 147.3, 146.7, 127.5, 127.3, 117.8, 79.6, 63.8, 61.5, 61.3, 61.0, 58.3, 58.2, 37.7, 28.1, 19.7, 14.3 ppm; HRMS (FAB) m/z $[M+H]^+$ calcd for $C_{24}H_{29}N_6O_6S_3$: 593.1310; found: 593.1301.

Boc-alanylpiperidine **23**: To a solution of **8** (262 mg, 4.42×10^{-1} mmol), DMAP (10.8 mg, 8.84×10^{-2} mmol), and NEt_3 (0.0678 mL, 4.86×10^{-1} mmol) in dry THF (4.4 mL) at 0 °C under Ar atmosphere was added Boc_2O (0.112 mL, 4.86×10^{-1} mmol). The solution was stirred at 0 °C for 1 h. The reaction was quenched with H_2O (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 chromatographed on silica gel (80–90% AcOEt/hexane) to afford the Boc-oxazolidinone (257 mg, 84%) as colorless solids: $[\alpha]_D^{27}$ +60.2 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=$1820, 1725, 1480, 1375, 1325, 1155, 1100, 1080, 1045, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) $\delta=$8.15 (s, 1H, thiazole H-5), 7.96 (s, 1H, thiazole H-5), 6.97 (s, 1H, thiazole H-5), 5.01 (d, $J=4.5$ Hz, 1H, oxazolidinone H-4), 4.90 (s, 1H, piperidine H-6), 4.56 (dq, 1H, $J=4.5$, 6.6 Hz, oxazolidinone H-5), 4.52–4.36 (m, 5H, piperidine H-2, $CO_2C\underline{H}_2CH_3\times2$), 2.78–2.62 (m, 1H, piperidine H-4β), 2.46–2.30 (m, 1H, piperidine), 2.16–1.96 (m, 2H, piperidine), 1.52 (d, $J=6.6$ Hz, 3H, oxazolidinone 5-Me), 1.46–1.37 (m, 6H, $CO_2CH_2C\underline{H}_3\times2$), 1.42 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): $\delta=$181.6, 173.7, 166.9, 161.5, 161.4, 154.1, 150.8, 148.7, 147.4, 147.0, 127.6, 127.2, 117.7, 84.7, 75.8, 63.8, 62.4, 61.5, 61.2, 58.3, 58.1, 37.9, 27.9, 27.8, 20.0, 14.3 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{29}H_{37}N_6O_8S_3$: 693.1835; found: 693.1839. To a solution of the above Boc-oxazolidinone (245 mg, 3.54×10^{-1} mmol), *N*-Boc-L-alanine **22** (134 mg, 7.08×10^{-1} mmol), HOAt (134 mg, 7.08×10^{-1} mmol), and iPr$_2$NEt (0.278 mL, 1.59 mmol) in CH_2Cl_2 (3.5 mL) at room temperature under Ar atmosphere was added CIP (197 mg, 7.08×10^{-1} mmol). The solution was stirred for 1 day and quenched with H_2O (4 mL). 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 dissolved in $CHCl_3$ and this was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (70–80% AcOEt/hexane) to afford **23** (284 mg, 93%) as colorless solids: $[\alpha]_D^{30}$ +20.9 (c 1.00, MeOH); IR ($CHCl_3$): $\tilde{\nu}=$1820, 1795, 1720, 1500, 1370, 1325, 1160, 1100, 1070, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=$8.54 (brs, 1H, amide NH), 8.12 (s, 1H, thiazole H-5), 7.84 (s, 1H, thiazole H-5), 6.89 (s, 1H, thiazole H-5), 5.45 (br d, $J=6.0$ Hz, 1H, BocNH), 5.17 (d, $J=$ 2.7 Hz, 1H, oxazolidinone H-4), 5.03 (dq, $J=2.7$, 6.3 Hz, 1H, oxazolidinone H-5), 4.59 (s, 1H, piperidine H-6), 4.46 (dd, $J=2.7$, 10.1 Hz, 1H, piperidine H-2), 4.41 (q, $J=7.2$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.40 (q, $J=7.2$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.16 (dq, $J=6.0$, 6.6 Hz, 1H, Ala H-α), 3.51 (br d, $J=$ 14.1 Hz, 1H, piperidine H-4α), 2.72 (ddd, $J=14.1$, 14.1, 3.4 Hz, 1H, piperidine H-4β), 2.24 (brd, $J=12.0$ Hz, 1H, piperidine H-3β), 2.01 (brddd, $J=12.0$, 14.1, 10.1 Hz, 1H, piperidine H-3α), 1.61 (d, $J=6.3$ Hz, 3H, oxazolidinone 5-Me), 1.46 (s, 9H, Boc), 1.45 (d, $J=6.6$ Hz, 3H, Ala Me), 1.39 (t, $J=7.2$ Hz, 4H, $CO_2C\underline{H}_2CH_3\times2$), 1.30 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): $\delta=$174.9, 173.3, 173.0, 167.4, 161.4, 161.3, 155.3, 152.8, 151.3, 148.9, 146.8, 127.3, 127.1, 119.7, 85.4, 79.7, 75.8, 64.9, 61.5, 61.4, 61.3, 61.2, 58.0, 51.4, 30.7, 28.2, 28.1, 27.8, 27.4, 20.4, 18.7, 14.3 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{37}H_{50}N_7O_{11}S_3$: 864.2731; found: 864.2726.

Dehydropiperidine **25**: To a solution of **23** (100 mg, 1.16×10^{-1} mmol) in THF (1.2 mL) at −78 °C under Ar atmosphere was added *tert*-butyl hypochlorite (0.144 mL, 1.28×10^{-1} mmol). The solution was stirred for 30 min and then DMAP (2.8 mg, 2.3×10^{-2} mmol) and NEt_3 (0.162 mL, 1.16 mmol) were added. The temperature was raised to room temperature and the reaction mixture was stirred for 5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1 mL) and saturated aqueous $NaHCO_3$ (1 mL). 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 (35–40% acetone/hexane) to afford **25** (94.6 mg, 95%) as pale yellow solids: $[\alpha]_D^{30}$ +23.3 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=$1820, 1720, 1500, 1370, 1330, 1160, 1100, 1070, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=$8.43 (brs, 1H, amide NH), 8.19 (s, 1H, thiazole H-5), 7.91 (s, 1H, thiazole H-5), 7.00 (brs, 1H, thiazole H-5), 5.43 (brs, 1H, piperidine H-6), 5.30–5.12 (m, 3H, BocNH, oxazolidinone H-4, oxazolidinone H-5), 4.51–4.34 (m, 4H, $CO_2C\underline{H}_2CH_3\times$ 2), 3.99 (dq, $J=7.2$, 5.7 Hz, 1H, Ala H-α), 3.63 (ddd, $J=13.8$, 5.4, 0.0 Hz, 1H, piperidine H-4α), 3.39 (m, 1H, piperidine H-3β), 3.12–2.92 (m, 1H, piperidine H-3β), 2.80 (ddd, $J=13.8$, 13.2, 6.0 Hz, 1H, piperidine H-4β), 1.61(d, $J=6.3$ Hz, 3H, oxazolidinone 5-Me), 1.50 (s, 9H, Boc), 1.47–1.35 (m, 6H, $CO_2CH_2C\underline{H}_3\times2$), 1.35 (d, $J=7.2$ Hz, 3H, Ala Me), 1.21 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): $\delta=$175.2, 173.7, 168.9, 167.6, 163.6, 161.2, 161.1, 155.2, 153.2, 150.5, 148.6, 147.9, 147.0, 130.0, 127.3, 120.0, 85.2, 79.6, 74.9, 66.7, 61.6, 61.4, 61.3, 59.8, 51.9, 27.9, 27.8, 26.9, 24.5, 20.5, 17.9, 14.25, 14.22 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{37}H_{48}N_7O_{11}S_3$: 862.2574; found: 862.2573.

Alanylpiperidine **24**: To a solution of **23** (50 mg, 5.79×10^{-2} mmol) in MeOH (0.25 mL), 1,4-dioxane (0.25 mL), and H_2O (0.5 mL) at 0 °C was added LiOH (6.9 mg, 2.9×10^{-1} mmol). The mixture was stirred at room temperature for 2 h. The mixture was quenched with 1 M aqueous HCl (1 mL) at 0 °C and extracted with AcOEt (1 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was dissolved in 1,4-dioxane (0.5 mL) and 1 M aqueous HCl (1 mL), and the mixture was stirred at room temperature for 1 h. The solvent was evaporated to afford the crude amino acid. This was dissolved in MeOH (0.1 mL). Acetone (5 mL) was added to the solution to form precipitates. The precipitates were filtered off to afford **24**·3HCl (30.2 mg, 76%) as solids: $[\alpha]_D^{30}$ +45.6 (c 1.21 (3HCl), 1 M aqueous HCl) [Ref. [10f]: $[\alpha]_D^{29}$ +45 (1 M aqueous HCl); Ref. [37]: $[\alpha]_D^{26}$ +44.7 (c 1.02, 1 M aqueous HCl)]; IR (KBr, HCl free): $\tilde{\nu}=$1685, 1580, 1380 cm^{-1} [Ref. [10f]: IR (KBr): $\tilde{\nu}=$1684 cm^{-1}; Ref. [37]: IR (KBr): $\tilde{\nu}=$1690, 1580, 1480, 1370 cm^{-1}]; ^{1}H NMR (D_2O, HCl salt): $\delta=$8.64 (s, 1H, thiazole H-5), 8.49 (s, 1H, thiazole H-5), 7.59 (s, 1H, thiazole H-5), 5.45 (s, 1H, piperidine H-6), 5.37 (br d, $J=10.5$ Hz, 1H, piperidine H-2), 4.94 (d, $J=6.9$ Hz, 1H, $H_2NC\underline{H}$), 4.50 (q, $J=6.9$ Hz, 1H, Ala H-α), 4.38 (dq, $J=6.9$, 6.6 Hz, 1H, $CHC\underline{H}(OH)CH_3$), 3.44 (br d, $J=14.7$ Hz, 1H, piperidine H-4α), 2.94 (br dd, $J=14.7$, 12.6 Hz, 1H, piperidine H-4β), 2.79 (br d, $J=12.6$ Hz, 1H, piperidine H-3β), 2.47 (br ddd, $J=10.5$, 12.6, 12.6 Hz, 1H, piperidine H-3α), 1.77 (d, $J=6.9$ Hz, 3H, Ala Me), 1.32 ppm (d, $J=6.6$ Hz, 3H, $CHCH(OH)C\underline{H}_3$) [Ref. [37]: ^{1}H NMR (D_2O, HCl salt): $\delta=$8.61 (s, 1H), 8.46 (s, 1H), 7.59 (s, 1H), 5.48 (s, 1H), 5.40 (1H), 4.52 (q, $J=8$ Hz, 1H), 4.40 (dq, $J=6.5$, 6.5 Hz, 1H), 3.6–3.3 (1H), 3.2–2.2 (3H), 1.77 (d, $J=$ 8 Hz, 3H), 1.30 ppm (d, $J=6.5$ Hz, 3H)]; ^{13}C NMR (D_2O, HCl salt): $\delta=$ 172.3, 171.5, 166.4, 166.2, 165.2, 164.9, 147.5, 147.2, 146.2, 132.5, 132.1, 126.5, 68.9, 62.6, 62.2, 58.4, 58.3, 51.3, 32.1, 26.3, 20.1, 18.1 ppm [Ref. [37]: ^{13}C NMR (D_2O, HCl salt): $\delta=$172.3, 171.4, 166.4, 165.8, 165.2, 164.8, 147.4, 147.1, 146.0, 132.6, 132.1, 126.6, 68.9, 62.6, 62.2, 58.4, 58.4, 51.4, 32.2, 26.2, 20.2, 18.2 ppm].

Adduct **20**: A solution of **14** (280 mg, 1.32 mmol), **15a** (205 mg, 1.32 mmol), $LiClO_4$ (1.40 g, 13.2 mmol), and NEt_3 (1.84 mL, 13.2 mmol) in dry THF (11 mL) was stirred at room temperature for 5 h under Ar atmosphere to form **12a**. The temperature was cooled to −40 °C and then **11** (500 mg, 1.32 mmol) was added to the above solution. The mixture was stirred at −25 °C for 1 day. The reaction mixture was quenched with H_2O (30 mL) and extracted with AcOEt (30 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (90–100% AcOEt/hexane) to afford **20** (628 mg, 65%) as colorless solids and its diastereomer (115 mg, 6%) as colorless solids, and **11** (129 mg, 26%) was recovered. **20**: ^{1}H NMR ($CDCl_3$): $\delta=$8.30 (s, 1H, thiazole H-5), 7.99 (s, 1H, thiazole H-5), 7.45 (d, $J=12.0$ Hz, 2H, toluene), 7.27 (d, $J=12.0$ Hz, 2H, toluene), 6.96 (s, 1H, thiazole H-5), 6.30 (brs, 1H, oxazolidinone NH), 5.72 (d, $J=12.0$ Hz, 1H, NHSO), 5.05 (d, $J=12.0$ Hz, 1H, C$\underline{H}$NHSO), 4.75 (dd, $J=9.6$, 1.8 Hz, 1H, oxazolidinone H-4), 4.51 (dq, $J=9.6$, 9.6 Hz, 1H, oxazolidinone H-5), 4.48–4.34 (m, 4H, $CO_2C\underline{H}_2CH_3\times2$), 3.20–3.06 (m, 2H, pyrrolidine H-3 × 2), 2.75–2.51 (m, 2H, pyrrolidine H-4 × 2), 2.42 (s, 3H, toluene), 1.51 (d, $J=9.6$ Hz, 3H, oxazolidinone 5-Me), 1.41 (t, $J=$ 10.5 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.39 ppm (t, $J=10.5$ Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$): $\delta=$174.3, 172.1, 168.3, 163.0, 161.3, 160.8, 158.2, 154.4, 148.6, 146.7, 141.6, 141.1, 131.0, 129.7, 128.0, 125.4, 117.5, 86.0,

79.7, 61.7, 61.4, 60.9, 59.7, 36.8, 31.5, 21.4, 19.7, 14.3, 14.2 ppm. Diastereomer of **20**: ^{1}H NMR ($CDCl_3$): δ = 8.38 (s, 1H, thiazole H-5), 8.11 (s, 1H, thiazole H-5), 7.13 (d, J = 8.4 Hz, 2H, toluene), 7.08 (d, J = 8.4 Hz, 2H, toluene), 7.08 (s, 1H, thiazole H-5), 6.25 (brs, 1H, oxazolidinone NH), 5.96 (d, J = 10.5 Hz, 1H, NHSO), 4.81 (d, J = 10.5 Hz, 1H, CHNHSO), 4.52 (dd, J = 6.0, 0.9 Hz, 1H, oxazolidinone H-4), 4.50–4.37 (m, 4H, $CO_2CH_2CH_3$ × 2), 4.34 (dq, J = 6.0, 6.0 Hz, 1H, oxazolidinone H-5), 3.07–2.92 (m, 1H, pyrrolidine H-3), 2.62–2.25 (m, 3H, pyrrolidine H-3, H-4 × 2), 2.38 (s, 3H, toluene), 1.47–1.36 ppm (m, 9H, oxazolidinone 5-Me, $CO_2CH_2CH_3$ × 2).

Aminopiperidine **26**: To a solution of **20** (235 mg, 3.22×10^{-1} mmol) in dry EtOH (3.2 mL) at 0 °C was added TFA (0.248 mL, 3.22 mmol). The solution was stirred at room temperature for 1 h. The reaction was quenched with aqueous $NaHCO_3$ (5 mL) at 0 °C. The mixture was extracted with AcOEt (5 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford the crude amine. This crude amine and AcOH (0.185 mL, 3.22 mmol) were dissolved in dry EtOH (1 mL). To the mixture was added $NaBH_3CN$ (60.8 mg, 9.67×10^{-1} mmol) in dry EtOH (2.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with aqueous $NaHCO_3$ (5 mL) at 0 °C. The mixture was extracted with AcOEt (5 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (90–100% AcOEt/hexane) to afford **26** (90.0 mg, 47%) as colorless solids: ^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1H, thiazole H-5), 7.97 (s, 1H, thiazole H-5), 6.98 (s, 1H, thiazole H-5), 6.31 (brs, 1H, oxazolidinone NH), 4.89 (s, 1H, piperidine H-6), 4.72 (dd, J = 6.0, 2.0 Hz, 1H, oxazolidinone H-4), 4.53–4.34 (m, 6H, piperidine H-2, oxazolidinone H-5, $CO_2CH_2CH_3$ × 2), 2.78–2.64 (m, 1H, piperidine H-4α), 2.50–2.25 (m, 1H, piperidine H-3), 2.15–1.96 (m, 2H, piperidine H-4β, H-3), 1.49 (d, J = 6.0 Hz, 3H, oxazolidinone 5-Me), 1.40 ppm (t, J = 7.0 Hz, 6H, $CO_2CH_2CH_3$ × 2); ^{13}C NMR ($CDCl_3$): δ = 181.2, 173.6, 169.1, 161.6, 161.4, 158.2, 154.5, 147.4, 147.0, 127.6, 127.2, 117.5, 79.8, 64.0, 61.6, 61.4, 60.9, 58.3, 58.1, 38.0, 28.1, 19.8, 14.3 ppm.

Boc-alanylpiperidine **27**: To a solution of **26** (85.8 mg, 1.45×10^{-1} mmol), DMAP (1.8 mg, 1.4×10^{-2} mmol), and NEt_3 (0.0222 mL, 1.59×10^{-1} mmol) in dry THF (1.5 mL) at 0 °C under Ar atmosphere was added Boc_2O (0.0366 mL, 1.59×10^{-1} mmol). The solution was stirred at 0 °C for 1 h. The reaction was quenched with H_2O (2 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 (80–100% AcOEt/hexane) to afford the Boc-oxazolidinone (83.0 mg, 83%) as colorless solids: m.p. 156–158 °C; $[\alpha]_D^{27}$ −109.2 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 1820, 1720, 1080, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1H, thiazole H-5), 7.97 (s, 1H, thiazole H-5), 7.01 (s, 1H, thiazole H-5), 5.02 (d, J = 3.9 Hz, 1H, oxazolidinone H-4), 4.93 (s, 1H, piperidine H-6), 4.54–4.34 (m, 6H, piperidine H-2, oxazolidinone H-5, $CO_2CH_2CH_3$ × 2), 2.82–2.64 (m, 1H, piperidine H-4α), 2.45–2.27 (m, 1H, piperidine), 2.15–1.95 (m, 2H, piperidine), 1.49 (d, J = 6.4 Hz, 3H, oxazolidinone 5-Me), 1.42 (s, 9H, Boc), 1.41 ppm (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$ × 2); ^{13}C NMR ($CDCl_3$): δ = 181.4, 173.7, 167.2, 161.6, 161.4, 154.2, 150.8, 148.6, 147.6, 147.0, 127.5, 127.2, 117.4, 84.7, 75.7, 64.0, 62.4, 61.5, 61.3, 58.4, 58.0, 37.9, 28.0, 27.9, 20.2, 14.4 ppm. To a solution of the above Boc-oxazolidinone (76.1 mg, 1.10×10^{-1} mmol), *N*-Boc-L-alanine **22** (41.6 mg, 2.20×10^{-1} mmol), HOAt (41.6 mg, 2.20×10^{-1} mmol), and iPr$_2$NEt (0.0861 mL, 4.94×10^{-1} mmol) in CH_2Cl_2 (1.1 mL) at room temperature under Ar atmosphere was added CIP (61.2 mg, 2.20×10^{-1} mmol). The solution was stirred at room temperature for 1 day and quenched with H_2O (2 mL). 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 dissolved in $CHCl_3$ and this was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (80% AcOEt/hexane) to afford **27** (94.9 mg, quantitative yield): ^{1}H NMR ($CDCl_3$): δ = 8.15 (s, 1H, thiazole H-5), 8.05 (brs, 1H, amide NH), 7.88 (s, 1H, thiazole H-5), 6.93 (s, 1H, thiazole H-5), 5.27 (brs, 1H, BocNH), 5.13 (d, J = 3.4 Hz, 1H, oxazolidinone H-4), 4.59 (s, 1H, piperidine H-6), 4.49 (dd, J = 2.8, 11.4 Hz, 1H, piperidine H-2), 4.49–4.22 (m, 6H, oxazolidinone H-5, Ala H-α, $CO_2CH_2CH_3$ × 2), 3.43 (brd, J = 14.0 Hz, 1H, piperidine H-4β), 2.86–2.71 (m, 1H, piperidine H-4α), 2.34–2.19 (m, 1H, piperidine H-3α), 2.07–1.85 (m, 1H, piperidine H-3β), 1.58 (d, J = 6.0 Hz, 3H, oxazolidinone 5-Me), 1.47 (s, 9H, Boc), 1.50–1.34 (m, 9H, Ala Me, $CO_2CH_2CH_3$ × 2), 1.38 ppm (s, 9H, Boc).

Alanylpiperidine **28**: To a solution of **27** (90.0 mg, 1.04×10^{-1} mmol) in MeOH (0.5 mL), 1,4-dioxane (0.5 mL), and H_2O (1 mL) at 0 °C was added LiOH (6.9 mg, 5.2×10^{-1} mmol). The mixture was stirred at room temperature for 2 h. The mixture was quenched with 1 M aqueous HCl (2 mL) at 0 °C and extracted with AcOEt (2 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was dissolved in 1,4-dioxane (1 mL) and 1 M aqueous HCl (2 mL), and the solution was stirred at room temperature for 1 h. The solvent was evaporated to afford the crude amino acid. This was dissolved in MeOH (0.1 mL). Acetone (5 mL) was added to the solution to form precipitates. The precipitates were filtered off to afford **28**·3HCl (50.6 mg, 70%) as solids: $[\alpha]_D^{30}$ −45.9 (c 1.21 (3HCl), 1 M aqueous HCl); ^{1}H NMR (D_2O, HCl salt): δ = 8.63 (s, 1H, thiazole H-5), 8.40 (s, 1H, thiazole H-5), 7.50 (s, 1H, thiazole H-5), 5.39 (s, 1H, piperidine H-6), 5.36 (dd, J = 12.6, 3.3 Hz, 1H, piperidine H-2), 4.88 (d, J = 7.5 Hz, 1H, H_2NCH), 4.57 (q, J = 7.2 Hz, 1H, Ala H-α), 4.46 (dq, J = 7.5, 6.3 Hz, 1H, $CHCH(OH)CH_3$), 3.52 (brd, J = 14.1 Hz, 1H, piperidine H-4β), 3.05 (ddd, J = 14.1, 14.1, 3.3 Hz, 1H, piperidine H-4α), 2.75 (brd, J = 15.0 Hz, 1H, piperidine H-3α), 2.54 (br ddd, J = 15.0, 14.1, 12.6 Hz, 1H, piperidine H-3β), 1.75 (d, J = 7.2 Hz, 3H, Ala Me), 1.35 ppm (d, J = 6.3 Hz, 3H, $CHCH(OH)CH_3$); ^{13}C NMR (D_2O, HCl salt): δ = 172.4, 171.9, 166.6, 166.5, 165.4, 165.1, 147.8, 147.6, 146.9, 132.3, 131.7, 126.4, 69.2, 63.3, 62.8, 58.5, 58.2, 50.7, 31.4, 26.2, 20.5, 17.7 ppm.

TMSE ester **29**: To a solution of **8** (4.94 g, 8.33 mmol) in 2-(trimethylsilyl)ethanol (11.9 mL, 83.5 mol) was added Ti(OiPr)$_4$ (2.44 mL, 8.33 mmol). After stirring at 100 °C for 6 h, the reaction mixture was quenched with H_2O (100 mL) and extracted with $CHCl_3$ (100 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (80% AcOEt/hexane) to afford **29** (4.61 g, 75%) as a colorless foam: R_f = 0.63 (100% AcOEt); $[\alpha]_D^{30}$ +95.4 (c 1.00, $CHCl_3$); m.p. 84–85 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3440, 3320, 1760, 1720, 1480, 1390, 1340, 1100, 1040, 970 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ = 8.08 (s, 1H, thiazole H-5), 7.89 (s, 1H, thiazole H-5), 6.92 (s, 1H, thiazole H-5), 6.70 (brs, 1H, oxazolidinone NH), 4.82 (s, 1H, piperidine H-6), 4.71 (br d, J = 6.3 Hz, 1H, oxazolidinone H-4), 4.51–4.34 (m, 6H, piperidine H-2, oxazolidinone H-5, and $Me_3SiCH_2CH_2$ × 2), 2.78–2.56 (m, 1H, piperidine H-4), 2.52–2.20 (m, 1H, piperidine H-3), 2.15–1.96 (m, 2H, piperidine H-3 and H-4), 1.50 (d, J = 6.3 Hz, 3H, oxazolidinone 5-Me), 1.18–1.04 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 0.06 (s, 9H, $Me_3SiCH_2CH_2$), 0.05 ppm (s, 9H, $Me_3SiCH_2CH_2$); ^{13}C NMR($CDCl_3$): δ = 181.47, 173.36, 169.22, 161.66, 161.40, 158.25, 154.37, 147.61, 147.13, 127.31, 126.94, 117.74, 79.72, 63.80, 63.73, 63.51, 61.01, 58.31, 58.09, 37.74, 27.81, 19.65, 17.43, 17.33, −1.47, −1.53 ppm; HRMS (FAB): m/z $[M-H]^-$ calcd for $C_{30}H_{43}N_6O_6S_3Si_2$: 735.1945; found: 735.1970.

Bpoc-alanylpiperidine **31**: To a solution of **29** (5.31 g, 7.20 mmol), DMAP (176 mg, 1.44 mmol), and NEt_3 (1.50 mL, 10.8 mmol) in dry THF (72 mL) at 0 °C under Ar atmosphere was added Boc_2O (1.66 mL, 7.23 mmol). After stirring at 0 °C for 1.5 h, the reaction mixture was quenched with H_2O (80 mL) and extracted with AcOEt (100 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 the Boc-oxazolidinone (5.61 g, 93%) as a colorless foam: R_f = 0.80 (70% AcOEt/hexane); ^{1}H NMR ($CDCl_3$): δ = 8.10 (s, 1H, thiazole H-5), 7.91 (s, 1H, thiazole H-5), 6.93 (s, 1H, thiazole H-5), 4.99 (d, J = 4.7 Hz, 1H, oxazolidinone H-4), 4.88 (brd, J = 6.3 Hz, 1H, piperidine H-2), 4.55 (dq, J = 4.7, 6.6 Hz, 1H, oxazolidinone H-5), 4.49–4.36 (m, 5H, piperidine H-6, $Me_3SiCH_2CH_2$ × 2), 2.74–2.58 (m, 1H, piperidine H-4), 2.43–2.24 (m, 1H, piperidine H-3), 2.12–1.94 (m, 2H, piperidine H-3 and H-4), 1.50 (d, J = 6.6 Hz, 3H, oxazolidinone 5-Me), 1.40 (s, 9H, Boc), 1.19–1.07 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 0.07 (s, 9H, $Me_3SiCH_2CH_2$), 0.06 ppm (s, 9H, $Me_3SiCH_2CH_2$). To a solution of this Boc-oxazolidinone (4.09 g, 4.89 mmol), Bpoc-L-Ala-OH (**30**) (3.20 g, 9.77 mmol), HOAt (1.33 g, 9.77 mmol), and iPr$_2$NEt (4.25 mL, 24.4 mmol) in dry CH_2Cl_2 (9.8 mL) at room temperature under Ar atmosphere was added CIP (2.72 g,

9.76 mmol). After stirring at room temperature for 3.5 h, the reaction mixture was quenched with H_2O (20 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 (40% AcOEt/hexane) to afford **31** (4.70 g, 84%) as a colorless foam: R_f = 0.56 (60% AcOEt/hexane); $[\alpha]_D^{32}$ +29.6 (*c* 1.00, $CHCl_3$); m.p. 100–102 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3420, 3370, 1820, 1720, 1490, 1420, 1370, 1320, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.47 (brs, 1H, CONH), 8.05 (s, 1H, thiazole H-5), 7.68 (s, 1H, thiazole H-5), 7.56–7.23 (m, 9H, Bpoc), 6.74 (s, 1H, thiazole H-5), 5.52 (brd, *J* = 6.0 Hz, 1H, NHBpoc), 5.06 (d, *J* = 2.7 Hz, 1H, oxazolidinone H-4), 4.96–4.80 (m, 1H, oxazolidinone H-5), 4.48 (s, 1H, piperidine H-6), 4.46–4.31 (m, 5H, piperidine H-2, $Me_3SiCH_2CH_2$ × 2), 4.10 (dq, *J* = 6.0, 6.3 Hz, 1H, Ala H-α), 3.46 (br d, *J* = 13.8 Hz, 1H, piperidine H-4), 2.71 (ddd, *J* = 3.3, 13.8, 13.8 Hz, 1H, piperidine H-4), 2.19 (br dd, *J* = 2.7, 13.8 Hz, 1H, piperidine H-3), 2.08–1.87 (m, 1H, piperidine H-3), 1.59 (d, *J* = 4.2 Hz, 3H, oxazolidinone 5-Me), 1.41 (s, 9H, Boc), 1.35 (d, *J* = 6.3 Hz, 3H, Ala Me), 1.16–1.04 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 0.05 (s, 9H, $Me_3SiCH_2CH_2$), 0.03 ppm (s, 9H, $Me_3SiCH_2CH_2$); ^{13}C NMR($CDCl_3$): δ = 174.69, 172.96, 172.81, 168.01, 161.25, 161.19, 154.53, 152.79, 150.60, 148.49, 146.96, 146.85, 145.12, 140.46, 139.43, 128.59, 127.10, 127.04, 126.82, 126.70, 124.66, 119.19, 84.85, 80.77, 75.50, 65.23, 63.60, 63.39, 61.48, 61.17, 58.06, 51.48, 30.51, 29.42, 27.73, 27.15, 20.30, 18.16, 17.34, 17.22, −1.55, −1.63 ppm; HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{54}H_{71}N_7O_{11}S_3Si_2Na$: 1168.3810; found: 1168.3782. Bpoc-L-Ala-OH **30** was prepapred as follows: To a solution of 4-acetylbiphenyl (15.0 g, 7.64×10^{-2} mol) in dry Et_2O (380 mL) at 0 °C under Ar atmosphere was added 3 M MeMgBr in Et_2O (56.1 mL, 1.68×10^{-1} mol). After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (500 mL) and H_2O (250 mL), and the mixture was extracted with Et_2O (500 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 1-(4-biphenylyl)-1-methylethanol (14.6 g, 90%) as colorless solids: ^1H NMR ($CDCl_3$): δ = 7.63–7.30 (m, 9H, biphenyl), 1.62 ppm (s, 6H, Me × 2). To a solution of 1-(4-biphenylyl)-1-methylethanol (4.14 g, 19.5 mmol) and dry pyridine (2.33 mL, 28.8 mmol) in dry CH_2Cl_2 (20 mL) at −5 °C under Ar atmosphere was added dropwise $ClCO_2Ph$ (2.94 mL, 23.4 mmol) in dry CH_2Cl_2 (10 mL) over 0.5 h. The reaction mixture was stirred at 0 °C for 1 day and quenched with ice-cold water (10 mL) and CH_2Cl_2 (20 mL) was added. The mixture was washed with H_2O (40 mL × 3). The organic layers were dried over Na_2SO_4, filtered through celite, and evaporated. The residual solid was recrystallized from AcOEt to afford 1-(4-biphenylyl)-1-methylethyl phenyl carbonate (5.65 g, 87%) as colorless solids: ^1H NMR ($CDCl_3$) δ = 7.63–7.23 (m, 14H, biphenyl and Ph), 1.63 ppm (s, 6H, Me × 2). L-alanine (1.02 g, 11.4 mmol) was dissolved in 40 wt% Triton B in MeOH (5.6 mL, 12.3 mmol) and the solvent was evaporated under reduced pressure. The residue was then evaporated twice more with DMF (17 mL) at 45 °C under vacuum in order to remove traces of water. The remaining syrup was treated with 1-(4-biphenylyl)-1-methylethyl phenyl carbonate (4.10 g, 12.3 mmol) in DMF (17 mL) at 50 °C for 2 h. The reaction mixture was quenched with H_2O (20 mL) at 0 °C and washed with Et_2O (20 mL × 3). The aqueous layer was acidified with cold 1 M aqueous citric acid to about pH 3 at 0 °C and extracted with Et_2O (20 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford Bpoc-L-Ala-OH **30** (2.50 g, 67%) as a colorless syrup: R_f = 0.74 (15/55/65 H_2O/MeOH/$CHCl_3$); ^1H NMR ($CDCl_3$): δ = 10.80–9.80 (brs, 1H, CO_2H), 7.62–7.26 (m, 9H, biphenyl), 5.31 (brd, *J* = 7.4 Hz, 1H, BpocNH), 4.28 (brdq, *J* = 6.8, 7.4 Hz, 1H, Ala H-α), 1.79 (brs, 6H, Bpoc Me × 2), 1.38 ppm (d, *J* = 6.8 Hz, 1H, Ala Me).

Segment A (**5**) : To a solution of **31** (805 mg, 7.02×10^{-1} mmol) in 2-(trimethylsilyl)ethanol (7.0 mL) at 0 °C under Ar atmosphere was added Cs_2CO_3 (229 mg, 7.03×10^{-1} mmol). After stirring at room temperature for 10 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and H_2O (10 mL), and the mixture was extracted with AcOEt (20 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was distilled under reduced pressure (15 mmHg, 59 °C) to recover 2-(trimethylsilyl)ethanol. The residue was chromatographed on silica gel (40% AcOEt/hexane) to afford theNHBoc-alcohol (629 mg, 80%) as a colorless foam: R_f = 0.73 (60% AcOEt/hexane); ^1H NMR ($CDCl_3$): δ = 8.56 (brs, 1H, piperidine 5-CONH), 8.07 (s, 1H, thiazole H-5), 7.62–7.23 (m, 10H, biphenyl and thiazole H-5), 6.49 (s, 1H, thiazole H-5), 5.58 (brd, *J* = 9.3 Hz, 1H, NHBoc), 5.43 (brd, *J* = 8.1 Hz, 1H, NHBpoc), 4.81 (brd, *J* = 9.3 Hz, 1H, Thr H-α), 4.77–4.64 (m, 1H, Thr H-β), 4.52–4.25 (m, 6H, piperidine H-2, H-6, and $Me_3SiCH_2CH_2$ × 2), 4.14 (brdq, *J* = 8.1, 8.4 Hz, 1H, Ala H-α), 3.61 (br d, *J* = 3.9 Hz, 1H, Thr β-OH), 3.38 (br d, *J* = 14.4 Hz, 1H, piperidine H-4), 2.82–2.66 (m, 1H, piperidine H-4), 2.59–2.44 (brs, 1H, piperidine H-3), 2.24 (brd, *J* = 12.0 Hz, 1H, piperidine H-3), 1.75 (s, 3H, Bpoc Me), 1.68 (s, 3H, Bpoc Me), 1.54–1.34 (m, 3H, Thr Me), 1.44 (s, 9H, Boc), 1.18–0.98 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 1.14 (d, *J* = 8.4 Hz, 3H, Ala Me), 0.07 (s, 9H, $Me_3SiCH_2CH_2$), 0.05 ppm (s, 9H, $Me_3SiCH_2CH_2$). To a solution of this NHBoc-alcohol (429 mg, 3.83×10^{-1} mmol) in dry THF (3.8 mL) at −78 °C under Ar atmosphere was added *tert*-butyl hypochlorite (0.0476 mL, 0.421 mmol). The reaction mixture was stirred at −78 °C for 1 h and then DMAP (9.4 mg, 7.7×10^{-2} mmol) and NEt_3 (0.533 mL, 3.83 mmol) were added. The temperature was raised to room temperature and the reaction mixture was stirred for 3 h. The reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$ (2 mL) and saturated aqueous $NaHCO_3$ (4 mL), and the mixture was extracted with AcOEt (5 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 **5** (324 mg, 76%) as a pale yellow foam: R_f = 0.45 (60% AcOEt/hexane); $[\alpha]_D^{32}$ +47.9 (*c* 1.00, $CHCl_3$); m.p. 102–103 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 3300, 1710, 1500, 1370, 1100, 1040 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 8.61 (brs, 1H, piperidine 5-CONH), 8.17 (s, 1H, thiazole H-5), 7.62–7.28 (m, 10H, biphenyl and thiazole H-5), 6.63 (s, 1H, thiazole H-5), 5.66 (brd, *J* = 9.6 Hz, 1H, NHBoc), 5.40 (brd, *J* = 7.5 Hz, 1H, NHBpoc), 5.20 (brs, 1H, piperidine H-6), 4.86 (brd, *J* = 9.3 Hz, 1H, Thr H-α), 4.63–4.52 (m, 1H, Thr H-β), 4.52–4.25 (m, 4H, $Me_3SiCH_2CH_2$ × 2), 3.97 (brdq, *J* = 6.6, 7.5 Hz, 1H, Ala H-α), 3.74–3.43 (m, 2H, piperidine H-3 and H-4), 3.35 (brd, *J* = 13.2 Hz, 1H, piperidine H-3), 2.81 (brd, *J* = 12.0 Hz, 1H, piperidine H-4), 1.73 (s, 3H, Bpoc Me), 1.65 (s, 3H, Bpoc Me), 1.47 (s, 9H, Boc), 1.35 (d, *J* = 6.6 Hz, 3H, Ala Me), 1.21–1.00 (m, 7H, Thr Me and $Me_3SiCH_2CH_2$ × 2), 0.09 (s, 9H, $Me_3SiCH_2CH_2$), 0.08 ppm (s, 9H, $Me_3SiCH_2CH_2$); ^{13}C NMR($CDCl_3$): δ = 175.91, 175.02, 173.56, 169.13, 162.90, 161.39, 161.31, 155.82, 154.87, 152.75, 148.01, 147.03, 144.74, 140.49, 139.62, 130.26, 128.75, 127.48, 127.22, 126.93, 124.68, 117.48, 81.54, 80.20, 68.33, 66.66, 63.77, 63.43, 59.95, 57.75, 51.36, 28.95, 28.52, 28.29, 26.40, 24.60, 20.15, 18.70, 17.40, 17.33, −1.48, −1.55 ppm; HRMS (FAB): *m/z* $[M+Na]^+$ calcd for $C_{53}H_{71}N_7O_{10}S_3Si_2Na$: 1140.3861; found: 1140.3877.

β-Lactone **42**: To a solution of L-threonine **18** (2.00 g, 16.8 mmol) in H_2O (8.4 mL) and 1,4-dioxane (8.4 mL) at room temperature were added NEt_3 (7.00 mL, 50.4 mmol) and TeocOPh(*p*-NO_2) (5.23 g, 18.5 mmol). After stirring at room temperature for 21 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the mixture was washed with Et_2O (50 mL × 1). The aqueous layer was acidified with 1 M aqueous HCl to pH 3 at 0 °C and extracted with AcOEt (100 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (70% AcOEt/$CHCl_3$) to afford the Teoc-L-Thr-OH (4.51 g, quantitative yield) as a colorless syrup: R_f = 0.50 (70% AcOEt/$CHCl_3$); ^1H NMR ($CDCl_3$): δ = 5.94–5.76 (m, 1H, TeocNH), 4.56–4.27 (m, 2H, H-α and H-β), 4.27–4.02 (m, 2H, $Me_3SiCH_2CH_2$), 1.24 (d, 3H, *J* = 6.2 Hz, Me-β), 1.00 (t, 2H, *J* = 8.6 Hz, $Me_3SiCH_2CH_2$), 0.02 ppm (s, 9H, $Me_3SiCH_2CH_2$). To a solution of the Teoc-L-Thr-OH (50.0 mg, 2.14×10^{-1} mmol) in acetone (1.9 mL) at 0 °C under Ar atmosphere were added acetone dimethylacetal (0.0700 mL, 5.67×10^{-1} mmol) and *p*-TsOH (3.3 mg, 1.9×10^{-2} mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and then NaCl (solid) was added. The mixture was extracted with AcOEt (10 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford acetonide **35** (65.0 mg, quantitative yield) as a colorless syrup: R_f = 0.90 (70% AcOEt/$CHCl_3$); ^1H NMR ($CDCl_3$): δ = 4.30–3.96 (m, 3H, $Me_3SiCH_2CH_2$ and H-β), 3.94–3.74 (m, 1H, H-α), 1.55 (s, 6H, oxazolidine 2-Me), 1.38 (d, *J* = 5.0 Hz, 3H, Me-β), 1.00 (brt, *J* = 8.2 Hz, 2H, $Me_3SiCH_2CH_2$), 0.02 ppm (s, 9H, $Me_3SiCH_2CH_2$). To a solu-

tion of **35** (50.0 mg, 1.65×10^{-1} mmol) and **36**[47] (49.5 mg, 1.81×10^{-1} mmol) in dry DMF (1.5 mL) at 0 °C under Ar atmosphere were added *i*Pr$_2$NEt (71.8 mL, 4.12×10^{-1} mmol) and PyBOP (103 mg, 1.98×10^{-1} mmol). After stirring at room temperature for 3.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with AcOEt (10 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (20% AcOEt/hexane) to afford **42** (42.1 mg, 66%) as a colorless foam: R_f=0.80 (5% MeOH/$CHCl_3$); $[\alpha]_D^{26}$ −4.78 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3682, 3620, 1832, 1698, 1520, 1478, 1420, 1456, 1048 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.56–6.64 (m, 1H, CONH), 5.60 (dd, *J*=6.0, 8.0 Hz, 1H, β-lactone H-α), 4.90 (dq, *J*=6.0, 6.0 Hz, 1H, β-lactone H-β), 4.38–4.10 (m, 1H, oxazolidine H-5), 4.16 (t, *J*=8.8 Hz, 2H, $Me_3SiCH_2C\underline{H}_2$), 3.90 (d, *J*=7.0 Hz, 1H, oxazolidine H-4), 1.63 (s, 3H, oxazolidine 2-Me), 1.57 (s, 3H, oxazolidine 2-Me), 1.45 (d, *J*=7.0 Hz, 3H, oxazolidine 5-Me), 1.40 (d, *J*=6.0 Hz, 3H, β-lactone Me), 1.10–0.90 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.02 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ=169.94, 168.81, 153.21(br), 95.29, 74.85, 74.02, 67.00, 64.22, 58.77, 27.31, 25.43, 19.01, 17.83, 15.02, −1.61 ppm. Elemental analysis (%) calcd for $C_{17}H_{30}N_2O_6Si$: C 52.83, H 7.82, N 7.25; found: C 52.76, H 7.82, N 7.23.

β-Lactone **43**: To a solution of **36** (9.15 g, 33.5 mmol) in dry THF (335 mL) were added *i*Pr$_2$NEt (7.01 mL, 40.2 mmol) and Boc_2O (15.4 mL, 67.0 mmol). The mixture was stirred at room temperature for 17 h. The reaction mixture was quenched with H_2O (300 mL) and the mixture was extracted with AcOEt (300 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (10% AcOEt/hexane) to afford **43** (5.22 g, 77%): $[\alpha]_D^{27}$ +29.4 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=1830, 1720, 1390, 1370, 1340, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=5.43 (dd, *J*=6.2, 8.0 Hz, 1H, H-α), 5.30 (br d, *J*=8.0 Hz, 1H, BocNH), 4.86 (dq, *J*=6.2, 6.2 Hz, 1H, H-β), 1.46 (s, 9H, Boc), 1.49–1.43 ppm (d, *J*=6.2 Hz, 3H, Me); ^{13}C NMR ($CDCl_3$): δ=170.0, 155.0, 81.5, 75.4, 60.4, 28.5, 15.3 ppm. Elemental analysis (%) calcd for $C_9H_{15}NO_4$: C 53.72, H 7.51, N 6.96; found: C 53.74, H 7.58, N 6.95.

Phenylselenobutanoic acid **44**: To a solution of **43** (4.35 g, 21.6 mmol) in degassed dry DMF (43 mL) at room temperature under Ar atmosphere was added benzeneselenol (3.44 mL, 32.4 mmol). The mixture was stirred at 80 °C for 2 h. The reaction mixture was quenched with 1 M aqueous NaOH (43 mL) and H_2O (85 mL), and the mixture was washed with Et_2O (100 mL×3). The aqueous layer was acidified with 1 M aqueous HCl to pH 3 and extracted with AcOEt (100 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (0–5% MeOH/$CHCl_3$) to afford **44** (7.75 g, quantitative yield): $[\alpha]_D^{27}$ +23.8 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=1715, 1500, 1370, 1160, 1080, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.65–7.54 (m, 2H, Ph), 7.36–7.23 (m, 3H, Ph), 6.10 (br s, 0.3H, BocNH), 5.24 (br d, *J*=7.8 Hz, 0.7H, BocNH), 4.51 (br s, 1H, H-α), 3.68 (m, 1H, H-β), 1.52–1.37 (m, 3H, Me-β), 1.44 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ=174.7, 155.5, 135.3, 129.2, 128.2, 128.1, 80.5, 57.9, 40.6, 28.2, 18.1 ppm; HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{21}NO_4{}^{80}Se$: 359.0636; found: 359.0629.

Tripeptide **46**: To a solution of **42** (42.1 mg, 1.09×10^{-1} mmol) in degassed dry DMF (0.22 mL) at room temperature under Ar atmosphere was added benzeneselenol (0.0174 mL, 1.64×10^{-1} mmol). After stirring at 80 °C for 2 h, the reaction mixture was quenched with 1 M aqueous NaOH (0.25 mL) and H_2O (0.50 mL), and the mixture was washed with Et_2O (1.0 mL×3). The aqueous layer was acidified with 1 M aqueous HCl to pH 3 at 0 °C and extracted with AcOEt (1.0 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (70% AcOEt/hexane) to afford **45** (55.7 mg, 94%) as a pale yellow foam: ^{1}H NMR ($CDCl_3$): δ=7.60–7.48 (m, 2H, PhSe), 7.32–7.18 (m, 3H, PhSe), 6.88–6.38 (m, 1H, CONH), 4.82–4.68 (m, 1H, phenylselenoamino acid H-α), 4.28–3.98 (m, 3H, $Me_3SiCH_2C\underline{H}_2$ and oxazolidine H-5), 3.83 (d, *J*=7.0 Hz, 1H, oxazolidine H-4), 3.74–3.60 (m, 1H, phenylselenoamino acid H-β), 1.62 (s, 3H, oxazolidine 2-Me), 1.57 (s, 3H, oxazolidine 2-Me), 1.45 (d, *J*=6.8 Hz, 3H, Me), 1.36 (d, *J*=6.0 Hz, 3H, Me), 1.04–0.88 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.02 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$). To a solution of **45** (55.7 mg, 1.02×10^{-1} mmol) and D-Ser-OMe·HCl **37** (17.5 mg, 1.12×10^{-1} mmol) in MeOH (1.0 mL) at 0 °C were added NMM (0.0270 mL, 2.46×10^{-1} mmol) and DMTMM (34.0 mg, 1.23×10^{-1} mmol). After stirring at room temperature for 6 h, the reaction mixture was quenched with H_2O (2 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 **46** (54.4 mg, 82%) as a colorless foam: R_f=0.80 (10% MeOH/$CHCl_3$); $[\alpha]_D^{27}$ −77.7 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3685, 3620, 3480, 3370, 1748, 1660, 1508, 1468, 1382, 1355, 1080, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.66–7.42 (m, 3H, CONH, PhSe), 7.36–7.21 (m, 3H, PhSe), 6.56–6.38 (br d, *J*=7.2 Hz, 1H, CONH), 4.58 (ddd, *J*=3.0, 5.0, 8.0 Hz, 1H, Ser H-α), 4.49 (dd, *J*=4.0, 7.2 Hz, 1H, phenylselenoamino acid H-α), 4.36–4.12 (m, 3H, $Me_3SiCH_2C\underline{H}_2$ and oxazolidine H-5), 4.10–3.82 (m, 3H, phenylselenoamino acid H-β and Ser H-β×2), 3.92 (d, *J*=9.0 Hz, 1H, oxazolidine H-4), 1.70 (s, 3H, oxazolidine 2-Me), 1.66 (s, 3H, oxazolidine 2-Me), 1.46 (d, *J*=6.0 Hz, 3H, Me), 1.42 (d, *J*=7.0 Hz, 3H, Me), 1.04–0.88 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.02 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$); ^{13}C NMR ($CDCl_3$): δ=170.43, 169.12, 168.59, 154.79, 134.74, 134.67, 129.36, 128.29, 127.73, 95.09, 74.22, 68.00, 65.88, 62.95, 56.13, 55.12, 52.28, 39.46, 27.37, 26.02, 18.41, 17.85, 16.30, −1.70 ppm. Elemental analysis (%) calcd for $C_{27}H_{43}N_3O_8{}^{80}SeSi$: C 50.30, H 6.72, N 6.52; found: C 50.20, H 7.04, N 6.56.

Carboxylic acid **33**: To a solution of **46** (1.00 g, 1.55 mmol) in MeOH (5.0 mL), H_2O (5.0 mL), and 1,4-dioxane (5.0 mL) at 0 °C was added 1 M aqueous NaOH (2.3 mL). After stirring at room temperature for 1 h, the reaction mixture was acidified with 1 M aqueous HCl to pH 3 at 0 °C and extracted with AcOEt (20 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford the crude **33** as a pale yellow foam, which was used for the next reaction without purification.

Olefin **48**: A solution of **40** (1.53 g, 8.25 mmol), **41** (1.00 g, 8.25 mmol), and Cs_2CO_3 (2.69 g, 8.25 mmol) in dry CH_2Cl_2 (45 mL) was stirred at room temperature for 2 h. The mixture was filtered through celite and evaporated. The residue was chromatographed on silica gel (30% AcOEt/hexane) to afford *tert*-butylsulfinamide **39** (2.50 g, quantitative yield) as a yellow syrup: R_f=0.80 (60% AcOEt/hexane); ^{1}H NMR ($CDCl_3$): δ=8.86 (d, *J*=1.2 Hz, 1H, imine-H), 8.38 (d, *J*=1.2 Hz, 1H, thiazole H-5), 4.48 (q, *J*=7.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 1.42 (t, *J*=7.0 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.28 ppm (s, 9H, *t*Bu). To a solution of (*Z*)-2-bromo-2-butene (1.32 mL, 13.0 mmol) in dry THF (19 mL) at −78 °C under Ar atmosphere was added 1.62 M *t*BuLi in pentane (16.0 mL, 26.0 mmol). After 5 min at −78 °C, 1.0 M $ZnCl_2$ in ether (13.0 mL, 13.0 mmol) was added and the temperature was raised to 0 °C during a period of 15 min. The solution was cooled to −78 °C and **39** (749 mg, 2.60 mmol) in dry THF (5.0 mL) was added and the temperature was raised to −40 °C. After stirring at −40 °C for 6 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (40 mL) and the mixture was extracted with Et_2O (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (55% AcOEt/$CHCl_3$) to afford **48** (778 mg, 87%) as a colorless syrup: R_f=0.40 (60% AcOEt/$CHCl_3$); $[\alpha]_D^{25}$ +144 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu}$=3450, 3255, 3195, 3120, 2978, 1724, 1478, 1370, 1340, 1320, 1238, 1210, 1062, 1020, 960, 900, 880, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=8.13 (s, 1H, thiazole H-5), 5.79 (br d, 1H, *t*BuS(O)N$\underline{H}$), 5.74 (q, *J*=7.0 Hz, 1H, H-γ), 4.80 (br d, 1H, H-α), 4.39 (q, *J*=7.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 1.89 (d, *J*=7.0 Hz, 3H, Me-γ), 1.61 (s, 3H, Me-β), 1.40 (t, *J*=7.0 Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.31 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ=171.17, 160.98, 146.68, 132.39, 127.93, 127.90, 61.26, 55.75, 54.51, 22.57, 18.13, 14.18, 13.42 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{15}H_{25}N_2O_3S_2$: 345.1304; found: 345.1307.

NHBoc olefin **38**: To a solution of **48** (778 mg, 2.26 mmol) in MeOH (15 mL) at 0 °C was added 10% HCl/MeOH (15 mL). After stirring at room temperature for 0.5 h, the reaction mixture was evaporated and to the residue was added saturated aqueous $NaHCO_3$ (20 mL). This was extracted with AcOEt (20 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford the amine as a pale yellow oil. To a solution of this amine in 1,4-dioxane (22 mL) under

Ar atmosphere were added NEt_3 (0.378 mL, 2.71 mmol) and Boc_2O (0.651 mL, 2.71 mmol). After stiring at room temperature for 2 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. The residue was chromatographed on silica gel (10% AcOEt/hexane) to afford **38** (635 mg, 83% from **48**) as a colorless oil: $R_f = 0.90$ (70% AcOEt/$CHCl_3$); $[\alpha]_D^{26}$ +80.0 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu} = 3425, 3355, 2975, 2938, 1720, 1500, 1368, 1322, 1238, 1210, 1166, 1098, 1060, 1016, 958, 880, 756\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 8.11$ (s, 1H, thiazole H-5), 6.06–5.74 (m, 2H, BocNH and H-α), 5.56 (q, $J = 7.0$ Hz, 1H, H-γ), 4.41 (q, $J = 7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 1.88 (d, $J = 7.0$ Hz, 3H, Me-γ), 1.59 (s, 3H, Me-β), 1.46 (s, 9H, Boc), 1.41 ppm (t, $J = 7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$): $\delta = 171.37, 161.16, 154.91, 146.68, 134.25, 127.86, 124.62, 79.93, 61.41, 52.59, 28.34, 18.11, 14.30, 13.47$ ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{25}N_2O_4S$: 340.1457; found: 340.1457.

Diol **49**: To a solution of OsO_4 (47.4 mg, 1.86×10^{-1} mmol) in *t*BuOH/H_2O (85:15, 6.0 mL) were added **38** (635 mg, 1.87 mmol) in *t*BuOH/H_2O (85:15, 8.0 mL), NMO (656 mg, 5.60 mmol) in *t*BuOH/H_2O (85:15, 4.0 mL), and DABCO (41.9 mg, 3.74×10^{-1} mmol). The reaction mixture was stirred in the dark at room temperature for 12 h and $Na_2S_2O_3$ was added. The resulting solution was stirred at room temperature for 1.5 h and then H_2O (20 mL) was added. The mixture was extracted with AcOEt (30 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (35% AcOEt/hexane) to afford **49** (390 mg, 56%) as a colorless foam and its diastereomer (175 mg, 25%) as a colorless foam. **49**: $R_f = 0.45$ (50% AcOEt/hexane); $[\alpha]_D^{29}$ −46.5 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu} = 3420, 2980, 1720, 1498, 1370, 1340, 1326, 1220, 1164, 1100, 1016, 876, 756\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 8.12$ (s, 1H, thiazole H-5), 6.02 (d, $J =$ 9.0 Hz, 1H, BocN<u>H</u>), 5.20 (d, $J = 9.0$ Hz, 1H, H-α), 4.38 (q, $J = 7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.30–4.16 (m, 1H, OH), 3.84–3.70 (m, 1H, H-γ), 3.16–3.02 (m, 1H, OH), 1.45 (s, 9H, Boc), 1.39 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.24 (d, $J = 6.4$ Hz, 3H, Me-γ), 1.12 ppm (s, 3H, Me-β); ^{13}C NMR ($CDCl_3$): $\delta = 170.02, 160.81, 156.58, 146.99, 127.04, 80.54, 69.35, 61.34, 57.19, 28.28, 18.46, 16.70, 14.21$ ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{27}N_2O_6S$: 375.1591; found: 375.1590. Diastereomer of **49**: $R_f = 0.30$ (50% AcOEt/hexane); $[\alpha]_D^{28}$ −39.0 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu} = 3420, 2980, 1720, 1498, 1370, 1340, 1326, 1220, 1164, 1100, 1016, 876, 756\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 8.12$ (s, 1H, thiazole H-5), 5.81 (d, $J =$ 9.2 Hz, 1H, BocN<u>H</u>), 5.20 (d, $J = 9.2$ Hz, 1H, H-α), 4.38 (q, $J = 7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 3.68 (d, $J = 8.0$ Hz, 1H, OH), 3.84–3.70 (dq, $J = 7.0$, 8.0 Hz, 1H, H-γ), 3.49 (s, 1H, OH), 1.45 (s, 9H, Boc), 1.39 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.32 (d, $J = 6.4$ Hz, 3H, Me-γ), 1.25 ppm (s, 3H, Me-β); ^{13}C NMR ($CDCl_3$): $\delta = 171.15, 160.76, 155.40, 146.11, 127.27, 80.04, 71.23, 69.35, 61.13, 56.42, 28.00, 18.64, 16.89, 13.95$ ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{16}H_{27}N_2O_6S$: 375.1591; found: 375.1590.

Aminodiol **50**: To a solution of **49** (50.0 mg, 1.34×10^{-1} mmol) in EtOH (1.0 mL) and 1,4-dioxane (0.5 mL) at 0 °C was added 1 M aqueous NaOH (0.2 mL). After stirring at room temperature for 0.5 h, the reaction mixture was acidified with 1 M aqueous HCl to pH 3 at 0 °C and extracted with AcOEt (3 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was purified using preparative TLC (ODS, 50% MeOH/H_2O) to afford carboxylic acid (35.5 mg, 77%) as a colorless syrup: $R_f = 0.45$ (50% MeOH/H_2O, ODS); ^1H NMR (CD_3OD): $\delta = 8.24$ (brs, 1H, thiazole H-5), 6.96 (br d, $J =$ 8.0 Hz, 1H, BocNH), 5.18 (brs, 1H, H-α), 3.77 (br q, $J = 5.8$ Hz, 1H, H-γ), 1.43 (s, 9H, Boc), 1.18 (d, $J = 5.8$ Hz, 3H, Me-γ), 1.07 ppm (s, 3H, Me-β). This carboxylic acid (35.5 mg, 1.02×10^{-1} mmol) was dissolved in 0.3 M HCl/AcOEt (1 mL). After stirring at room temperature for 1 h, the precipitates were filtered and washed with AcOEt to afford **50** (HCl salt, 25.3 mg, 87%) as yellow solids: ^1H NMR (CF_3CO_2D): $\delta = 8.69$ (s, 1H, thiazole H-5), 5.56 (brs, 1H, H-α), 4.34 (br q, $J = 6.2$ Hz, 1H, H-γ), 1.53 (d, $J = 6.2$ Hz, 3H, Me-γ), 1.23 ppm (s, 3H, Me-β) [Ref. [10d]: ^1H NMR (CF_3CO_2H): 8.69 (s, 1H), 5.56 (s, 1H), 4.39 (m, 1H), 1.56 (d, 3H), 1.28 (s, 3H)]. Compound **50** (HCl salt) was applied to an ion-exchange chromatography (DOWEX 50W). Pyridine–acetic acid buffer (0.2 M, pH 3.1) was used as eluent to afford **50** (AcOH salt) as yellow solids: $[\alpha]_D^{28}$ −2.8 (*c* 1.00, 1 M AcOH) [Ref. [2c]: $[\alpha]_D^{25}$ −4 (*c* 1, 1 M AcOH); Ref. [8a]: $[\alpha]_D^{20}$ −2.8 (*c* 1, AcOH); Ref. [10d]: $[\alpha]_D^{25}$ −4.4 (*c* 1, 1 M AcOH)]. The optical rotation of the enantiomer of **50**, prepared from the enantiomer of **41**, was +4.4 (*c* 1.00, 1 M AcOH, 28 °C). In addition, the ^1H NMR spectrum of the diastereomer of **50**, prepared from the diastereomer of **49**, was different from that of **50**.

TES ether **34**: To a solution of **49** (300 mg, 8.01×10^{-1} mmol) in dry CH_2Cl_2 (8 mL) at 0 °C under Ar atmosphere were added 2,6-lutidine (0.560 mL, 4.81 mmol) and TESOTf (0.725 mL, 3.20 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with H_2O (20 mL) and the mixture was extracted with $CHCl_3$ (20 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (20% AcOEt/hexane) to afford **34** (371 mg, 92%) as a colorless syrup: $R_f =$ 0.70 (40% AcOEt/hexane); $[\alpha]_D^{24}$ −23.5 (*c* 1.00, $CHCl_3$); IR (neat): $\tilde{\nu} =$ 3385, 2956, 2905, 2880, 1720, 1458, 1418, 1370, 1322, 1238, 1200, 1118, 1012, 960, 740, 724 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 8.11$ (s, 1H, thiazole H-5), 4.39 (dq, $J = 2.4$, 7.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.31 (s, 1H, H-α), 4.04 (q, $J = 6.2$ Hz, 1H, H-γ), 1.38 (t, $J = 7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.26 (s, 3H, Me-β), 1.18 (d, $J = 6.2$ Hz, 3H, Me-γ), 0.92 (t, $J = 7.8$ Hz, 9H, Si($CH_2C\underline{H}_3)_3$), 0.91 (t, $J = 7.8$ Hz, 9H, Si($CH_2C\underline{H}_3)_3$), 0.68–0.46 ppm (m, 12H, Si($C\underline{H}_2CH_3)_3 \times 2$); ^{13}C NMR ($CDCl_3$): $\delta = 175.93, 161.63, 146.30, 127.86, 80.34, 71.70, 61.06, 60.48, 19.28, 18.09, 14.24, 7.17, 6.83, 6.73, 5.08$ ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{23}H_{47}N_2O_4SSi_2$: 503.2802; found: 503.2795.

β-Hydroxyamide pentapeptide **32**: To a solution of **34** (199 mg, 3.96×10^{-1} mmol), **33** (275 mg, 4.36×10^{-1} mmol), and HOAt (64.7 mg, 4.75×10^{-1} mmol) in dry CH_2Cl_2 (4.0 mL) at 0 °C under Ar atmosphere were added *i*Pr_2NEt (0.166 mL, 9.53×10^{-1} mmol) and CIP (132 mg, 4.74×10^{-1} mmol). After stirring at room temperature for 0.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (5 mL) and the mixture was extracted with AcOEt (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 **32** (364 mg, 83% from **34**) as a colorless foam: $R_f = 0.40$ (40% AcOEt/hexane); $[\alpha]_D^{26}$ −15.5 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3685, 3620, 3420, 1686, 1602, 1518, 1478, 1420, 1044\ cm^{-1}$; ^1H NMR ($CDCl_3$): $\delta = 8.09$ (s, 1H, thiazole H-5), 7.60–7.48 (m, 2H, PhSe), 7.38 (d, $J = 9.2$ Hz, 1H, CONH), 7.32–7.18 (m, 3H, PhSe), 7.14–6.74 (m, 2H, CONH × 2), 5.39 (d, $J = 9.2$ Hz, 1H, Ile H-α), 4.70–4.56 (m, 1H, phenylselenoamino acid H-α), 4.40–4.04 (m, 3H, Ser H-α and $Me_3SiCH_2C\underline{H}_2$), 4.34 (q, $J = 6.8$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.02–3.80 (m, 3H, Ser H-β × 2 and oxazolidine H-5), 3.80–3.52 (m, 3H, phenylselenoamino acid H-β, Ile H-γ, and oxazolidine H-4), 1.63 (s, 3H, Me), 1.59 (s, 3H, Me), 1.46 (d, $J = 6.8$ Hz, 3H, Me), 1.34 (t, $J = 6.8$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.29 (s, 3H, Me), 1.08 (d, $J =$ 6.0 Hz, 3H, Me), 0.96 (t, $J = 9.0$ Hz, 9H, Si($CH_2C\underline{H}_3)_3$), 0.84 (t, $J =$ 9.0 Hz, 9H, Si($CH_2C\underline{H}_3)_3$), 0.89–0.76 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.68 (q, $J =$ 9.0 Hz, 6H, Si($C\underline{H}_2CH_3)_3$), 0.58–0.44 (m, 6H, Si($C\underline{H}_2CH_3)_3$), 0.02 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$); ^{13}C NMR ($CDCl_3$): $\delta = 170.01, 169.38, 169.32, 168.12, 161.19, 153.50$ (br), $145.56, 135.02, 129.18, 128.52, 128.09, 127.91, 95.09, 78.23, 74.10, 72.30, 67.41, 64.10, 62.71, 61.24, 60.88, 57.28, 56.36, 40.32, 27.40, 25.45, 19.20, 18.98, 18.47, 17.91, 17.67, 14.24, 7.14, 7.02, 6.81, 6.76, 5.05, 4.65, −1.61$ ppm. Elemental analysis (%) calcd for $C_{49}H_{85}N_5O_{11}SSeSi_3$: C 52.76, H 7.68, N 6.28; found: C 52.65, H 7.56, N 6.22.

β-Hydroxythioamide pentapeptide **52**: To a solution of **32** (516 mg, 4.63×10^{-1} mmol) in dry CH_2Cl_2 (4.6 mL) at −78 °C under Ar atmosphere was added DAST (0.0917 mL, 0.690 mmol) in dry CH_2Cl_2 (4.6 mL). After stirring at −78 °C for 5 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL) and extracted with AcOEt (15 mL × 3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (20% AcOEt/hexane) to afford **51** (432 mg, 85%) as a colorless foam: $R_f = 0.50$ (25% AcOEt/hexane); ^1H NMR ($CDCl_3$): $\delta = 8.06$ (s, 1H, thiazole H-5), 7.75 (d, $J = 9.4$ Hz, 1H, CONH), 7.65–7.57 (m, 2H, PhSe), 7.34–7.22 (m, 3H, PhSe), 7.00–6.82 (m, 1H, CONH), 5.47 (d, $J = 9.4$ Hz, 1H, Ile H-α), 5.04 (dd, $J = 6.4$, 8.0 Hz, 1H, phenylselenoamino acid H-α), 4.70 (dd, $J =$ 8.2, 9.2 Hz, 1H, Ser H-α), 4.52–4.30 (m, 2H, Ser H-β × 2), 4.36 (q, $J =$ 7.0 Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.24–4.02 (m, 3H, $Me_3SiCH_2C\underline{H}_2$ and oxazoli-

dine H-5), 3.84–3.64 (m, 3H, oxazolidine H-4, phenylselenoamino acid H-β, and Ile H-γ), 1.62 (s, 3H, Me), 1.59 (s, 3H, Me), 1.52 (d, $J=6.8$ Hz, 3H, Me), 1.35 (t, $J=7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.34 (s, 3H, Me), 1.14 (d, $J=5.8$ Hz, 3H, Me), 1.11 (d, $J=6.0$ Hz, 3H, Me), 0.96 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.91 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 1.04–0.80 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.66 (q, $J=7.2$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.59 (q, $J=7.2$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.02 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$). A solution of **51** (432 mg, 3.94×10^{-1} mmol) in MeOH (2.0 mL) and NEt_3 (2.0 mL) was saturated with H_2S and stirred at room temperature for 10 h. Ar was bubbled through the reaction mixture for 15 min and the mixture was evaporated. The residue was chromatographed on silica gel (20% AcOEt/hexane) to afford **52** (401 mg, 90%) as a colorless foam: $R_f=0.40$ (30% AcOEt/hexane); $[\alpha]_D^{27}$ +21.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3685$, 3620, 3418, 1682, 1518, 1475, 1420, 1340, 1046 cm^{-1}; ^1H NMR ($CDCl_3$) $\delta=8.60$–8.42 (m, 1H, CSNH), 8.11 (s, 1H, thiazole H-5), 7.61–7.48 (m, 2H, PhSe), 7.37–7.20 (m, 4H, CONH, PhSe), 7.05 (d, $J=7.6$ Hz, 1H, CONH), 5.42 (d, $J=9.2$ Hz, 1H, Ile H-α), 4.88–4.78 (m, 1H, phenylselenoamino acid H-α), 4.76–4.65 (m, 1H, Ser H-α), 4.37 (q, $J=7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.30–4.00 (m, 5H, $Me_3SiCH_2C\underline{H}_2$, Ser H-β, oxazolidine H-5, and phenylselenoamino acid H-β), 4.00–3.82 (m, 2H, oxazolidine H-4 and Ser H-β), 3.66 (q, $J=6.2$ Hz, 1H, Ile H-γ), 1.65 (s, 3H, Me), 1.61 (s, 3H, Me), 1.46 (d, $J=6.8$ Hz, 3H, Me), 1.41 (d, $J=6.2$ Hz, 3H, Me), 1.36 (t, $J=7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.28 (s, 3H, Me), 1.09 (d, $J=6.2$ Hz, 3H, Me), 1.06–0.85 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.98 (t, $J=7.8$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.86 (t, $J=7.8$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.71 (q, $J=6.8$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.62–0.44 (m, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.20 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$); ^{13}C NMR ($CDCl_3$): $\delta=201.39$, 168.87, 168.71, 168.12, 161.14, 154.50–151.50 (br), 145.53, 134.43, 129.24, 128.55, 128.18, 127.99, 95.06, 78.10, 74.14, 72.38, 67.56, 64.15, 62.82, 62.01, 61.77, 61.24, 60.99, 42.82, 27.42 (br), 25.31 (br), 19.29, 17.91, 17.61, 14.23, 7.14, 6.84, 6.74, 5.10, −1.63 ppm. Elemental analysis (%) calcd for $C_{49}H_{85}N_5O_{10}S_2SeSi_3$: C 52.01, H 7.57, N 6.19; found: C 51.87, H 7.30, N 6.11.

Thiazoline **54**: To a solution of **52** (33.1 mg, 2.93×10^{-2} mmol) in dry CH_2Cl_2 (0.3 mL) at −78°C under Ar atmosphere was added DAST (0.0043 mL, 3.3×10^{-2} mmol) in dry CH_2Cl_2 (0.3 mL). After stirring at −78°C for 5 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL) and the mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford **53**. To a solution of **53** in dry CH_2Cl_2 (0.15 mL) and TFE (0.15 mL) at 0°C under Ar atmosphere was added 4.89 M TBHP in CH_2Cl_2 (0.0598 mL, 0.292 mmol). After stirring at room temperature for 2 h, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ (1.5 mL) and the mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (25% AcOEt/hexane) to afford **54** (16.1 mg, 57% from **52**) 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, 498 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.09$ (s, 1H, thiazole H-5), 7.73 (br s, 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, Ser H-α), 4.35 (q, $J=7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.42–4.24 (m, 1H, oxazolidine H-5), 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, Ser H-β, Ile H-γ), 3.57 (dd, $J=9.2$, 11.0 Hz, 1H, Ser H-β), 1.82 (d, $J=7.0$ Hz, 3H, ΔAbu Me-β), 1.67 (s, 3H, Me), 1.64 (s, 3H, Me), 1.46 (d, $J=5.6$ Hz, 3H, Me), 1.36 (t, $J=7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.35 (s, 3H, Me), 1.12 (d, $J=6.0$ Hz, 3H, Me), 1.06–0.87 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.94 (t, $J=7.6$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.87 (t, $J=7.6$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.72–0.42 (m, 12H, $Si(C\underline{H}_2CH_3)_3\times2$), 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.

Segment B (**3**) : To a solution of **52** (30.0 mg, 2.65×10^{-2} mmol) in EtOH (0.180 mL) and 1,4-dioxane (0.090 mL) at 0°C was added 1 M aqueous NaOH (0.080 mL). After stirring at room temperature for 5 h, the reaction mixture was acidified with 1 M aqueous HCl to pH 3 at 0°C and extracted with AcOEt (1 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford **3** as a colorless foam, which was used for the next step without purification: $R_f=0.10$ (30% AcOEt/hexane); $[\alpha]_D^{24}$ +22.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3680$, 3620, 3418, 1748, 1682, 1520, 1478, 1420, 1338, 1044, 498 cm^{-1}; ^1H NMR ($CDCl_3$); $\delta=9.14$–8.90 (br s, 1H, CSNH), 8.21 (s, 1H, thiazole H-5), 7.62–7.48 (m, 2H, PhSe), 7.48–7.35 (m, 1H, CONH), 7.34–7.18 (m, 3H, PhSe), 6.95–6.66 (m, 1H, CONH), 5.52–5.20 (m, 1H, Ile H-α), 5.10–4.66 (m, 2H, Ser H-α and phenylselenoamino acid H-α), 4.43–4.17 (m, 4H, $Me_3SiCH_2C\underline{H}_2$, oxazolidine H-5, and phenylselenoamino acid H-β), 4.12 (br dd, 1H, Ser H-β), 4.01 (br dd, 1H, Ser H-β) 3.93 (d, $J=7.6$ Hz, 1H, oxazolidine H-4), 3.73 (br q, 1H, Ile H-γ), 1.66 (s, 6H, Me), 1.42 (d, $J=6.0$ Hz, 3H, Me), 1.38–1.18 (m, 6H, Me×2), 1.11 (d, $J=5.8$ Hz, 3H, Me), 1.05–0.95 (m, 2H, $Me_3SiC\underline{H}_2CH_2$), 0.98 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.84 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.72 (q, $J=7.8$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.52 (q, $J=7.8$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.20 ppm (s, 9H, $\underline{Me}_3SiCH_2CH_2$).

Aminoalcohol **55**: To a solution of **52** (32.0 mg, 2.83×10^{-2} mmol) in CH_3NO_2 (0.28 mL) at 0°C under Ar atmosphere was added 1.0 M $ZnCl_2$ in ether (0.42 mL, 4.2×10^{-1} mmol). After stirring at room temperature for 15 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL) and the mixture was extracted with AcOEt (3 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (5–10% MeOH/$CHCl_3$) to afford **55** (15.1 mg, 58%) as a colorless foam: $R_f=0.50$ (8% MeOH/$CHCl_3$); $[\alpha]_D^{26}$ +41.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3682$, 3620, 3420, 1722, 1676, 1518, 1478, 1420, 1044, 498 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.90$–8.72 (m, 1H, CSNH), 8.11 (s, 1H, thiazole H-5), 8.11–8.04 (m, 1H, CONH), 7.62–7.54 (m, 2H, PhSe), 7.38–7.20 (m, 4H, CONH, PhSe), 5.43 (d, $J=9.2$ Hz, 1H, Ile H-α), 4.98–4.87 (m, 1H, phenylselenoamino acid H-α), 4.81–4.72 (m, 1H, Ser H-α), 4.38 (q, $J=7.0$ Hz, 2H, $CO_2C\underline{H}_2CH_3$), 4.27 (dq, $J=3.2$, 6.4 Hz, 1H, oxazolidine H-5), 4.18–4.04 (m, 2H, Ser H-β and phenylselenoamino acid H-β), 3.94 (dd, $J=3.6$, 12.4 Hz, 1H, Ser H-β), 3.71 (q, $J=6.4$ Hz, 1H, Ile H-γ), 3.37 (br s, 1H, oxazolidine H-4), 1.41 (d, $J=7.0$ Hz, 3H, Me), 1.37 (t, $J=7.0$ Hz, 3H, $CO_2CH_2C\underline{H}_3$), 1.29 (s, 3H, Me), 1.21 (d, $J=6.4$ Hz, 3H, Me), 1.08 (d, $J=6.4$ Hz, 3H, Me), 0.97 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.87 (t, $J=7.2$ Hz, 9H, $Si(CH_2C\underline{H}_3)_3$), 0.69 (q, $J=7.2$ Hz, 6H, $Si(C\underline{H}_2CH_3)_3$), 0.59–0.48 ppm (m, 6H, $Si(C\underline{H}_2CH_3)_3$); ^{13}C NMR ($CDCl_3$): $\delta=201.77$, 173.79, 169.35, 168.48, 161.21, 145.56, 134.71, 129.23, 128.59, 128.44, 128.03, 78.40, 72.26, 68.03, 63.07, 61.73, 61.57, 61.36, 60.63, 59.63, 42.75, 29.67, 19.54, 18.69, 17.80, 17.39, 14.28, 7.20, 6.89, 6.78, 5.11 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{40}H_{70}N_5O_8S_2SeSi_2$: 948.3375; found: 948.3369.

Epoxy alcohols **67** and **68** from **63**: To a solution of **63** (100 mg, 3.20×10^{-1} mmol) in dry toluene (3.2 mL) at −78°C under Ar atmosphere were added HMPA (0.0613 mL, 3.52×10^{-1} mmol) and 3 M MeMgBr in Et_2O (0.117 mL, 3.51×10^{-1} mmol). After stirring at −78°C for 0.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and the mixture was extracted with AcOEt (5 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 **67** (50.0 mg, 48%) as a colorless foam, **68** (15.8 mg, 15%) as a colorless foam, and the recovered **63** (20.0 mg, 20%) as a colorless foam. **67**: $R_f=0.39$ (70% AcOEt/hexane); m.p. 125–126°C (not recrystallized); $[\alpha]_D^{28}$ −22.3 (91% *ee*) (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3620$, 1730, 1440, 1422, 1309, 1125, 876 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.40$ (s, 1H, H-3), 5.39 (dq, $J=3.2$, 6.4 Hz, 1H, $C\underline{H}(CH_3)OH$), 5.34 (ddd, $J=1.8$, 1.8, 5.4 Hz, 1H, H-5), 4.40 (d, $J=3.4$ Hz, 1H, H-8), 4.02 (s, 3H, CO_2Me), 3.98–3.93 (m, 1H, H-7), 3.12 (ddd, $J=1.8$, 1.8, 16.8 Hz, 1H, H-6), 2.51 (ddd, $J=0.9$, 5.4, 16.8 Hz, 1H, H-6), 2.21 (d, $J=3.2$ Hz, 1H, $CH(CH_3)O\underline{H}$), 1.51 ppm (d, $J=6.4$ Hz, 3H, $CH(C\underline{H}_3)OH$); ^{13}C NMR ($CDCl_3$): $\delta=165.07$, 154.68, 152.54, 147.91, 130.48, 122.55, 64.19, 54.04, 53.10, 34.92, 30.38, 24.61 ppm; HRMS (FAB): *m/z* $[M+H]^+$ calcd for $C_{13}H_{15}NO_4Br$: 328.0184; found: 328.0187. **68**: $R_f=0.24$ (70% AcOEt/hexane); m.p. 128–129°C (not recrystallized); $[\alpha]_D^{29}$ +21.0 (91% *ee*) (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3620$, 1728, 1440, 1423, 1310, 1128, 879 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta=8.29$ (s, 1H, H-3), 5.66 (ddd, $J=1.5$, 1.5, 5.2 Hz, 1H, H-5), 5.30 (dq, $J=4.2$, 6.4 Hz, 1H, $C\underline{H}(CH_3)OH$), 4.41 (d, $J=1.5$, 1.5, 3.8 Hz, 1H, H-8), 4.02 (s, 3H, CO_2Me), 3.99–3.94 (m, 1H, H-7), 3.13 (ddd, $J=1.5$, 1.5, 16.8 Hz, 1H, H-

6), 2.53 (ddd, $J=0.8$, 5.4, 16.8 Hz, 1H, H-6), 1.94 (d, $J=4.2$ Hz, 1H, CH-(CH_3)OH), 1.66 ppm (d, $J=6.4$ Hz, 3H, CH(CH_3)OH); ^{13}C NMR ($CDCl_3$): $\delta=165.14$, 153.13, 147.75, 131.78, 122.85, 64.10, 54.23, 53.38, 53.15, 34.81, 30.83, 23.69 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{13}H_{15}NO_4Br$: 328.0184; found: 328.0181.

Methoxyquinoline **69**: To a solution of **67** (24.5 mg, 7.47×10^{-2} mmol) in dry THF (0.75 mL) at 0°C under Ar atmosphere was added DBU (0.0335 mL, 2.24×10^{-1} mmol). The reaction mixture was stirred at room temperature for 1 h and then 1 M aqueous HCl (0.75 mL) was added at 0°C. After stirring at room temperature for 1 h, to the reaction mixture was added 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 to afford the crude 8-quinolinol (18.2 mg). The crude 8-quinolinol was dissolved in MeOH (0.6 mL), followed by addition of CH_2N_2 in Et_2O. After stirring at room temperature for 1 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 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 (15% acetone/hexane) to afford **69** (15.9 mg, 83%) as colorless solids: $R_f=0.46$ (30% acetone/$CHCl_3$); $[\alpha]_D^{28}$ −76.3 (c 1.00, EtOH); UV (EtOH) λ_{max} nm (log ε): 343 (3.15), 303 (3.23), 254 (4.18); m.p. 170–171°C (not recrystallized); IR (nujol): $\tilde{\nu}=3400$, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.38$ (s, 1H, H-3), 7.58 (d, $J=3.4$ Hz, 1H, H-5), 7.55 (d, $J=4.8$ Hz, 1H, H-7), 7.05 (dd, $J=3.4$, 4.8 Hz, 1H, H-6), 5.61 (q, $J=6.6$ Hz, 1H, CH(CH_3)OH), 4.08 (s, 3H, CO_2Me), 4.04 (s, 3H, OMe), 2.55 (brs, CH(CH_3)OH), 1.65 ppm (d, $J=$ 6.6 Hz, 3H, CH(CH_3)OH); ^{1}H NMR (CD_3CO_2D): $\delta=8.37$ (s, 1H, H-3), 7.60 (m, 2H, aromatic H), 7.16 (d, $J=7.2$ Hz, 1H, aromatic H), 5.70 (q, $J=6.5$ Hz, 1H, CH(CH_3)OH), 4.01 (s, 3H, CO_2Me), 3.98 (s, 3H, OMe), 1.61 ppm (d, $J=6.5$ Hz, 3H, CH(CH_3)OH); ^{13}C NMR($CDCl_3$): $\delta=$ 166.06, 156.44, 152.80, 146.52, 139.63, 129.08, 127.58, 117.22, 114.49, 107.66, 66.46, 56.14, 53.05, 24.35 ppm; HRMS (FAB): m/z $[M+H]^+$ calcd for $C_{14}H_{16}NO_4$: 262.1079; found: 262.1081 [Ref. [8a]: $[\alpha]_D^{20}$ −79 (c 1.00, EtOH); m.p. darkened at 161–168°C , melted at 174°C; IR (nujol): $\tilde{\nu}=$ 3300, 1735 cm^{-1}; UV λ_{max}^{alc} nm ($E_{1cm}^{1\%}$): 347 (128), 317, 307, 254 (1553); ^{1}H NMR (CD_3CO_2D): $\delta=8.37$ (aromatic H), 7.58 (side chain αH), 7.16, 4.00 (OMe), 1.60 ppm (d, 3H). Elemental analysis (%) calcd for $C_{14}H_{15}NO_4$: C 64.36, H 5.79, N 5.36, O 24.49; found: C 63.72, H 6.00, N 5.48, O 24.05; Ref. [2c]: $[\alpha]_D^{20}$ −78 (c 1.6, EtOH); m.p. about 161–168°C to 175–177°C; IR: $\tilde{\nu}=3400$, 1750 cm^{-1}; UV λ_{max}^{alc} nm ($E_{1cm}^{1\%}$): 347 (115), 254 (1500); ^{1}H NMR (CD_3CO_2D): $\delta=8.24$ (s, pyridine H-3), 7.50 (d, 2H), 7.17 (m, 1H), 5.63 (d, 1H, side-chain α-carbon proton), 3.96 (s, 6H, OMe), 1.59 ppm (d, $J=6.5$ Hz, 3H). Elemental analysis (%) calcd for $C_{14}H_{15}NO_4$: C 64.36, H 5.79, N 5.36; found: C 64.50, H 6.09, N 5.58].

Dihydroquinoline **59**: To a solution of **61** (9.50 g, 49.7 mmol) in acetaldehyde (350 mL) and H_2O (250 mL) at 0°C were slowly added TFA (3.69 mL, 49.7 mmol), $FeSO_4{\cdot}7H_2O$ (1.38 g, 4.96 mmol), and 31% aqueous H_2O_2 (9.74 mL, 97.7 mmol). After stirring at room temperature for 4 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (500 mL), saturated aqueous $Na_2S_2O_3$ (250 mL), and H_2O (250 mL). The mixture was extracted with AcOEt (1 L×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (5% acetone/$CHCl_3$) to afford methyl 4-acetyl-5,6,7,8-tetrahydroquinoline-2-carboxylate **60** (9.73 g, 84%) as colorless solids: $R_f=0.62$ (50% AcOEt/hexane); ^{1}H NMR ($CDCl_3$): $\delta=$ 8.05 (s, 1H, H-3), 4.02 (s, 3H, CO_2Me), 3.10 (t, $J=6.0$ Hz, 2H, H-8), 2.97 (t, $J=6.0$ Hz, 2H, H-5), 2.61 (s, 3H, CH_3C(O)), 1.91–1.82 ppm (m, 4H, H-6 and H-7). To a solution of **60** (11.3 g, 48.4 mmol) in CH_2Cl_2 (162 mL) at 0°C was slowly added 65% MCPBA (25.7 g, 96.8 mmol). After stirring at room temperature for 7 h, saturated aqueous $NaHCO_3$ (150 mL), saturated aqueous $Na_2S_2O_3$ (100 mL), and H_2O (100 mL) were slowly added and the resulting mixture was extracted with $CHCl_3$ (250 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 **70** (10.6 g, 88%) as colorless solids. To a solution of **70** (7.00 g, 28.1 mmol) in dry CH_2Cl_2 (280 mL) at 0°C under Ar atmosphere was added dropwise Tf_2O (5.60 mL, 33.3 mmol) over 10 min. After stirring at 0°C for 10 min, a solution of NEt_3 (19.6 mL, 141 mmol) in dry CH_2Cl_2 (280 mL) was added dropwise over 1 h. The reaction mixture was stirred at room temperature for 5 h, quenched with H_2O (450 mL), and extracted with $CHCl_3$ (1 L×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (40:60:2 acetone/hexane/NEt_3) to afford **59** (6.36 g, 98%) as a colorless syrup: $R_f=0.63$ (70% AcOEt/hexane); m.p. 118–120°C (not recrystallized); IR ($CHCl_3$): $\tilde{\nu}=1720$, 1695, 1450, 1425, 1315, 1240, 1155, 980, 895, 785 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.08$ (s, 1H, H-3), 6.82 (dt, $J=1.6$, 10.0 Hz, 1H, H-8), 6.49 (dt, $J=4.5$, 10.0 Hz, 1H, H-7), 4.02 (s, 3H, CO_2Me), 3.12 (t, $J=8.0$ Hz, 2H, H-5), 2.64 (s, 3H, CH_3C(O)), 2.45–2.32 ppm (m, 2H, H-6); ^{13}C NMR ($CDCl_3$): $\delta=200.63$, 165.46, 155.26, 145.51, 144.11, 136.06, 132.81, 129.20, 121.12, 52.98, 29.73, 23.93, 22.12 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_{13}H_{13}NO_3$: 231.0895; found: 231.0889.

Epoxytetrahydroquinoline **79**: To a solution of **59** (13.9 mg, 0.0601 mmol) and 97% 4-phenylpyridine N-oxide (5.1 mg, 0.030 mmol) in CH_3CN (0.12 mL) at −10°C were added (*R*,*R*)-Mn-salen catalyst **81** (2.9 mg, 0.0046 mmol) and iodosobenzene (26.4 mg, 0.120 mmol). After stirring at −10°C for 15 h, the reaction mixture was filtered through celite and evaporated. H_2O (2 mL) was added 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 (20% acetone/hexane) to afford epoxide **79** (10.9 mg, 73%, 82% *ee*) as colorless solids. The enantiomeric exess of **79** was determined by chiral HPLC analysis (Daicel Chiralcel OD column, 4.6×250 mm, 90:10 hexane–IPA; 1 mL min^{-1}, 254 nm, $t=20.6$ min; enantiomer of **79**, $t=30.8$ min). **79**: $R_f=0.40$ (30% acetone/hexane); m.p. 90–93°C (not recrystallized); $[\alpha]_D^{27}$ +58.8 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3010$, 2960, 1715, 1685, 1550, 1440, 1410, 1300, 1245, 1155, 1075, 1005, 820, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.20$ (s, 1H, H-3), 4.29 (d, $J=4.0$ Hz, 1H, H-8), 4.05 (s, 3H, CO_2Me), 3.85 (m, 1H, H-7), 3.06 (dddd, $J=1.4$, 1.4, 5.4, 17.2 Hz, 1H, H-5), 2,76 (ddd, $J=6.8$, 13.2, 17.2 Hz, 1H, H-5), 2.61 (s, 3H, CH_3C(O)), 2.57–2.43 (m, 1H, H-6), 1.76 ppm (ddd, $J=5.4$, 13.2, 14.1 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): $\delta=200.42$, 165.00, 155.45, 145.70, 145.51, 133.74, 122.40, 55.10, 53.81, 53.15, 30.01, 20.88, 20.30 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_{13}H_{13}NO_4$: 247.0845; found: 247.0846 [**80**: $R_f=0.56$ (30% acetone/hexane); ^{1}H NMR ($CDCl_3$): $\delta=8.55$ (dd, $J=1.0$, 8.8 Hz, 1H, H-8), 8.45 (s, 1H, H-3), 8.36 (brd, $J=8.4$, 1H, H-5), 7.86 (ddd, $J=$ 0.8, 7.6, 8.8 Hz, 1H, H-7), 7.76 (ddd, $J=1.0$, 7.6, 8.4 Hz, 1H, H-6), 4.13 (s, 3H, CO_2Me), 2.82 ppm (s, 3H, CH_3C(O))].

Epoxybromide **58** and its epimer **82**: To a solution of **79** (4.80 g, 19.4 mmol) in CCl_4 (200 mL) were added NBS (3.83 g, 21.5 mmol) and AIBN (321 mg, 1.95 mmol). The reaction mixture was stirred and irradiated with a 140-W sun lamp at 60°C for 5 h. H_2O (200 mL), saturated aqueous $Na_2S_2O_3$ (100 mL), and saturated aqueous $NaHCO_3$ (100 mL) were added and the mixture was extracted with $CHCl_3$ (500 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 **58** (4.28 g, 67%) as colorless solids and **82** (685 mg, 11%) as colorless solids. **58**: $R_f=0.45$ (40% AcOEt/$CHCl_3$); m.p. 159–161°C (not recrystallized); $[\alpha]_D^{28}$ −92.7 (c 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}=3085$, 3005, 2955, 1720, 1560, 1420, 1320, 1250, 1150, 1130, 780 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta=8.19$ (s, 1H, H-3), 6.04 (ddd, $J=1.8$, 1.8, 5.8, Hz, 1H, H-5), 4.40 (d, $J=3.8$ Hz, 1H, H-8), 4.07 (s, 3H, CO_2Me), 4.01–3.95 (m, 1H, H-7), 3.07 (ddd, $J=1.8$, 1.8, 17.2 Hz, 1H, H-6), 2.68 (s, 3H, CH_3C(O)), 2.57 ppm (brdd, $J=5.8$, 17.2 Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$): $\delta=200.70$, 164.46, 154.18, 147.63, 145.72, 132.12, 122.49, 54.45, 53.37, 53.04, 33.63, 30.00, 29.78 ppm; HRMS (EI): m/z $[M]^+$ calcd for $C_{13}H_{12}NO_4{}^{79}Br$: 324.9950; found: 324.9960. **82**: $R_f=0.61$(40% AcOEt/$CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta=8.22$ (s, 1H, H-3), 5.86 (dd, $J=4.8$, 5.2 Hz, 1H, H-5), 4.23 (d, $J=3.8$ Hz, 1H, H-8), 4.07 (s, 3H, CO_2Me), 3.94–3.86 (m, 1H, H-7), 2.94 (ddd, $J=3.5$, 5.2, 16.0 Hz, 1H, H-6), 2.71 (ddd, $J=1.8$, 4.8, 16.0 Hz, 1H, H-6), 2.68 ppm (s, 3H, CH_3C(O)).

Epoxy alcohols **67** and **68** from **58**: To a solution of **58** (4.60 g, 14.1 mmol) in MeOH (141 mL) at −78°C under Ar atmosphere was added $NaBH_4$ (2.40 g, 63.4 mmol). After stirring at −78°C for 19 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (50 mL) and H_2O (50 mL). The mixture was extracted with AcOEt (100 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite,

and evaporated. The residue was chromatographed on silica gel (60% AcOEt/hexane) to afford alcohol **67** (4.38 g, 95%) as a colorless foam and **68** (170 mg, 4%) as a colorless foam.

TBS ether **85**: To a solution of **67** (20.6 mg, 6.28×10^{-2} mmol) in dry CH_2Cl_2 (0.63 mL) at 0°C under Ar atmosphere were added 2,6-lutidine (0.0146 mL, 1.25×10^{-1} mmol) and TBSOTf (0.0173 mL, 7.53×10^{-2} mmol). After stirring at 0°C for 0.5 h, the reaction mixture was quenched with H_2O (2 mL) and saturated aqueous $NaHCO_3$ (0.50 mL). 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% AcOEt/hexane) to afford the silylated bromide (22.7 mg, 82%) as a colorless syrup: R_f= 0.65 (70% AcOEt/hexane); $[\alpha]_D^{29}$ −35.3 (91% *ee*) (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3622, 1730, 1440, 1424, 1315, 1300, 1130, 875 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.37 (s, 1H, H-3), 5.31–5.22 (m, 2H, H-5 and C<u>H</u>-(CH_3)OTBS), 4.37 (d, *J*=3.9 Hz, 1H, H-8), 4.00 (s, 3H, CO_2Me), 3.94–3.90 (m, 1H, H-7), 3.08 (br d, *J*=16.8 Hz, 1H, H-6), 2.46 (br dd, *J*=5.2, 16.8 Hz, 1H, H-6), 1.39 (d, *J*=6.3 Hz, 3H, CH(C<u>H</u>$_3$)OTBS) 0.91 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.09 (s, 3H, Si<u>Me</u>$_2$*t*Bu), −0.05 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu); ^{13}C NMR ($CDCl_3$): δ=165.26, 155.62, 152.37, 147.84, 129.95, 122.77, 65.38, 53.91, 53.22, 34.85, 30.48, 26.58, 25.70, 17.97, −4.78, −4.93 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{29}NO_4Si^{81}Br$: 444.1029; found: 444.1032. To a solution of this sample (1.17 g, 2.64 mmol) in dry THF (26 mL) at 0°C under Ar atmosphere was added DBU (1.38 mL, 9.23 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with H_2O (20 mL) and the mixture was extracted with AcOEt (30 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (40% AcOEt/hexane) to afford **85** (909 mg, 95%) as a colorless foam: R_f=0.35 (30% AcOEt/hexane); ^1H NMR ($CDCl_3$): δ=8.31 (s, 1H, H-3), 7.08 (dd, *J*=1.4, 10.0 Hz, 1H, H-5), 6.67 (dd, *J*=3.4, 10.0 Hz, 1H, H-6), 5.17 (q, *J*= 6.5 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.82 (d, *J*=3.8 Hz, 1H, H-8), 4.16 (ddd, *J*= 1.4, 3.4, 3.8 Hz, 1H, H-7), 4.02 (s, 3H, CO_2Me), 1.40 (d, *J*=6.5 Hz, 3H, CH(C<u>H</u>$_3$)OTBS), 0.87 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.04 (s, 3H, Si<u>Me</u>$_2$*t*Bu), −0.08 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu); ^{13}C NMR ($CDCl_3$): δ=165.43, 153.05, 152.07, 146.33, 129.24, 126.18, 125.12, 122.56, 67.53, 58.51, 53.16, 52.96, 25.97, 25.63, 18.02, −4.93, −5.01 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{28}NO_4Si$: 362.1788; found: 362.1787.

tert-Butyl ester **56**: To a solution of **85** (12.8 mg, 3.54×10^{-2} mmol) in dry Et_2O (0.35 mL) at 0°C under Ar atmosphere was added 90% TMSOK (5.1 mg, 3.6×10^{-2} mmol). After stirring at 0°C for 0.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (2 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 to afford **86** (12.4 mg, quantitative yield) as colorless solids: ^1H NMR ($CDCl_3$): δ= 8.41 (s, 1H, H-3), 7.15 (dd, *J*=1.8, 9.8 Hz, 1H, H-5), 6.74 (dd, *J*=3.8, 9.8 Hz, 1H, H-6), 5.21 (q, *J*=6.0 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.73 (d, *J*= 3.8 Hz, 1H, H-8), 4.23 (ddd, *J*=1.8, 3.8, 3.8 Hz, 1H, H-7), 1.43 (d, *J*= 6.0 Hz, 3H, CH(C<u>H</u>$_3$)OTBS) 0.89 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.08(s, 3H, Si-<u>Me</u>$_2$*t*Bu), −0.04 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu). To a solution of **86** (12.4 mg, 3.54×10^{-2} mmol) in *t*BuOH (0.35 mL) under Ar atmosphere were added DMAP (1.3 mg, 1.1×10^{-2} mmol) and Boc_2O (0.0163 mL, 7.09×10^{-2} mmol). After stirring at room temperature for 3 h, the reaction mixture was diluted with toluene (2 mL) and evaporated. The residue was chromatographed on silica gel (30% AcOEt/hexane) to afford **56** (12.3 mg, 86% from **85**) as a colorless foam: R_f=0.65 (50% AcOEt/hexane); $[\alpha]_D^{26}$ −3.4 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3620, 2975, 1720, 1370, 1310, 1150, 1140, 1090, 1050, 880 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.23 (s, 1H, H-3), 7.01 (dd, *J*=1.8, 9.9 Hz, 1H, H-5), 6.65 (dd, *J*=3.6, 9.9 Hz, 1H, H-6), 5.18 (q, *J*=6.3 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.84 (d, *J*=3.6 Hz, 1H, H-8), 4.16 (ddd, *J*=1.8, 3.6, 3.6 Hz, 1H, H-7), 1.64 (s, 1H, *t*Bu), 1.41 (d, *J*=6.3 Hz, 3H, CH(C<u>H</u>$_3$)OTBS) 0.90 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.06 (s, 3H, Si<u>Me</u>$_2$*t*Bu), −0.07 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu); ^{13}C NMR($CDCl_3$): δ=163.72, 152.94, 152.00, 147.83, 128.89, 125.44, 125.02, 121.78, 82.21, 67.17, 58.69, 53.13, 28.05, 26.02, 25.66, 18.02, −4.88, −5.03 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{22}H_{34}NO_4Si$: 404.2257; found: 404.2278.

Adduct **87**: To a solution of **56** (75% *ee*; 20.0 mg, 4.96×10^{-2} mmol) and H-L-Val-OFm **57** (29.3 mg, 9.92×10^{-2} mmol) in CH_2Cl_2 (0.025 mL) was added $Yb(OTf)_3$ (6.1 mg, 9.9×10^{-3} mmol) in H_2O (0.050 mL). The reaction mixture was stirred at room temperature for 5 days, then diluted with $CHCl_3$ (2 mL), and the mixture was washed with brine (2 mL×2). The organic layers were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (30% AcOEt/hexane) to afford **87** (16.6 mg, 48%) as a colorless foam, the diastereomer of **87** (2.4 mg, 7%) as a colorless foam, the regioisomer of **87** (2.1 mg, 6%) as a colorless foam, and the recovered **56** (2.6 mg, 13%) as a colorless foam. **87**: R_f=0.59 (30% AcOEt/hexane); $[\alpha]_D^{26}$ −56.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3620, 2975, 1725, 1470, 1180, 1095, 1045, 900, 880 cm^{-1}; ^1H NMR ($CDCl_3$): δ=8.08 (s, 1H, quinoline H-3), 7.76–7.68 (m, 2H, Fm H-4 and H-5), 7.66–7.58 (m, 2H, Fm H-3 and H-6), 7.40–7.22 (m, 4H, Fm H-1, H-2, H-7 and H-8), 6.71 (dd, *J*=2.4, 10.0 Hz, 1H, quinoline H-5), 6.09 (dd, *J*=1.8, 10.0 Hz, 1H, quinoline H-6), 5.01 (q, *J*= 6.5 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.80 (br s, 1H, NH), 4.66 (d, *J*=12.0 Hz, 1H, quinoline H-8), 4.53 (d, *J*=6.5 Hz, 2H, Fm C<u>H</u>$_2$), 4.21 (t, *J*=6.5, 1H, Fm H-9), 3.40 (ddd, *J*=1.8, 2.4, 12.0 Hz, 1H, quinoline H-7), 3.29 (d, *J*= 5.6 Hz, 1H, Val H-α), 2.43 (s, 1H, OH), 1.95 (dqq, *J*=5.6, 6.8 Hz, 1H, Val H-β), 1.61 (s, 9H, CO_2*t*Bu), 1.41 (d, *J*=6.5 Hz, 3H, CH(C<u>H</u>$_3$)OTBS), 0.96 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.94 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.91 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.07 (s, 3H, Si<u>Me</u>$_2$*t*Bu), −0.05 ppm (s, 3H, Si-<u>Me</u>$_2$*t*Bu); ^{13}C NMR($CDCl_3$): δ=174.82, 163.79, 156.11, 150.50, 145.95, 143.69, 141.27, 135.02, 127.62, 127.03, 126.99, 126.08, 124.94, 121.50, 120.68, 119.87, 81.86, 72.73, 67.66, 65.98, 64.48, 59.30, 46.99, 31.85, 28.06, 25.68, 19.47, 18.25, 18.05, −4.91, −5.03 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{41}H_{55}N_2O_6Si$: 699.3829; found: 699.3807. Diastereomer of **87**: R_f=0.54 (30% AcOEt/hexane); ^1H NMR ($CDCl_3$): δ=8.08 (s, 1H, quinoline H-3), 7.78–7.69 (m, 2H, Fm H-4 and H-5), 7.67–7.57 (m, 2H, Fm H-3 and H-6), 7.42–7.20 (m, 4H, Fm H-1, H-2, H-7 and H-8), 6.68 (dd, *J*=2.5, 10.4 Hz, 1H, quinoline H-5), 5.92 (dd, *J*=1.8, 10.4 Hz, 1H, quinoline H-6), 5.01 (q, *J*=6.3 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.78 (br s, 1H, NH), 4.72 (d, *J*=11.2 Hz, 1H, quinoline H-8), 4.55 (dd, *J*=6.4, 10.8 Hz, 1H, Fm C<u>H</u>$_2$), 4.49 (dd, *J*=6.4, 10.8 Hz, 1H, Fm C<u>H</u>$_2$), 4.22 (dd, *J*=6.4, 6.4 Hz, 1H, Fm H-9), 3.66 (d, *J*=5.8 Hz, 1H, Val H-α), 3.55 (ddd, *J*=1.8, 2.5, 11.2 Hz, 1H, quinoline H-7), 2.08–1.76 (m, 2H, Val H-β and OH), 1.62 (s, 9H, CO_2*t*Bu), 1.40 (d, *J*=6.3 Hz, 3H, CH(C<u>H</u>$_3$)OTBS), 0.97 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.91 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.90 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.06 (s, 3H, Si<u>Me</u>$_2$*t*Bu), −0.06 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu). Regioisomer of **87**: R_f=0.41 (30% AcOEt/hexane); ^1H NMR ($CDCl_3$): δ=8.10 (s, 1H, quinoline H-3), 7.78–7.69 (m, 2H, Fm H-4 and H-5), 7.66–7.58 (m, 2H, Fm H-3 and H-6), 7.42–7.18 (m, 4H, Fm H-1, H-2, H-7 and H-8), 6.56 (dd, *J*=2.0, 10.4 Hz, 1H, quinoline H-5), 6.24 (dd, *J*=1.8, 10.4 Hz, 1H, quinoline H-6), 5.07 (q, *J*=6.4 Hz, 1H, C<u>H</u>(CH_3)OTBS), 4.68 (dd, *J*=6.2, 10.8 Hz, 1H, Fm C<u>H</u>$_2$), 4.50–4.37 (m, 2H, quinoline H-7, Fm C<u>H</u>$_2$), 4.22 (dd, *J*=6.2, 6.2 Hz, 1H, Fm H-9), 3.87 (d, *J*=12.0 Hz, 1H, quinoline H-8), 3.69 (d, *J*=4.4 Hz, 1H, NH), 2.96 (d, *J*=3.0 Hz, 1H, Val H-α), 2.20–2.02 (m, 1H, Val H-β), 1.55 (s, 9H, CO_2*t*Bu), 1.33 (d, *J*= 6.4 Hz, 3H, CH(C<u>H</u>$_3$)OTBS), 1.01 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.92 (d, *J*=6.8 Hz, 3H, Val Me-β), 0.91 (s, 9H, SiMe_2*t*<u>Bu</u>), 0.06 (s, 3H, Si-<u>Me</u>$_2$*t*Bu), −0.04 ppm (s, 3H, Si<u>Me</u>$_2$*t*Bu). H-L-Val-OFm **57** was prepared as follows: To a solution of L-valine (3.29 g, 28.1 mmol) and 1 M aqueous NaOH (28.0 mL) in 1,4-dioxane (60 mL) and H_2O (30 mL) was added Boc_2O (7.10 mL, 30.9 mmol). The reaction mixture was stirred at room temperature for 3 h and washed with Et_2O (50 mL×3). The aqueous layer was acidified with 1 M aqueous HCl (30 mL) at 0°C and extracted with Et_2O (50 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford Boc-L-Val-OH (6.10 g, quantitative yield) as a colorless syrup. To a solution of Boc-L-Val-OH (1.67 g, 7.69 mmol) and 9-fluorenylmethanol (1.51 g, 7.69 mmol) in CH_2Cl_2 (30 mL) were added DMAP (93.9 mg, 7.69×10^{-1} mmol) and DCC (1.59 g, 7.69 mmol). After stirring at room temperature for 2 h, the reaction mixture was evaporated and AcOEt was added to the residue. The suspension was filtered through celite and the filirate was evaporated. The residue was chromatographed on silica gel (8% AcOEt/hexane) to afford Boc-L-Val-OFm (2.76 g, 91%) as colorless solids. To a solution of Boc-L-Val-OFm (39.3 mg, 9.92×10^{-2} mmol) in CH_2Cl_2 (0.5 mL) at 0°C was added TFA (0.5 mL). The reaction mixture was stirred at room tem-

perature for 1 h and evaporated. The residue was dissolved in Et_2O (3 mL) and this was basified with aqueous $NaHCO_3$, and the mixture was extracted with Et_2O (3 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford H-L-Val-OFm **57** (29.3 mg, quantitative yield) as a colorless syrup: ^{1}H NMR ($CDCl_3$): δ=7.80–7.72 (m, 2H, Fm H-4 and H-5), 7.65–7.54 (m, 2H, Fm H-3 and H-6), 7.46–7.24 (m, 4H, Fm H-1, H-2, H-7 and H-8), 4.58–4.42 (m, 2H, Fm C$\underline{H}_2$), 4.21 (br dd, J=6.2, 6.2 Hz, 1H, Fm H-9), 3.31 (d, J=5.0 Hz, 1H, H-α), 1.97 (m, 1H, H-β), 0.92 (d, J=6.8 Hz, 3H, Me-β), 0.81 ppm (d, J=6.8 Hz, 3H, Me-β).

Segment C (**6**) : To a solution of **87** (27.4 mg, 3.92×10^{-2} mmol) in dry CH_2Cl_2 (0.39 mL) at 0°C under Ar atmosphere were added 2,6-lutidine (0.0457 mL, 7.84×10^{-2} mmol) and TBSOTf (0.0270 mL, 4.70×10^{-2} mmol). After stirring at 0°C for 15 min, the reaction mixture was quenched with H_2O (2 mL) and saturated aqueous $NaHCO_3$ (0.50 mL). The mixture was extracted with $CHCl_3$ (3 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (10% AcOEt/hexane) to afford the TBS ether (30.5 mg, 96%) as a colorless syrup. To a solution of TBS ether (20.6 mg, 2.53×10^{-2} mmol) in dry CH_2Cl_2 (0.25 mL) at 0°C under Ar atmosphere was added *B*-bromocatecholborane (10.1 mg, 5.07×10^{-2} mmol). After stirring at room temperature for 1 day, the reaction mixture was quenched with H_2O (2 mL). The mixture was extracted with $CHCl_3$ (3 mL×1) and AcOEt (3 mL×2). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (3% MeOH/$CHCl_3$) to afford carboxylic acid **6** (15.1 mg, 79%) as a colorless syrup: R_f=0.60 (10% MeOH/$CHCl_3$); $[\alpha]_D^{27}$ −113.7 (*c* 1.00, $CHCl_3$); IR (KBr): $\tilde{\nu}$=2955, 2925, 2360, 2855, 1775, 1725, 1260, 1140, 1100, 840, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ= 8.28 (s, 1H, quinoline H-3), 7.81–7.68 (m, 2H, Fm H-4 and H-5), 7.64–7.52 (m, 2H, Fm H-3 and H-6), 7.45–7.22 (m, 4H, Fm H-1, H-2, H-7 and H-8), 6.76 (dd, J=0.8, 10.2 Hz, 1H, quinoline H-5), 6.15 (dd, J=3.4, 10.2 Hz, 1H, quinoline H-6), 5.09 (q, J=6.1 Hz, 1H, C$\underline{H}$(CH$_3$)OTBS), 4.69 (d, J=7.6 Hz, 1H, quinoline H-8), 4.56 (dd, J=6.3, 10.8 Hz, 1H, Fm C$\underline{H}_2$), 4.50 (dd, J=6.3, 10.8 Hz, 1H, Fm C$\underline{H}_2$), 4.17 (dd, J=6.3, 6.3 Hz, 1H, Fm H-9), 3.47 (ddd, J=0.8, 3.4, 7.6 Hz, 1H, quinoline H-7), 3.10 (d, J=5.5 Hz, 1H, Val H-α), 1.81 (dqq, J=5.5, 7.0, 7.0 Hz, 1H, Val H-β), 1.37 (d, J=6.1 Hz, 3H, CH(C$\underline{H}_3$)OTBS), 0.93 (s, 9H, SiMe$_2$*t*$\underline{Bu}$), 0.89 (s, 9H, SiMe$_2$*t*$\underline{Bu}$), 0.85 (d, J=7.0 Hz, 3H, Val Me-β), 0.79 (d, J=7.0 Hz, 3H, Val Me-β), 0.16 (s, 3H, Si$\underline{Me}_2$*t*Bu), 0.06 (s, 3H, Si$\underline{Me}_2$*t*Bu), 0.04 (s, 3H, Si$\underline{Me}_2$*t*Bu), −0.04 ppm (s, 3H, Si$\underline{Me}_2$*t*Bu); ^{13}C NMR($CDCl_3$): δ= 174.55, 164.18, 155.82, 152.38, 143.55, 143.22, 141.36, 133.38, 128.25, 127.81, 127.10, 127.06, 124.84, 124.75, 121.33, 120.50, 120.03, 74.04, 67.29, 66.02, 63.80, 56.95, 47.01, 31.73, 25.74, 25.69, 25.58, 19.37, 18.16, −4.23, −4.53, −4.87, −4.95 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{43}H_{61}N_2O_6Si_2$: 757.4068; found: 757.4076.

Phenylselenoalanine **89**: To a solution of **88** (1.00 g, 5.34 mmol) in degassed dry DMF (13 mL) at room temperature under Ar atmosphere was added benzeneselenol (0.681 mL, 6.41 mmol). After stirring at room temperature for 2 h, the reaction mixture was quenched with 1M aqueous NaOH (6 mL) and H_2O (10 mL), and the mixture was washed with Et_2O (10 mL×3). The aqueous layer was acidified with 1M aqueous HCl to pH 2 at 0°C and extracted with AcOEt (30 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (0–5% MeOH/$CHCl_3$) to afford **89** (1.84 g, quantitative yield): R_f=0.61 (10% MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$): δ=7.60–7.48 (m, 2H, Ph), 7.30–7.18 (m, 3H, Ph), 5.50 (br d, J=7.2 Hz, 1H, BocN$\underline{H}$), 4.70–4.56 (m, 1H, H-α), 3.44 (dd, J=12.0, 4.6 Hz, 1H, H-β), (dd, J=12.0, 5.2 Hz, 1H, H-β), 1.40 ppm (s, 9H, Boc).

Phenylselenoalanine Fm ester **90**: To a solution of **89** (996 mg, 2.89 mmol) and 9-fluorenylmethanol (568 mg, 2.89 mmol) in dry CH_2Cl_2 (15 mL) at 0°C under Ar atmosphere were added DMAP (35.3 mg, 2.89×10^{-1} mmol) and DCC (597 mg, 2.89 mmol). After stirring at room temperature for 4 h, the reaction mixture was evaporated and AcOEt was added to the residue. The suspension was filtered through celite and the filtrate was evaporated. The residue was chromatographed on silica gel (10% AcOEt/hexane) to afford **90** (1.23 g, 82% from **88**): R_f=0.61 (20% AcOEt/hexane); m.p. 109–110°C (not recrystallized); $[\alpha]_D^{29}$ +18.6 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3620, 3435, 2980, 1765, 1710, 1580, 1420, 1300, 1130, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.80–7.72 (m, 2H, Fm), 7.57–7.15 (m, 11H, Fm and PhSe), 5.34 (br d, J=8.0 Hz, 1H, N$\underline{H}$Boc), 4.72 (dt, J=5.0, 8.0 Hz, 1H, H-α), 4.24 (br dd, J=6.5, 9.2 Hz, 1H, Fm C$\underline{H}_2$), 4.14–4.01 (m, 2H, Fm C$\underline{H}_2$ and H-9), 3.28 (d, J=5.0 Hz, 2H, H-β), 1.42 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ=170.57, 154.92, 143.36, 143.24, 141.24, 141.17, 133.67, 129.10, 128.78, 127.83, 127.50, 127.12, 127.09, 125.03, 124.93, 120.00, 119.97, 80.06, 67.16, 53.28, 46.49, 30.50, 28.23 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{28}H_{30}NO_4{}^{80}Se$: 524.1340; found: 524.1342.

Dipeptide **91**: To a solution of **90** (1.23 g, 2.35 mmol) in dry CH_2Cl_2 (6.0 mL) at 0°C under Ar atmosphere was slowly added TFA (6.0 mL). The reaction mixture was stirred at room temperature for 2 h and evaporated to afford the crude amine·TFA. To a solution of this crude amine·TFA in dry CH_2Cl_2 (12 mL) at 0°C under an Ar atmosphere were added *i*Pr$_2$NEt (1.00 mL, 5.74 mmol), **89** (895 mg, 2.60 mmol), HOAt (354 mg, 2.60 mmol), and CIP (724 mg, 2.60 mmol). After stirring at room temperature for 2 h, the reaction mixture was quenched with H_2O (10 mL) and saturated aqueous $NaHCO_3$ (2 mL). The mixture was extracted with $CHCl_3$ (15 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residue was chromatographed on silica gel (20% AcOEt/hexane) to afford **91** (1.66 g, 94%) as a colorless foam: R_f=0.59 (40% AcOEt/hexane); m.p. 120°C (not recrystallized); $[\alpha]_D^{31}$ 0.00 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$=3620, 3420, 2975, 1765, 1710, 1680, 1580, 1475, 1420, 1370, 875 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ=7.79–7.15 (m, 18H, Fm and PhSe×2), 6.95 (br d, J=7.0 Hz, 1H, CONH), 5.05 (br s, 1H, N$\underline{H}$Boc), 4.82 (ddd, J=4.6, 4.6, 7.0 Hz, 1H, PhSeAla H-α), 4.34–4.16 (m, 1H, PhSeAla H-α), 4.27 (dd, J=6.6, 10.0 Hz, 1H, Fm C$\underline{H}_2$), 4.10 (dd, J=6.6, 10.0 Hz, 1H, Fm C$\underline{H}_2$), 4.02 (dd, J=6.6, 6.6 Hz, 1H, Fm H-9), 3.31 (dd, J=4.6, 12.4 Hz, 1H, PhSeAla H-β), 3.24–3.04 (m, 3H, PhSeAla H-β×3), 1.43 ppm (s, 9H, Boc); ^{13}C NMR ($CDCl_3$): δ= 169.96, 169.66, 155.05, 143.26, 143.13, 141.24, 141.15, 133.70, 133.04, 129.15, 128.78, 127.86, 127.60, 127.37, 127.16, 127.12, 124.93, 124.85, 120.00, 80.39, 67.28, 54.18, 52.46, 46.40, 29.69, 29.56, 28.23 ppm; HRMS (FAB): *m*/*z* $[M+H]^+$ calcd for $C_{37}H_{39}N_2O_5{}^{80}Se_2$: 751.1189; found: 751.1174.

Segment D (**7**): Compound **91** (480 mg, 6.41×10^{-1} mmol) in 3M HCl/AcOEt (2.9 mL) was stirred at room temperature for 2 h and the solvent was evaporated. The residue was dissolved in AcOEt (2 mL) and this was basified with aqueous $NaHCO_3$, and the mixture was extracted with AcOEt (3 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford **7** (416 mg, quantitative yield), which was used for the next step without purification.

Dipeptide **92**: To a solution of **89** (1.05 g, 3.05 mmol) in dry THF (30 mL) at −15°C under Ar atmosphere were added NEt_3 (0.447 mL, 3.21 mmol) and $ClCO_2Et$ (0.306 mL, 3.20 mmol). After stirring at −15°C for 10 min, 28% aqueous NH_3 (6.2 mL, 90 mmol) was slowly added. The reaction mixture was stirred for 30 min at −15°C and then at room temperature for 2 h. The reaction mixture was evaporated and H_2O (20 mL) was added. The mixture was extracted with AcOEt (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 the amide (826 mg, 79%) as a colorless syrup: R_f=0.18 (50% AcOEt/hexane); ^{1}H NMR ($CDCl_3$): δ=7.59–7.53 (m, 2H, PhSe), 7.32–7.22 (m, 3H, PhSe), 6.40 (br s, 1H, CONH$_2$), 5.98 (br s, 1H, CONH$_2$), 5.39 (br d, J=6.8 Hz, 1H, BocN$\underline{H}$), 4.37 (m, 1H, H-α), 3.25 (m, 2H, H-β×2), 1.42 ppm (s, 9H, Boc). To a solution of this amide (75.3 mg, 2.08×10^{-1} mmol) in dry CH_2Cl_2 (2.0 mL) at 0°C under Ar atmosphere was slowly added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 1 h and evaporated to afford the crude amine·TFA (102 mg). To a solution of this crude amine·TFA in dry DMF (2.2 mL) at 0°C under Ar atmosphere were added *i*Pr$_2$NEt (0.151 mL, 8.67×10^{-1} mmol), **89** (82.3 mg, 2.40×10^{-1} mmol), HOAt (32.5 mg, 2.39×10^{-1} mmol), and CIP (66.6 mg, 2.39×10^{-1} mmol). After stirring at room temperature for 5 h, the reaction mixture was quenched with H_2O (4 mL). The mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated. The residual solid was recrystallized from acetone/hexane to

afford **92** (115 mg, 92%) as colorless crystals: R_f=0.78 (10% MeOH/$CHCl_3$); m.p. 167–168 °C; $[\alpha]_D^{23}$ −72.9 (*c* 1.02, $CHCl_3$); IR (KBr): $\tilde{\nu}$=3320, 3195, 2980, 1690, 1655, 1625, 1525, 1480, 1385, 1165, 735, 690, 670 cm^{-1}; ^1H NMR ($CDCl_3$): δ=7.59–7.43 (m, 4H, PhSe), 7.33–7.21 (m, 6H, PhSe), 6.93 (br d, *J*=8.4 Hz, 1H, CONH), 6.72 (br s, 1H, $CONH_2$), 5.44 (br s, 1H, $CONH_2$), 5.05 ppm (br d, *J*=5.4 Hz, 1H, NHBoc); ^{13}C NMR ($CDCl_3$): δ=172.04, 170.22, 155.80, 133.31, 133.07, 129.43, 129.28, 127.91, 127.63, 81.21, 54.79, 52.74, 29.10, 28.74, 28.25 ppm; HRMS (ESI): *m/z* $[M+Na]^+$ calcd for $C_{23}H_{29}N_3NaO_4{}^{80}Se_2$: 594.0386; found: 594.0388.

Segment E (**4**) : To a solution of **92** (47.1 mg, 8.27×10^{-2} mmol) in dry CH_2Cl_2 (0.67 mL) at 0 °C under Ar atmosphere was slowly added TFA (0.67 mL). The reaction mixture was stirred at room temperature for 2 h and evaporated. The residue was dissolved in AcOEt (5 mL) and this was basified with aqueous $NaHCO_3$, and the mixture was extracted with AcOEt (5 mL×3). The combined extracts were dried over Na_2SO_4, filtered through celite, and evaporated to afford **4** (36.1 mg, 93%) as colorless solids, which was used for the next step without purification.

Acknowledgements

This research was partially supported by a Grant-in-Aid for the 21st Century COE program "KLCC" (T.M.), for Scientific Research on Priority Areas (A) "Exploitation of Multi-Element Cyclic Molecules" (M.N.), and on Priority Areas 17035076 and 18032067 (M.N.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan (MEXT).

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Received: February 2, 2008
Published online: May 7, 2008

