CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801024

Total Synthesis and Determination of the Absolute Configuration of Guadinomines B and C_2

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Abstract: This article describes the determination of the absolute configurations of the guadinomines, which are novel cyclic guanidyl natural products that are inhibitors of the type III secretion system (TTSS) of bacteria. Any compound that interrupts the TTSS of bacteria is potentially an ideal anti-infectious drug. The reliable asymmetric synthesis of guadinomines has revealed their absolute configurations, which could not have been defined without this synthetic approach. Our report not only describes the asymmetric total synthesis of the title compounds, but also demonstrates the novel concise synthesis of tri-substituted piperazinone cores as optically pure forms. The novel feature of our method is an intramolecular S_N2 cyclization that uses PPh_3 and I_2 to construct the unique 5-membered cyclic guanidine substructure.

Keywords: configuration determination · guadinomines · natural products · total synthesis · type III secretion system

Introduction

Extracts from culture broths of *Streptomyces* sp. K01-0509 have been recognized for their ability to inhibit the type III secretion system (TTSS) of bacteria.[1] The property has been traced to the novel guadinomines A to D (**1**–**5**), and three of them, **1**, **2**, and **5**, have been identified as being selective inhibitors of the TTSS.[1–3] In the process of isolation, a new compound, guadinomic acid (K01–0509 B) **6**, was detected, which occurred as a biosynthetic intermediate.[1,3] The TTSS is expressed by many Gram-negative pathogens, including enteropathogenic *Escherichia coli* (EPEC),[4] enterohemoragic *E. coli* (EHEC), *Pseudomonas aeruginosa*, *Salmonella* spp., and *Shigella* spp.[5] where it helps deliver effector proteins into the host cell during the infection process.[6] Consequently, guadinomines may prove to be novel anti-infectious drugs.[7]

Original structural analysis was mainly carried out by NMR spectroscopic methods to elucidate the novel cyclic guanidine natural products.[3] However, the relative and absolute configurations of guadinomines **1** to **5** remained undetermined, except for the peptide moiety. It is difficult to determine exact configurations, even with highly advanced spectroscopic methods, especially for linear portions that include consecutive stereocenters for 1,2-diamine or piperazinone and polyol. Moreover, work was hampered by insufficient quantities of the natural products. These difficulties encouraged establishment of the configurations of guadinomines by chemical synthesis. Our previous research demonstrated the asymmetric preparation of **6**, which allowed the determination of the configuration of two stereocenters.[8] The stereo information of **6** suggested that the configuration of C7 (or C2′) and C4′ (or C4′′) in **1** to **5** should be related to C5 and C4′ in **6**, respectively. Nevertheless, other configurations of **1** to **5** remained unclear. Herein, we report the total assignment of the configuration of **2** (B) and **4** (C_2), through the first asymmetric total synthesis of these natural products.

Results and Discussion

In our synthetic strategy, we made an intuitive assumption that the prediction of the relative and absolute configuration for C5 and C6 with C3 in **4** would be more conclusively ac-

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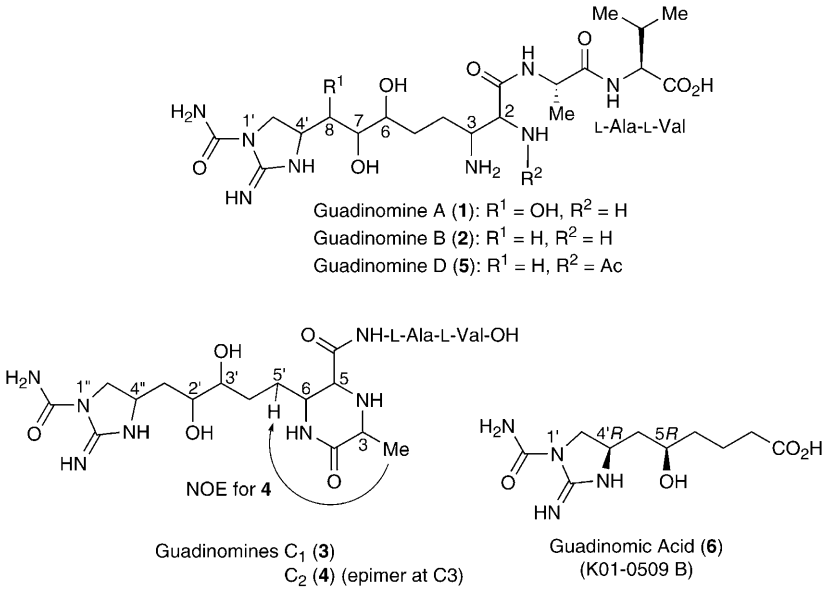
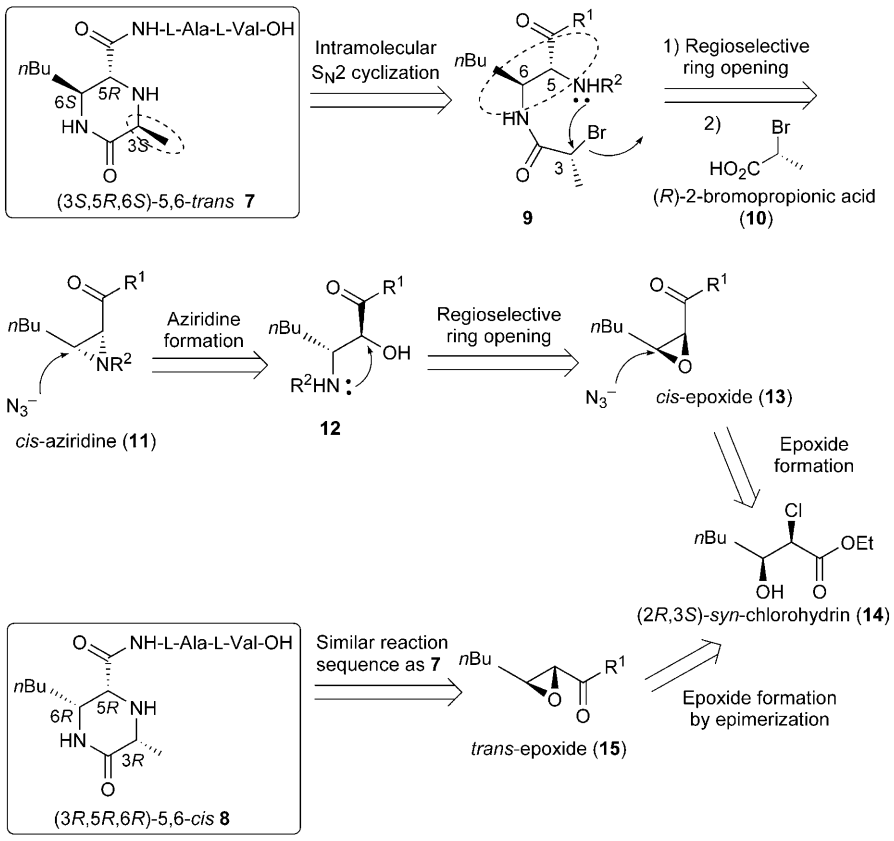
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801024.



complished by comparison with simple piperazinone compounds.[9] Moreover, evidence for the *syn*-relationship between C3 and C6 in **4** was conclusive because of the observation of an NOE between H-5′ and CH_3-3 by detailed analysis of its ^{1}H NMR spectra.[10] Therefore, our first aim was to elucidate the relative and absolute configuration of the piperazinone moiety of **4** by comparing **4** with simple piperazinone model compounds, which contain the peptide moiety (**7**, **8**; Scheme 1).

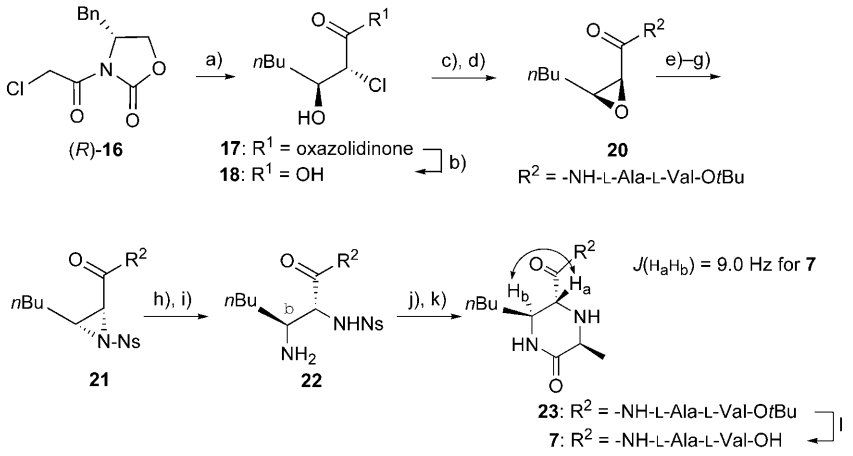
Retrosynthetic analysis of piperazinone core: Our retrosynthetic analysis of piperazinone model compounds, as shown in Scheme 1, involved installing the stereogenic centers from optically active reagents in a reliable fashion. To avoid any doubt about the configurations, optically active 2-bromopropionic acid (**10**) and *syn*-chlorohydrin (**14**) were selected as chiral sources. We envisaged that it would be efficient to construct each stereocenter by S_N2 cyclization for C3 and regioselective azidolysis of aziridine[11] for the C5 and C6 positions. The optically active aziridine could be prepared from 1,2-hydroxylamine (**12**), derived from **14** by epoxide chemistry.[12] Additionally, the C3, C6-epi model compound **8** could be



Scheme 1. Retrosynthetic analysis of model compounds **7** and **8**.

constructed in a similar fashion to **7** from *trans*-epoxide **15**, which can also be generated from **14**.[12]

Synthesis of the 5,6-*trans*-piperazinone 7: The route to (3*S*,5*R*,6*S*)-5,6-*trans*-3,6-*syn*-piperazinone **7** (Scheme 2) commenced with (*R*)-oxazolidinone ((*R*)-**16**), which was subjected to the Evans aldol reaction[13] with valeraldehyde, followed by hydrolytic removal of the auxiliary, which afforded α-chloro-β-hydroxy acid **18** as a single enantiomer. Condensation with the known peptide section (NH_2-L-Ala-L-Val-O*t*Bu) **19** and subsequent epoxide formation under mild basic conditions afforded *cis*-epoxide **20** as a single form. Azidolysis of **20** followed by reduction of the azide gave 1,2-hydroxylamine, which led to *cis*-Ns-aziridine **21** (Ns = 2-nitrobenzenesulfonyl) as a single form upon the formation of an Ns-aziridine via ring closure of the *N*,*O*-bis-

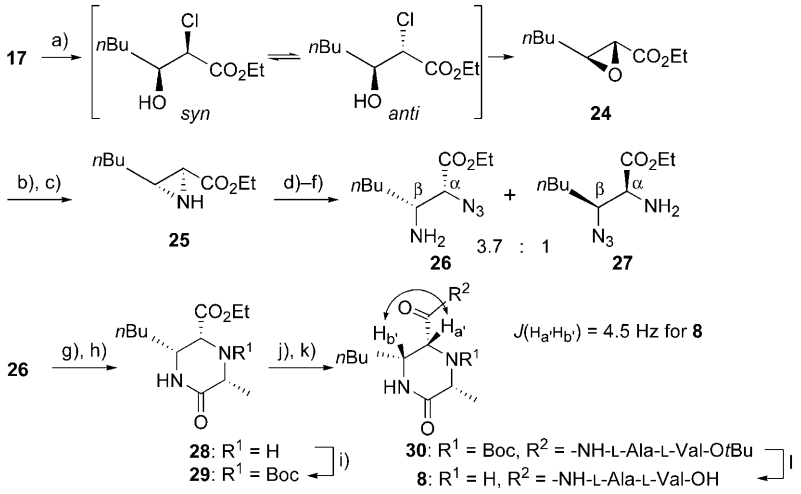


Scheme 2. Reagents and conditions: a) valeraldehyde, nBu$_2$BOTf, iPr$_2$NEt, CH_2Cl_2, −78 to 0 °C, 1 h, 72 % (dr > 20:1); b) LiOH, H_2O_2, THF/H_2O (5/1), 0 °C, 25 min; c) bromotrispyrrolidinophosphonium hexafluorophosphate (PyBrop), iPr$_2$NEt, H$_2$N-L-Ala-L-Val-OtBu **19**, CH_2Cl_2, 0 °C to RT, 1 h, 82 % (2 steps); d) K_2CO_3, H_2O, DMF, RT, 2.5 h, 100 %; e) NaN_3, NH_4Cl, MeOH/H_2O (20:1), 70 °C, 56 h, 91 % (predominantly the β-N_3 isomer); f) 10 % Pd/C, H_2, EtOAc, RT, 9 h; g) *p*-nitrobenzenesulfonyl chloride (NsCl) (3 equiv), Et_3N (3 equiv), 4-(dimethylamino)pyridine (0.05 equiv), CH_2Cl_2, RT, 12 h, 91 % (2 steps); h) NaN_3, DMF, 0 °C to RT, 2.5 h, 91 %; i) PPh_3, H_2O, THF, 45 °C, 20 h, 85 %; j) (*R*)-**10**, 1-hydroxybenzotriazole (HOBt), *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI), 0 °C, 1 h, 91 %; k) iPr$_2$NEt, MeCN, 60 °C, 19 h, then PhSH, 60 °C, 21 h, 100 %; l) TFA/H_2O (3:1), RT, 3 h, 100 %.

Ns intermediate.[14] Regioselective azidolysis of **21** gave only the β-azide, which upon reduction by Staudinger amination followed by condensation with (*R*)-2-bromopropionic acid ((*R*)-**10**) and intramolecular S_N2 cyclization, ended with formation of the piperadinone ring. This reaction proceeded without any epimerization and subsequent elimination of the Ns group gave piperadinone compound **23** as a single isomer. Final deprotection of the *t*-butyl group yielded the desired model compound **7**.[15]

Synthesis of the 5,6-*cis*-piperazinone 8: The route to (3*R*,5*R*,6*R*)-5,6-*cis*-3,6-*syn*-piperazinone (**8**, Scheme 3) commenced from **17** in similar reaction sequence to the preparation of **7**. The requisite epoxy geometry was installed through a modified Azerad protocol[12] under harsh basic conditions in EtOH, involving in situ ester preparation and isomerization at the α position of the ester followed by ring closure due to the fast cyclization rate of the *anti* isomer. This gave the desired *trans*-epoxy ester **24** as a major isomer (5.4:1). The selectivity was critical for our planned formation of the C5,C6 *cis*-piperazinone. Subsequent *cis*-aziridine formation was accomplished by Staudinger ring closure[16] via azidolysis of the epoxide. Azidolysis of **24** gave us a mixture of α and β azido products, leading to the same chiral product **25**. The Ns group was introduced to activate aziridine followed by azidolysis of the resulting Ns-aziridine to the inseparable regioisomers of azidoamine, which upon elimination of the Ns group, yielded separable isomers **26** and **27** with moderate selectivity (**26**/**27** = 3.7:1). Azido **26** was condensed with (*S*)-2-bromopropionic acid ((*S*)-**10**), which upon intramolecular S_N2 cyclization through Staudinger amination, yielded the desired piperazinone core **28**. *tert*-Butoxycarbonyl (Boc) protection of **28**, followed by hydrolysis, and condensation with peptide **19**, finally led to the target model piperazinone **8**[15] by total deprotection.

Comparison of ^{1}H NMR spectra of natural 3 and the model compounds: The respective NMR spectra of the synthetic piperazinone compounds were compared to naturally occurring **3** and **4**. Clearly, the coupling constants between $H_{a'}$ and $H_{b'}$ of **8** (J = 4.5 Hz in 1 % trifluoroacetic acid (TFA)/



Scheme 3. Reagents and conditions: a) NaH, EtOH, 0 °C, 20 min, 98 % (as a mixture of *trans*/*cis*-epoxide; predominantly the *trans* isomer; 5.4:1); b) NaN_3, NH_4Cl, 1,4-dioxane/H_2O (1:1), 60 °C, 40 h, 55 %; c) PPh_3, dehydrated MeCN, 80 °C, 89 % as only the *trans*-isomer; d) NsCl, Et_3N, 4-(dimethylamino)pyridine (0.1 equiv), CH_2Cl_2, RT, 20 h; e) NaN_3, DMF, 0 °C to RT, 0.5 h; f) PhSH, iPr$_2$NEt, MeCN, RT, 2.5 h, 53 % for **26**, 14 % for **27** (3 steps); g) (*S*)-**10**, (benzotriazol-1-yloxy)trispyrrolidinophosphonium hexafluorophosphate (PyBOP), iPr$_2$NEt, RT, 80 min, 94 %; h) PPh_3, Et_3N, MeCN, RT, 1 h; then H_2O, 60 °C, 1.5 h, 73 %; i) Boc_2O, EtOAc, 80 °C, 20 min, 73 %; j) LiOH, MeOH/THF/H_2O (2:2:1), RT, 85 min; k) PyBOP, iPr$_2$NEt, H$_2$N-L-Ala-L-Val-OtBu **19**, CH_2Cl_2, RT, 1 h, 67 % (2 steps); l) TFA/H_2O (3/1), RT, 2.5 h, 98 %.

D_2O) confirmed the structures of guadinomine Cs (**3** and **4**; both 4.2 Hz for *J* values; Schemes 2 and 3). Therefore, it was convincing that the *cis*-conformation of the 5,6 position of piperazinone is an essential part of natural **3** and **4**. To indicate the absolute configuration of the piperazinone moiety of **4**, NH-D-Ala-D-Val-OH derivative **31** (Figure 1), which can be likened to the (3*S*,5*S*,6*S*)-analogue containing the L-peptide, *ent*-**31**, used to compare **4** with **31**, was concisely

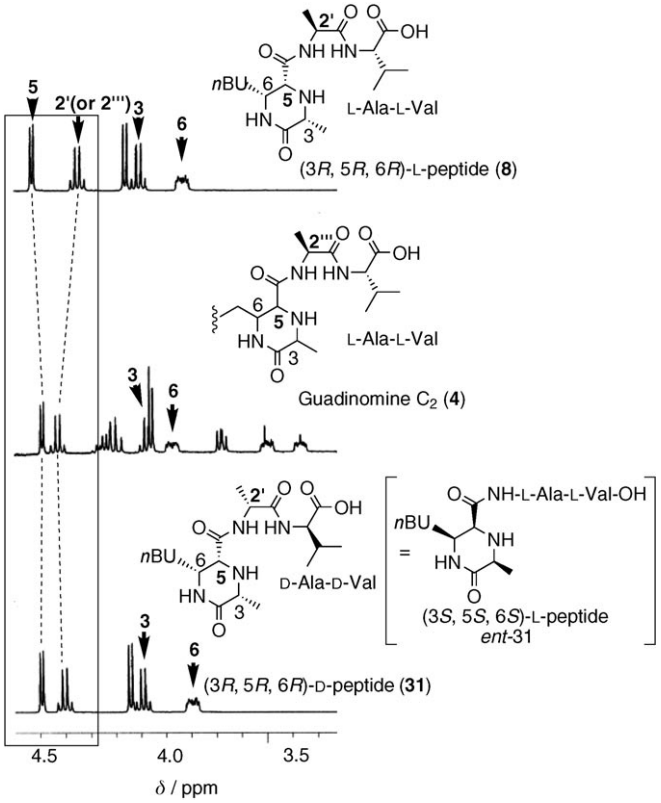


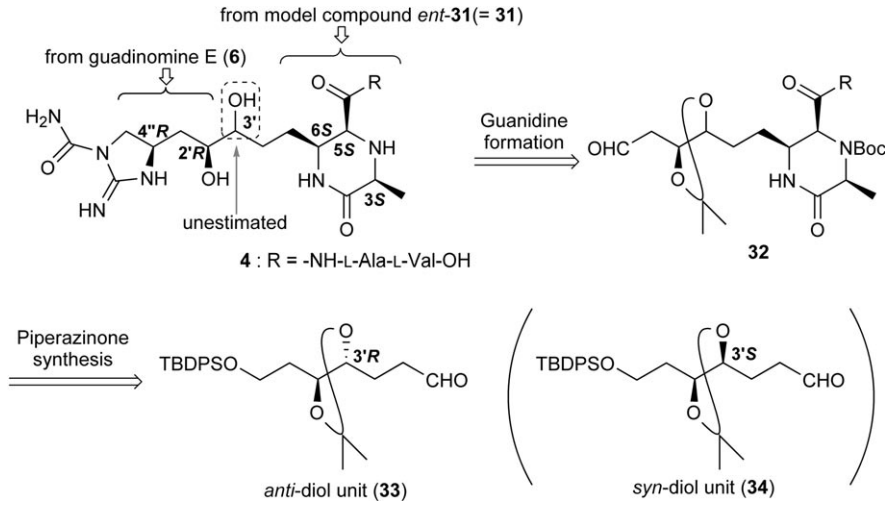
Figure 1. Comparison between ^{1}H NMR spectra of **4**, **8**, and **31**.

prepared from piperazinone ester **29** in the same manner.

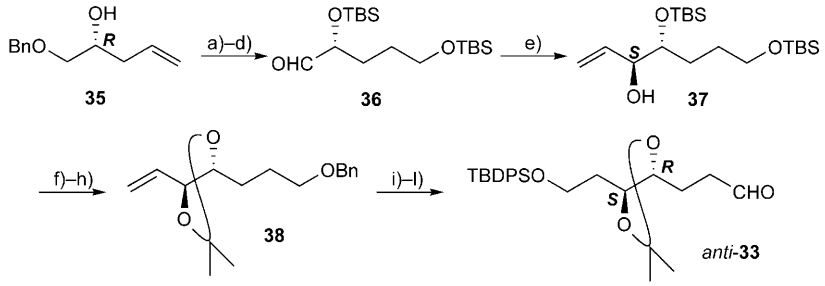
As can be seen in Figure 1, the correlation between H-5 ($\delta = 4.49$ ppm (d, $J = 4.5$ Hz)) and H-2′ ($\delta = 4.40$ ppm (q, $J = 7.2$ Hz)) of **31** in the ^{1}H NMR spectra recorded in 1% TFA/D_2O show better agreement with natural **4** ($\delta = 4.50$ ppm (d, $J = 4.2$ Hz) for H-5; $\delta = 4.44$ ppm (q, $J = 7.2$ Hz) for H-2‴) than **8** ($\delta = 4.53$ ppm (d, $J = 4.5$ Hz) for H-5; $\delta = 4.35$ ppm (q, $J = 7.2$ Hz) for H-2′). H-2′ in the peptide moiety for this NMR spectrum observation is situated closest to the piperazinone core. Therefore, the relationship between H-5 and H-2′ should be the most affected signals in the diastereomers (**8** and **31**). The ^{13}C NMR spectroscopy data are also in good agreement with the natural structures.[17] From these observations described and prior work on guadinomine E (**6**), the absolute configuration of guadinomine C_2 (**4**) was envisaged and narrowed down to two stereoisomers, as shown in Scheme 4, from the 2^6 possible stereoisomers (six stereocenters exist). However, the absolute configuration for C3′ remained undetermined. To verify the absolute structure of **4**, and to facilitate the discovery of novel analogues with advantageous pharmaceutical profiles, we executed the first asymmetric total synthesis of both key stereoisomers of **4**.

Retrosynthetic analysis of 4: Our targets were both C3′-epimers of **4** (Scheme 4), which can be crafted from *syn*- (**33**) and *anti*-diol (**34**) derivatives through a sequence that involves the introduction of a piperazinone core, by applying the protocol described in Scheme 3, and the construction of a cyclic guanidine possessing a carbamoyl function, as established in our earlier preparation of **6**.[8]

Preparation of *anti*-diol 33: The route to (3′*R*)-**4** began with the preparation of protected *anti*-diol **33** (Scheme 5). Chiral alcohol **35**, prepared from (*R*)-benzylglycidol with vinylmagnesium bromide by Boinin's protocol,[18] was subjected to hydroboration and oxidation with protection chemistry to give aldehyde **36**. A construction of the *anti*-diol unit, the diastereoselective vinylation of **36**, proceeded with a diastereomeric ratio (dr) of 5:1, but the resulting isomers could not be separated. After removal of the bis-TBS (TBS = *tert*-butyldimethylsilyl) groups, protection of the diol with a cyclic acetal and the primary alcohol with a benzyl group gave **38** as a single diastereomer after chromatographic separation.[19,20] Sequential hydroboration and oxidation with protection techniques gave the desired *anti*-diol product *anti*-**33**.

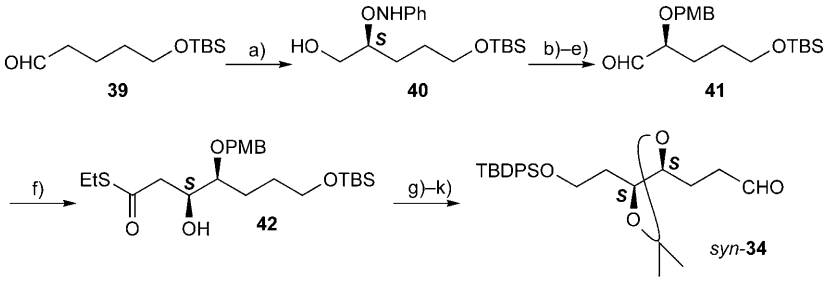


Scheme 4. Proposed structure and retrosynthetic analysis of **4**.



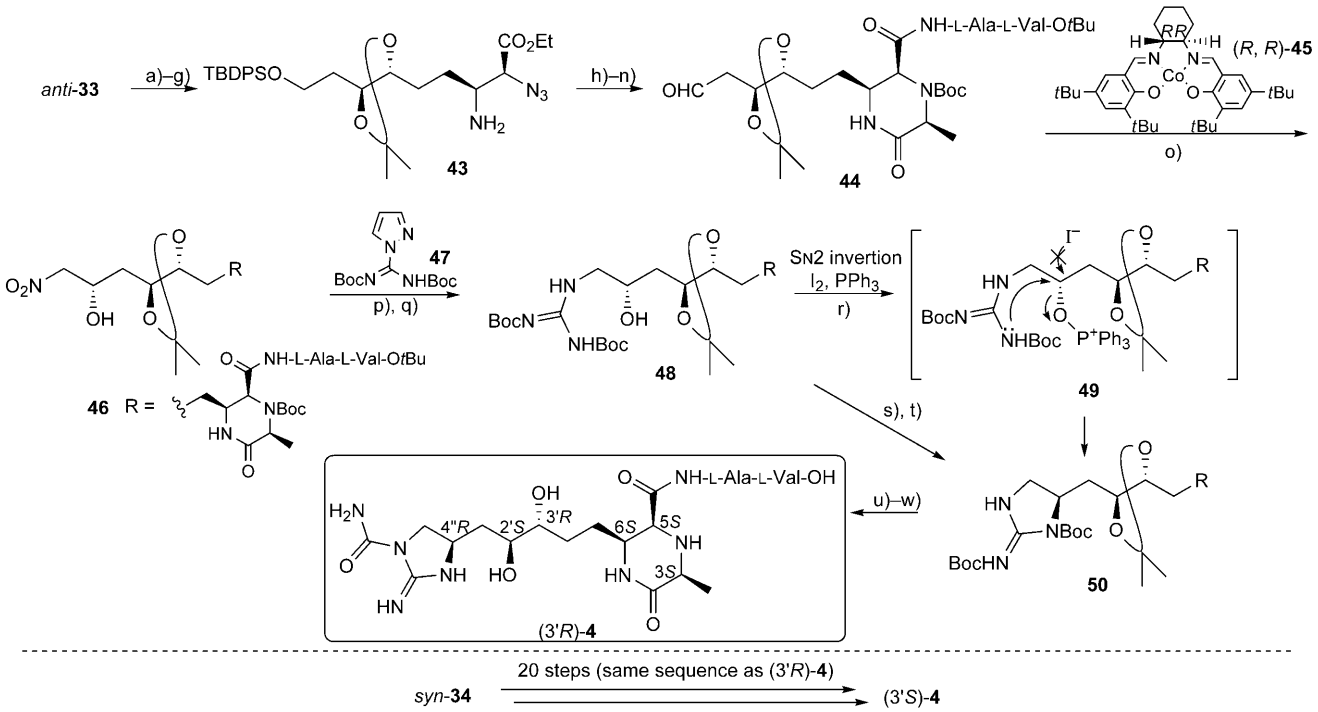
Scheme 5. Reagents and conditions: a) BH_3·Me_2S, THF, 0 °C to RT, 2 h; then aqueous H_2O_2, 4 N aqueous NaOH, RT, 2 h, 87 %; b) TBSCl, imidazole, DMF, RT, 2 h, 95 %; c) H_2, $Pd(OH)_2$/C, EtOAc, RT, 20 min, 96 %; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0 °C, 15 min; e) CH_2=CHMgBr, Et_2O, −78 °C, 35 min, 84 % (2 steps) (dr = 5:1); f) 4 N HCl in dioxane, RT, 20 min, 94 %; g) 2,2-dimethoxypropane, TsOH·H_2O (TsOH = *p*-toluenesulfonic acid), acetone, RT, 15 min, 92 %; h) BnBr, tetrabutylammonium iodide (TBAI), NaH, THF, 70 °C, 6.5 h, 85 % (dr > 20:1); i) BH_3·Me_2S, THF, 0 °C to RT, 2 h; then $NaBO_3$, 4 N aqueous NaOH, 50 °C, 1.5 h, 69 %; j) *tert*-butyldiphenylsilyl chloride (TBDPSCl), imidazole, DMF, RT, 40 min; k) H_2, $Pd(OH)_2$, EtOAc, RT, 2.5 h, 78 % (2 steps); l) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0 °C, 20 min.

Preparation of *syn*-diol unit 34: Synthesis of *syn*-diol **34** (Scheme 6) began with the introduction of a stereocenter at the α position of aldehyde **39**[21] by an α-aminooxylation developed by McMillan et al.[22] The resulting aminooxylated aldehyde was reduced to alcohol **40** with excellent enantioselectivity (99 % enantiomeric excess (*ee*)).[23] Cleavage of the N−O bond by hydrogenation, followed by protection of the secondary alcohol, and oxidation, gave aldehyde **41**. The chiral aldehyde was then transformed in a Ti-chelation-controlled Mukaiyama aldol reaction, using the trimethylsilyl (TMS) enolate of thioethylacetate in the presence of $TiCl_3$(O-*i*Pr), to give *syn*-aldol **42** with exceptional diastereoselectivity (> 99 % diastereomeric excess (*de*)).[20,24,25] Subsequent reduction of the thioester unit in the stepwise sequence of protection, deprotection, and oxidation of the hydroxy group, yielded the desired aldehyde of *syn*-**34**.



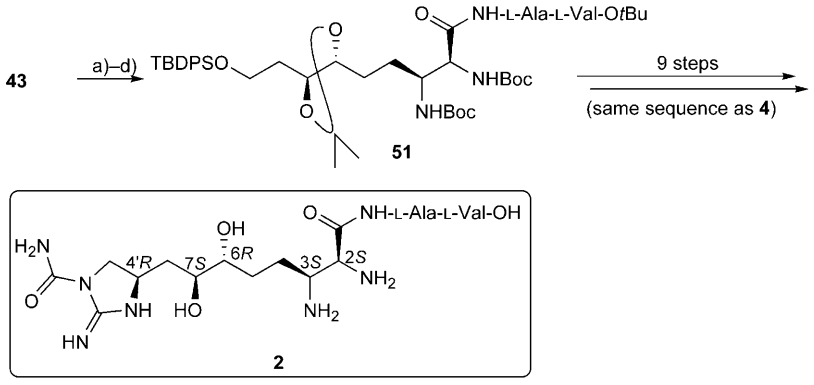
Scheme 6. Reagents and conditions: a) D-proline, nitrosobenzene, $CHCl_3$, 0 °C, 105 min; then $NaBH_4$, EtOH, 0 °C, 0.5 h; b) H_2, 10 % Pd/C, EtOAc, RT, 4 h, 40 % (2 steps), > 98 % *ee*; c) PMB(OMe)$_2$ (PMB = *p*-methoxybenzyl), pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2, 0 °C, 100 min, 92 %; d) DIBAL-H, CH_2Cl_2, −78 °C, 1 h, 93 %; e) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0 °C, 15 min; f) 1-ethylthio-1-trimethylsilyloxyethene, $TiCl_3$(O*i*Pr), CH_2Cl_2, −78 °C, 2 h, 64 % (> 99 % *de*); g) $LiBH_4$, THF, −10 °C, 2 h, 88 %; h) TBDPSCl, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, RT, 3.5 d; i) $Pd(OH)_2$/C, H_2, RT, 2 h, 90 % (2 steps); j) 2,2-dimethoxypropane, TsOH·H_2O, acetone, RT, 5 min, 97 %; k) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 0 °C, 15 min.

Total synthesis of 4: With both diol units in hand, we turned our attention to completing the synthesis of guadinomine C_2 with the construction of the piperazinone and cyclic guanidine moieties (Scheme 7). Introduction of the piperazinone moiety with designated stereo configurations from *anti*-**33** was adapted to our procedure (indicated in Scheme 3). Although the diol unit has additional functions compared with the model piperazinone compound all reaction sequences progressed quite smoothly[26] to form piperazinone aldehyde **44** in a pure form.[20] We subsequently applied Yamada's conditions for the asymmetric nitro aldol reaction,[27] which have been examined under various conditions with simpler substrates, as discussed in our previous paper.[8] Thus **44** was treated with the (*R,R*)-salen–cobalt catalyst **45** under modified conditions to eventually give **46** with high stereoselectivity (90 % *de*). Introduction of a guanidyl group was achieved through reduction of the nitro group followed by guanylation with **47**[28] to give **48**. We have previously investigated the S_N2 cyclization procedure for cyclic guanidine by mesylation of the alcohol followed by ring closure under basic conditions.[8] Applying this two-step procedure with **48**, however, resulted in low reproducibility for production of **50** due to mesylation on the other amide moiety, a yield of 82 % could only be obtained once. This problem was overcome by using S_N2 cyclization conditions via a phosphonium intermediate, which is generated from I_2 and PPh_3. The S_N2 cyclization proceeded very smoothly under mild conditions without any side reactions, such as iodination of the hydroxy group. This reaction has not only great advantages regarding simplicity for purification, but also better efficiency than the standard Mitsunobu-type reaction in the case of the 5-membered cyclic guanidine formation. The final sequence for the formation of the carbamoyl and total deprotection proceeded as expected, and (3′*R*)-guadinomine C_2 ((3′*R*)-**4**) was obtained. Access to the isomer, (3′*S*)-**4**, was also obtained by applying an identical reaction sequence as that used for the preparation of (3′*R*)-**4** from *syn*-**34**. The spectral characteristics of (3′*R*)-**4** showed a clear match with the data from naturally occurring **4**. Thus, we established that guadinomine C_2 has the configuration 3*S*,5*S*,6*S*,2′*S*,3′*R*,4″*R* with the L-peptide moiety.



Scheme 7. Reagents and conditions: a) (*S*)-**16**, nBu$_2$BOTf, Et_3N, CH_2Cl_2, −78 to 0 °C, 65 % (2 steps); b) NaH, EtOH, 0 °C, 20 min, 88 % (as a mixture of the *trans*/*cis*-epoxide; predominantly the *trans* isomer; 5.8:1); c) NaN_3, NH_4Cl, EtOH/H_2O (20:1), 60 °C, 38 h, 56 %; d) PPh_3, dehydrated MeCN, 80 °C, 21 h, 76 % as only the *trans*-aziridine isomer; e) NsCl, 4-(dimethylamino)pyridine, Et_3N, CH_2Cl_2, 0 °C to RT, 4 h; f) NaN_3, DMF, RT, 1 h, 93 % (2 steps) (>20:1 = α/β-N_3); g) PhSH, DIPEA, MeCN, RT, 6 h, 65 %; h) (*R*)-**10**, PyBOP, iPr$_2$NEt, CH_2Cl_2, RT, 1 h, 95 %; i) PPh_3, Et_3N, MeCN, 1 h; then H_2O, 60 °C, 7 h; j) Boc_2O, EtOAc, 80 °C, 1 h, 68 % (2 steps); k) LiOH, THF/MeOH/H_2O (2:2:1), RT, 1 h; l) H_2N-L-Ala-L-Val-OtBu **19**, PyBOP, HOBt, iPr$_2$NEt, CH_2Cl_2, RT, 4 h, 70 % (2 steps); m) tetrabutylammonium fluoride (TBAF), THF, RT, 3 h, 79 %; n) SO_3·pyridine, DMSO, Et_3N, CH_2Cl_2, 0 °C to RT, 1 h; o) (*R*,*R*)-**45**, $MeNO_2$, iPr$_2$NEt, CH_2Cl_2, −40 °C, 46 h, 53 % (2 steps), 90 % *de*; p) HCO_2NH_4, 10 % Pd/C, MeOH, RT, 2 h; q) **47**, iPr$_2$NEt, MeCN, RT, 1 h, 57 % (2 steps); r) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to RT, 2 h, 88 %; s) Ms_2O (Ms = methanesulfonyl), pyridine, 4-(dimethylamino)pyridine, CH_2Cl_2, 0 °C, 0.5 h; t) iPr$_2$NEt, MeCN, 65 °C, 4 h, ≈82 %; u) *p*-methoxyphenylisocyanate, PhH, RT, 10 min; v) ceric ammonium nitrate (CAN), MeCN/H_2O (1/1), 0 °C, 2.5 h; w) TFA/H_2O (3/1), RT, 5 h 60 % (3 steps); for the reaction sequence from *syn*-**34** to (3′*S*)-**4**, see the Supporting Information.

Total synthesis of guadinomine B: We next approached the total synthesis of guadinomine B (**2**), which differs only in the diamine part from **4** (diamine is converted to piperazinone in **4**). Therefore, to access **2**, 1, 2-azidoamine **43** was converted to 1,2-bis(Boc-amine) **51**, which subsequently underwent the same reaction sequence as that for the synthesis of **4** to give **2** (Scheme 8). Synthetic **2** was identical to naturally occurring **2** in all respects. Hence, we established that guadinomine B has the configuration 2*S*,3*S*,6*R*,7*S*,4′*R* with the L-peptide moiety.



Scheme 8. Reagents and conditions: a) H_2, 10 % Pd/C, EtOAc, RT, 1 h; b) Boc_2O, EtOAc, 60 °C, 45 min, 91 % (2 steps); c) LiOH, THF/MeOH/H_2O (2:2:1), RT, 0.5 h; d) H_2N-L-Ala-L-Val-OtBu **19**, PyBOP, HOBt, iPr$_2$NEt, CH_2Cl_2, RT, 3 h, 89 % (2 steps); for the reaction sequence from **51** to **2**, see the Supporting Information.

Inhibitory activity of TTSS for natural and synthetic guadinomine B and C_2: By using the synthetic guadinomines B and C_2 thus obtained, a TTSS assay with TTSS-expressing EPEC was conducted. TTSS activity was measured as the hemolytic activity caused by TTSS of EPEC in a 96-well microplate, as reported previously.[1] TTSS-expressing EPEC and erythrocytes were mixed and placed in contact, and the hemolytic activity was measured spectrometrically. Namely, the noninfectious strain EPEC DCesT, which was defective of the chaperon protein of the translocated intimin receptor (Tir), was used in this assay. As shown in Figure 2, the inhibitory activity

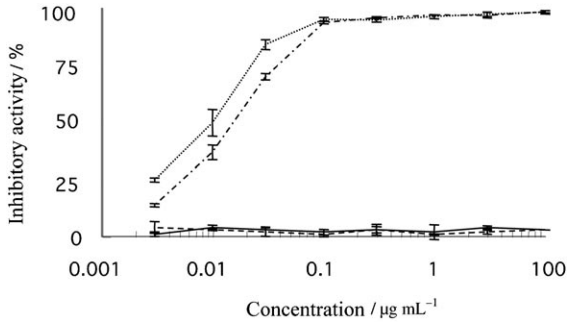


Figure 2. Inhibitory activity of TTSS-induced hemolysis for synthetic and natural guadinomine B and C_2: natural guadinomine B (–•–•), synthetic guadinomine B (•••••), natural guadinomine C_2 (– – –), and synthetic guadinomine C_2 (——).

of synthetic **2** was almost the same as that of natural **2** (Actually, natural **2** was slightly less active than synthetic **2** due to its impurity). On the other hand, natural and synthetic guadinomine C_2, (3′*R*)-**4**, showed no activity at 100 μg mL^{-1} in this assay. The basic structure of guadinomines with the piperazinone moiety on 1,2-diamine lost activity. Thus, the activity of synthetic and natural guadinomines B and C_2 were essentially identical.

Conclusion

In summary, the first asymmetric total synthesis of guadinomines B (**2**) and C_2 (**4**) has been achieved. The longest linear sequence proceeded in 32 steps for **2** and 33 steps for **4**. This synthetic process not only provides viable routes to these guadinomines, as well as to potential analogues thereof, but also establishes the absolute configurations of natural **2** and **4**.

Experimental Section

General remarks: Dry THF, toluene, ethyl ether, and CH_2Cl_2 were purchased from Kanto Chemical. Precoated silica gel plates with a fluorescent indicator (Merck 60 F254) were used for analytical and preparative thin layer chromatography. Flash column chromatography was carried out with Kanto Chemical silica gel (Kanto Chemical, silica gel 60N, spherical neutral, 0.040–0.050 mm, Cat.-No. 37563–84). ^{1}H NMR spectra were recorded at 270, 300, or 400 MHz and ^{13}C NMR spectra were recorded at 67.5, 75, or 100 MHz on JEOL JNM-EX270 (270 MHz), Varian VXR-300 (300 MHz), Varian XL-400 (400 MHz), or Varian UNITY-400 (400 MHz) spectrometers. The chemical shifts are expressed in ppm downfield from the internal solvent peaks for $CHCl_3$ (7.26 ppm, ^{1}H NMR), CH_3OH (3.31, 4.84 ppm, ^{1}H NMR), H_2O (4.76 ppm, ^{1}H NMR), $CDCl_3$ (77.0 ppm, ^{13}C NMR), CD_3OD (49.0 ppm, ^{13}C NMR), or D_2O (the end of both fields; 0, 200 ppm, ^{13}C NMR) and *J* values are given in hertz. The coupling patterns are denoted s (singlet), d (doublet), dd (double doublet), ddd (double double doublet), t (triplet), dt (double triplet), q (quartet), m (multiplet), or br (broad). All infrared spectra were measured on a Horiba FT-210 spectrometer. High- and low-resolution mass spectra were measured on a JEOL JMS-DX300 and JEOL JMS-AX505 HA spectrometer. Liquid chromatographic preparation was conducted on a Jasco PU-980 with Senshu Pak-PEGASIL ODS. Optical rotations were measured by using JASCO DIP-370 polarimeter. Melting points were measured on a Yanagimoto Micro Apparatus.

(4*R*,2′*R*,3′*S*)-4-Benzyl-(2′-chloro-3′-hydroxyheptanoyl)-2-oxazolizinone (17): DIPEA (2.62 mL, 18.0 mmol), and *n*Bu_2BOTf (1.0 M in CH_2Cl_2, 14.0 mL, 14.0 mmol) were added to a solution of chloroacetyloxazolidinone (*R*)-**16** (2.4 g, 10.0 mmol) in CH_2Cl_2 (104 mL) at −78 °C. After stirring for 1 h at RT, the reaction mixture was cooled to −78 °C. Then, valeraldehyde (2.69 mL, 14.0 mmol) was added to the reaction solution. After stirring for 5 min, the solution was warmed to 0 °C and stirred for 1 h. Phosphate buffer (pH 7.2; 6 mL) and 30% aqueous H_2O_2/MeOH (1:2) (20 mL) were added to the reaction solution at 0 °C, then the mixture was stirred for 1 h. The organic layer was separated and water layer was extracted with $CHCl_3$ (40 mL × 3). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl (20 mL) and brine (20 mL), then dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc 4:1) gave **17** as a colorless oil (1.93 g, 72%). R_f = 0.58 (silica gel, hexane/EtOAc 1:1); $[\alpha]_D^{27} = -46.4$ (*c* = 1.93, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 5H; 4-CH_2*Ph*), 5.68 (d, *J* = 3.0 Hz, 1H; 2′-H), 4.72 (dddd, *J* = 2.3, 3.3, 5.6, 9.6 Hz, 1H; 4-H), 4.28 (dd, *J* = 5.6, 9.2 Hz, 1H; 5-H_2), 4.23 (dd, *J* = 2.3, 9.2 Hz, 1H; 5-H_2), 4.10 (m, 1H; 3′-H), 3.32 (dd, *J* = 3.3, 13.5 Hz, 1H; 4-CH_2Ph), 2.83 (dd, *J* = 9.6, 13.5 Hz, 1H; 4-CH_2Ph), 2.70 (d, *J* = 5.5 Hz, 1H; 3′-O*H*), 1.72–1.54 (complex m, 2H; 4′-H_2), 1.52–1.31 (complex m, 2H; 6′-H_2), 1.43–1.31 (complex m, 2H; 5′-H_2), 0.92 ppm (t, *J* = 6.6 Hz, 3H; 7′-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 169.3, 153.6, 135.2, 130.2 (2C), 130.1 (2C), 128.2, 71.7, 66.9, 60.4, 55.8, 37.3, 33.8, 27.6, 22.5, 13.9 ppm; IR (NaCl) $\tilde{\nu}$ = 3523 (br, OH), 1780 (C=O, ester), 1711 (C=O, imide), 1389, 1365, 1209, 1113, 1057, 1001, 750, 698 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{17}H_{23}NO_4Cl$: 340.1316 [*M*+H]; found: 340.1309 [*M*+H]$^+$.

(2″*R*,3″*S*)-*tert*-Butyl-[*N*′-(2″-chloro-3″-hydroxyheptanoyl)-L-alanyl]-L-valinate (52): 30% aqueous H_2O_2 (1.55 mL, 13.7 mmol) and 1N aqueous LiOH (5.27 mL, 5.27 mmol) were added to a solution of **17** (896 mg, 2.64 mmol) in THF/H_2O (5:1) (26.4 mL) at 0 °C. After stirring for 25 min at the same temperature, a saturated aqueous solution of Na_2SO_3 (5.0 mL) and $CHCl_3$ (50 mL) were added to the reaction mixture. The organic layer was separated, and 1N aqueous HCl (10 mL) was added to the aqueous layer, which was then extracted with $CHCl_3$ (50 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Crude product **18** was used in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (24.2 mL) and then *tert*-butyl L-alanyl-L-valinate **19** (886 mg, 3.63 mmol), DIPEA (829 μL, 4.84 mmol), PyBrop (1.69 g, 3.63 mmol) were added. After stirring for 10 min at 0 °C under argon, the reaction mixture was warmed up to RT, and stirred for 1 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (20 mL × 2). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 3:1) gave **52** as a colorless oil (876 mg, 82% in 2 steps). R_f = 0.35 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{26} = +10.2$ (*c* = 1.30, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.97 (d, *J* = 6.9 Hz, 1H; 2′-NH), 6.76 (d, *J* = 8.9 Hz, 1H; 2-NH), 4.45 (dq, *J* = 6.9, 6.9 Hz, 1H; 2′-H), 4.44 (dd, *J* = 4.5, 8.9 Hz, 1H; 2-H), 4.36 (d, *J* = 1.7 Hz, 1H; 2″-H), 4.21 (m, 1H; 3″-H), 4.11 (d, *J* = 6.3 Hz, 1H; 3″-O*H*), 2.09 (dqq, *J* = 4.5, 7.3, 7.6 Hz, 1H; 3-H), 1.74–1.66 (m, 1H; 4″-H_2), 1.61–1.52 (m, 1H; 4″-H_2), 1.47 (d, *J* = 6.9 Hz, 3H; 3′-H_3), 1.45 (s, 9H; 1-OC(CH_3)$_3$), 1.41–1.31 (complex m, 4H; 5″-H_2, 6″-H_2), 0.91 (t, *J* = 6.6 Hz, 3H; 7″-H_3), 0.90 (d, *J* = 7.6 Hz, 3H; 3-CH_3), 0.87 ppm (d, *J* = 7.3 Hz, 3H; 3-CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.7, 171.5, 168.7, 82.3, 71.6, 64.5, 57.5, 49.9, 33.5, 31.4, 27.8 (3C), 27.5, 22.2, 18.7, 17.8, 17.5, 13.8 ppm; IR (KBr) $\tilde{\nu}$ = 3313 (br, -NH), 3072 (br, -OH), 1732 (C=O, ester), 1651 (C=O, amide), 1520, 1456, 1369, 1313, 1223, 1155 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{19}H_{36}N_2O_5Cl$: 407.2313 [*M*+H]: found: 407.2312 [*M*+H]$^+$.

(2″*S*,3″*S*)-(−)-*tert*-Butyl-[*N*′-(2″,3″-epoxyheptanoyl)-L-alanyl]-L-valinate (20): H_2O (47.0 μL, 2.61 mmol) and milled K_2CO_3 (144 mg, 1.04 mmol) were added to a solution of chlorohydrin **52** (212 mg, 522 μmol) in DMF

(2.60 mL) at RT. After stirring for 2.5 h, the reaction mixture was diluted with EtOAc (10 mL) and H_2O (2.0 mL) was added. The organic layer was separated, and the aqueous layer was extracted with EtOAc (10 mL × 2). The combined organic extracts were washed with H_2O (10 mL × 5) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 4:1) gave **20** (193 mg, 100%) as a colorless oil. R_f = 0.41 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{26} = -30.6$ (c = 1.10, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.73 (d, J = 7.3 Hz, 1H; 2′-NH), 6.42 (d, J = 8.9 Hz, 1H; 2-NH), 4.53 (dq, J = 6.9, 7.3 Hz, 1H; 2′-H), 4.41 (dd, J = 4.6, 8.9 Hz, 1H; 2-H), 3.45 (d, J = 4.6 Hz, 1H; 2″-H), 3.17 (m, 1H; 3″-H), 2.09 (dqq, J = 4.6, 6.6, 6.6 Hz, 1H; 3-H), 1.57–1.32 (complex m, 2H; 4″-H_2), 1.57–1.32 (complex m, 4H; 5″-H_2, 6″-H_2), 1.47 (s, 9H; 1-OC(CH_3)$_3$), 1.39 (d, J = 6.9 Hz, 3H; 3′-H_3), 0.93, 0.90 (d, J = 6.6 Hz, each 3H; 3-(CH_3)$_2$), 0.90 ppm (t, J = 6.9 Hz, 3H; 7″-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.3, 170.6, 167.3, 82.0, 58.4, 57.6, 54.9, 48.4, 31.2, 28.0, 28.0 (3C), 27.2, 22.3, 18.9, 18.5, 17.5, 13.8 ppm; IR (KBr): $\tilde{\nu}$ = 3317 (br, -NH), 1734 (C=O, ester), 1684 (C=O, amide), 1655 (C=O, amide), 1541, 1522, 1458, 1369, 1157 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{19}H_{35}N_2O_5$: 371.2546 [M+H]; found: 371.2545 [M+H]$^+$.

(2″*S*,3″*R*)-(−)-*tert*-Butyl-[*N*′-(3″-azido-2″-hydroxyheptanoyl)-L-alanyl]-L-valinate (53): NaN_3 (67.6 mg, 1.04 mmol) and NH_4Cl (55.6 mg, 1.04 mmol) were added to a solution of **20** (193 mg, 520 μmol) in MeOH/H_2O (20:1) (5.20 mL) at RT and the reaction mixture was warmed to 70°C. After stirring for 56 h, the reaction mixture was cooled to RT, diluted with $CHCl_3$ (15 mL), and H_2O (2.0 mL) was added. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL × 3). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 2:1) gave **53** as colorless needles (197 mg, 91%). R_f = 0.39 (silica gel, hexane/EtOAc = 1:1); m.p. 189.5–191.0°C; $[\alpha]_D^{29} = -46.1$ (c = 0.80, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.23 (d, J = 7.3 Hz, 1H; 2′-NH), 6.48 (d, J = 8.6 Hz, 1H; 2-NH), 4.53 (dq, J = 6.9, 7.3 Hz, 1H; 2′-H), 4.39 (dd, J = 4.6, 8.6 Hz, 1H; 2-H), 4.11 (dd, J = 2.6, 6.6 Hz, 1H; 2″-H), 3.79 (ddd, J = 2.6, 6.6, 8.6 Hz, 1H; 3″-H), 3.66 (d, J = 6.6 Hz, 1H; 2″-OH), 2.16 (dqq, J = 4.5, 6.6, 6.6 Hz, 1H; 3-H), 1.74–1.58 (complex m, 2H; 4″-H_2), 1.51–1.33 (complex m, 4H; 5″-H_2, 6″-H_2), 1.47 (s, 9H; 1-OC(CH_3)$_3$), 1.46 (d, J = 6.9, 3H; 3′-H_3), 0.94 (t, J = 6.9 Hz, 3H; 7″-H_3), 0.92 (d, J = 6.6 Hz, 3H; 3-(CH_3)$_2$), 0.90 ppm (d, J = 6.6 Hz, 3H; 3-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 173.2, 171.8, 170.4, 81.9, 73.4, 63.3, 57.8, 48.6, 31.1, 29.9, 28.3, 27.9 (3C), 22.4, 18.8, 18.5, 17.6, 13.9 ppm; IR (KBr): $\tilde{\nu}$ = 3369 (br, -NH), 3297 (br, -NH), 3103 (br, -OH), 2108 (N=N$^+$=N$^-$), 1734 (C=O, ester), 1647 (C=O, amide), 1547, 1458, 1371, 1261, 1159, 1144 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{19}H_{36}N_5O_5$: 414.2716 [M+H]; found: 414.2712 [M+H]$^+$.

(2″*R*,3″*R*)-(+)-*tert*-Butyl-{*N*′-[2″,3″-(*N*″-*o*-nitrobenzenesulfonylimino)-heptanoyl]-L-alanyl}-L-valinate (21): 10% Pd on carbon (25.8 mg, 24.2 μmol) was added to a solution of **53** (100 mg, 242 μmol) in EtOAc (2.42 mL) under H_2 at RT. After stirring for 8.5 h, the reaction solution was filtered through a Celite pad to remove the catalyst, and the pad was washed with EtOAc. The filtrate solution was evaporated to remove the solvent, the residue was dissolved in CH_2Cl_2 (4.84 mL), and then 2-nitrobenzenesulfonyl chloride (161 mg, 726 μmol), TEA (100 μL, 726 μmol), and DMAP (1.5 mg, 12.1 μmol) were added to the solution. After stirring for 11.5 h under argon at RT, the reaction solution was quenched with a saturated aqueous solution of NH_4Cl (3.0 mL), the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 mL × 2). The combined organic extracts were washed with brine (5.0 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 2:1) gave **21** as a yellow oil (121 mg, 91% in 2 steps). R_f = 0.46 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{25} = +3.9$ (c = 0.87, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.19–8.15 (m, 1H; N″-S(O_2)-*Ph*-NO_2), 7.85–7.76 (m, 3H; N″-S(O_2)-*Ph*-NO_2), 6.92 (d, J = 7.6 Hz, 1H; 2′-NH), 6.38 (d, J = 8.9 Hz, 1H; 2-NH), 4.44 (dq, J = 7.3, 7.6 Hz, 1H; 2′-H), 4.36 (dd, J = 4.3, 8.9 Hz, 1H; 2-H), 3.65 (d, J = 7.6 Hz, 1H; 2″-H), 3.24 (ddd, J = 5.9, 7.6, 7.6 Hz, 1H; 3″-H), 2.12 (dqq, J = 4.3, 6.9, 6.9 Hz, 1H; 3-H), 1.60–1.50 (complex m, 2H; 4″-H_2), 1.45–1.35 (complex m, 2H; 5″-H_2), 1.45 (s, 9H; 1-OC(CH_3)$_3$), 1.39 (d, J = 7.3, 3H; 3′-H_3), 1.31–1.20 (complex m, 2H; 6″-H_2), 0.87 (d, J = 6.9 Hz, 3H; 3-(CH_3)$_2$), 0.86 (d, J = 6.9 Hz, 3H; 3-(CH_3)$_2$), 0.81 ppm (t, J = 6.9 Hz, 3H; 7″-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.1, 170.5, 164.2, 148.6, 135.0, 132.3, 131.3, 130.9, 124.6, 81.9, 57.4, 48.8, 48.2, 44.5, 31.1, 28.8, 27.9 (3C), 26.7, 21.8, 18.7, 17.8, 17.4, 13.6 ppm; IR (KBr): $\tilde{\nu}$ = 3317 (br, -NH), 1728 (C=O, ester), 1687 (C=O, amide), 1658 (C=O, amide), 1547 (NO_2), 1367 (NO_2), 1344 (N-SO_2), 1167 (N-SO_2), 960, 852, 781, 739, 602 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{25}H_{38}N_4O_8SNa$: 577.2308 [M+Na]; found: 577.2310 [M+Na]$^+$.

(2″*R*,3″*S*)-(−)-*tert*-Butyl-{*N*′-[3″-azido-2″-(*o*-nitrobenzenesulfonamido)-heptanoyl]-L-alanyl}-L-valinate (54): NaN_3 (33.4 mg, 428 μmol) was added to a solution of **21** (142 mg, 257 μmol) in DMF (2.57 mL) under Ar at 0°C. After stirring for 30 min, the reaction solution was warmed to RT and stirred for 2 h. The mixture was diluted with EtOAc (5.0 mL), H_2O (5.0 mL) was added, and the organic layer was separated. The aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with H_2O (10.0 mL × 3) and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 3:1) gave **54** as a white solid (140 mg, 91%). R_f = 0.47 (silica gel, hexane/EtOAc = 1:1); m.p. 153–157°C; $[\alpha]_D^{27} = -31.2$ (c = 1.70, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.11 (m, 1H; N″-S(O_2)-*Ph*-NO_2), 7.91 (m, 1H; N″-S(O_2)-*Ph*-NO_2), 7.75 (complex m, 2H; N″-S(O_2)-*Ph*-NO_2), 7.04 (d, J = 7.3 Hz, 1H; 2′-NH), 6.37 (d, J = 8.3 Hz, 1H; 2-NH), 4.38 (dd, J = 4.3, 8.3 Hz, 1H; 2-H), 4.38 (dq, J = 6.9, 7.3 Hz, 1H; 2′-H), 4.13 (ddd, J = 2.6, 6.0, 7.6 Hz, 1H; 3″-H), 4.04 (d, J = 2.6 Hz, 1H; 2″-H), 2.14 (dqq, J = 4.3, 6.9, 7.3 Hz, 1H; 3-H), 1.69–1.56 (complex m, 2H; 4″-H_2), 1.48–1.32 (complex m, 2H; 5″-H_2), 1.46 (s, 9H; 1-OC(CH_3)$_3$), 1.32–1.10 (complex m, 2H; 6″-H_2), 1.24 (d, J = 6.9 Hz, 3H; 3′-H_3), 0.89 (d, J = 6.9 Hz, 3H; 3-(CH_3)$_2$), 0.88 (d, J = 6.9 Hz, 3H; 3-(CH_3)$_2$), 0.82 ppm (t, J = 7.3 Hz, 3H; 7″-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.1, 170.5, 168.1, 147.7, 133.9, 133.5, 132.9, 130.7, 125.3, 81.9, 63.4, 59.7, 57.5, 49.1, 31.1, 30.7, 27.9 (3C), 27.9, 22.2, 18.6, 18.0, 17.4, 13.6 ppm; IR (KBr): $\tilde{\nu}$ = 3373 (br, -NH), 3315 (br, -NH), 2108 (N=N$^+$=N$^-$), 1728 (C=O, ester), 1649 (C=O, amide), 1543 (NO_2), 1454, 1362 (N-SO_2), 1163 (N-SO_2), 847, 789, 741, 588 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{25}H_{39}N_7O_8SNa$: 620.2479 [M+Na]; found: 620.2503 [M+Na]$^+$.

(2″*R*,3″*S*)-(+)-*tert*-Butyl-{*N*′-[3″-amino-2″-(*o*-nitrobenzenesulfonamido)-heptanoyl]-L-alanyl}-L-valinate (22): H_2O (30.4 μL, 1.69 mmol) and PPh_3 (66.5 mg, 0.253 mmol) were added to a solution of **54** (101 mg, 169 μmol) in THF (1.70 mL) at RT. After stirring for 20 h at 45°C, the reaction solution was cooled to RT. Then the solution was evaporated under reduced pressure to remove the solvent. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH = 50:1) gave **22** as a yellow powder (82.5 mg, 85%). R_f = 0.31 (silica gel, $CHCl_3$/MeOH = 10:1); $[\alpha]_D^{29} = +1.66$ (c = 0.84, MeOH); ^{1}H NMR (270 MHz, CD_3OD): δ = 7.94 (m, 1H; N″-S(O_2)-*Ph*-NO_2), 7.70–7.58 (complex m, 3H; N″-S(O_2)-*Ph*-NO_2), 4.12 (q, J = 7.3 Hz, 1H; 2′-H), 4.05 (d, J = 5.9 Hz, 1H; 2-H), 3.85 (d, J = 3.3 Hz, 1H; 2″-H), 3.15 (dt, J = 3.3, 6.9 Hz, 1H; 3″-H), 2.01 (m, 1H; J = 6.9 Hz, 3-H), 1.64–1.42 (m, 1H; 4″-H_2), 1.39–1.12 (complex m, 5H; 4″-H_2, 5″-H_2, 6″-H_2), 1.37 (s, 9H; 1-OC(CH_3)$_3$), 1.12 (d, J = 7.3 Hz, 3H; 3′-H_3), 0.86 (d, J = 6.9 Hz, 6H; 3-(CH_3)$_2$), 0.79 ppm (t, J = 6.9 Hz, 3H; 7″-H_3); ^{13}C NMR (67.5 MHz, CD_3OD): δ = 175.0, 173.9, 172.1, 149.2, 137.0, 133.9, 133.2, 131.2, 125.3, 82.8, 61.5, 60.1, 55.6, 50.3, 32.5, 31.7, 28.8, 28.3 (3C), 23.5, 19.5, 18.5, 18.1, 14.2 ppm; IR (KBr): $\tilde{\nu}$ = 3375 (-NH), 3321 (-NH), 1730 (C=O, ester), 1655 (C=O, amide), 1541 (NO_2), 1456, 1369 (N-SO_2), 1165 (N-SO_2), 850, 787, 737, 658 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{25}H_{41}N_5O_8SNa$: 594.2574 [M+Na]; found: 594.2568 [M+Na]$^+$.

(2″*R*,3″*S*,2‴*R*)-(−)-*tert*-Butyl-{*N*′-[3″-(2‴-bromopropanamido)-2″-(*o*-nitrobenzenesulfonamido)heptanoyl]-L-alanyl}-L-valinate (55): Compound (*R*)-**10** (19.0 μL, 211 μmol), HOBt (32.4 mg, 239 μmol), and EDCI (40.5 mg, 211 μmol) were added to a solution of **22** (80.5 mg, 141 μmol) in CH_2Cl_2 (1.40 mL) under argon at 0°C. After stirring for 1 h, H_2O (1.0 mL) was added to the reaction and the organic layer was separated. The aqueous layer was extracted with $CHCl_3$ (10 mL × 3). The combined organic extracts were washed with H_2O (5.0 mL) and brine (5.0 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH = 100:1)

gave **55** as a yellow powder (90.5 mg, 91%). R_f=0.49 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{26}=-21.0$ (c=0.47, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=8.12 (m, 1H; N''-S(O_2)-*Ph*-NO_2), 7.85 (m, 1H; N''-S(O_2)-*Ph*-NO_2), 7.77–7.64 (complex m, 2H; N''-S(O_2)-*Ph*-NO_2), 7.15 (d, J=6.9 Hz, 1H; 2′-NH), 7.00 (d, J=8.2 Hz, 1H; 3″-NH), 6.38 (d, J=8.6 Hz, 1H; 2-NH), 4.37 (q, J=7.3 Hz, 1H; 2′-H), 4.36 (q, J=6.9 Hz, 1H; 2‴-H), 4.34 (dd, J=4.6, 8.6 Hz, 1H; 2-H), 4.21 (d, J=4.3 Hz, 1H; 2″-H), 4.05 (ddd, J=4.3, 8.2, 8.9 Hz, 1H; 3″-H), 2.11 (dq, J=4.6, 6.9 Hz, 1H; 3-H), 1.95–1.60 (complex m, 2H; 4″-H_2), 1.80 (d, J=8.2 Hz, 3H; 3‴-H_3), 1.45 (s, 9H; 1-OC(CH_3)$_3$), 1.30–1.13 (complex m, 4H; 5″-H_2, 6″-H_2), 1.23 (d, J=7.3 Hz, 3H; 3′-H_3), 0.87 (d, J=6.9 Hz, 3H; 3-(CH_3)$_2$), 0.86 (d, J=6.9 Hz, 3H; 3-(CH_3)$_2$), 0.77 ppm (t, J=6.6 Hz, 3H; 7″-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=171.5, 170.8, 170.5, 169.2, 147.6, 133.7, 133.7, 133.0, 131.2, 124.9, 82.0, 61.2, 57.6, 52.4, 49.1, 43.9, 31.0, 29.8, 28.0, 28.0 (3C), 22.2, 22.1, 18.8, 18.7, 17.7, 13.8 ppm; IR (KBr): $\tilde{\nu}$=3315 (-NH), 1730 (C=O, ester), 1662 (C=O, amide), 1541 (NO_2), 1454, 1363 (N-SO_2), 1163 (N-SO_2), 785, 739, 586 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{28}H_{45}N_5O_9SBr$: 706.2121 [M+H]; found: 706.2135 [M+H]$^+$.

(3*S*,5*R*,6*S*)-(−)-6-Butyl-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-3-methyl-2-piperazinone (23): DIPEA (37.0 μL, 428 μmol) was added to a solution of **55** (75.0 mg, 106 μmol) in MeCN (2.12 mL) under argon at RT. After stirring for 19 h at 60°C, the reaction solution was cooled to RT. Then thiophenol (16.3 μL, 159 μmol) and DIPEA (27.7 μL, 159 μmol) were added and the solution was stirred for 21 h at RT. The solution was then evaporated under reduced pressure to remove the solvent. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH=60:1) gave **23** as a colorless oil (40.4 mg, 100%). R_f=0.27 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{29}=-40.5$ (c=0.86, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.89 (d, J=8.0 Hz, 1H; 2′-NH), 6.97 (d, J=8.8 Hz, 1H; 2″-NH), 6.45 (d, J=2.5 Hz, 1H; 1-H), 4.59 (dq, J=6.8, 8.0 Hz, 1H; 2′-H), 4.38 (dd, J=4.6, 8.8 Hz, 1H; 2″-H), 3.87 (dddd, J=2.5, 4.8, 5.0, 8.3 Hz, 1H; 6-H), 3.41 (q, J=7.0 Hz, 1H; 3-H), 3.36 (d, J=4.8 Hz, 1H; 5-H), 2.11 (dqq, J=4.6, 7.8, 7.8 Hz, 1H; 3″-H), 1.73–1.64 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.61–1.52 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.44 (s, 9H; 1″-OC(CH_3)$_3$), 1.41–1.25 (complex m, 4H; 6-CH$_2$CH_2CH$_2$CH$_3$), 1.37 (d, J=7.0 Hz, 3H; 3-CH_3), 1.34 (d, J=6.8 Hz, 3H; 3′-H_3), 0.88 (d, J=7.8 Hz, 3H; 3″-(CH_3)$_2$), 0.88 (t, J=7.0 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$CH_3), 0.86 ppm (d, J=7.8 Hz, 3H; 3″-(CH_3)$_2$); ^{13}C NMR (75.0 MHz, $CDCl_3$): δ=172.8 (C-2), 171.9 (C-1′), 170.9 (C-1″), 170.3 (5-*C*O-), 81.9 (1″-O*C*H-(CH_3)$_3$), 57.5 (C-2″), 56.9 (C-5), 52.1 (C-6), 50.1 (C-3), 48.6 (C-2′), 35.1 (1C, 6-*C*H$_2$CH$_2$CH$_2$CH$_3$), 31.1 (C-3″), 28.0 (1″-O*C*(CH_3)$_3$), 27.4 (1C, 6-CH$_2$*C*H$_2$CH$_2$CH$_3$), 22.4 (1C, 6-CH$_2$CH$_2$*C*H$_2$CH$_3$), 18.8 (1C, 3″-(CH_3)$_2$), 18.5 (C-3′), 17.8 (1C, 3-*C*H$_3$), 17.6 (1C, 3″-(CH_3)$_2$), 13.9 ppm (1C, 6-CH$_2$CH$_2$CH$_2$*C*H$_3$); IR (KBr) $\tilde{\nu}$=3662, 3288 (-NH), 1730 (C=O, ester), 1655 (C=O, amide), 1545, 1466, 1379, 1155, 935, 841, 627 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{22}H_{40}N_4O_5Na$: 463.2896 [M+Na]; found: 463.2896 [M+Na]$^+$.

(3*S*,5*R*,6*S*)-(−)-6-Butyl-3-methyl-5-(L-valinyl-L-alanyl)carbonyl-2-piperazinone (7): After dissolving **23** (45.8 mg, 104 μmol) in a solution of TFA/H_2O (3:1) (2.08 mL), the reaction solution was stirred for 3 h at RT. The solution was diluted with H_2O (3.0 mL), and evaporated under reduced pressure to remove the solvent. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH=10:1) gave **7** as a white powder (40.4 mg, 100%). R_f=0.12 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{24}=-35.2$ (c=1.50, MeOH); ^{1}H NMR (400 MHz, 1% TFA in D_2O): δ=4.35 (q, J=7.0 Hz, 1H; 2′-H), 4.17 (q, J=7.2 Hz, 1H; 3-H), 4.16 (d, J=6.0 Hz, 1H; 2″-H), 4.02 (d, J=9.0 Hz, 1H; 5-H), 3.81 (ddd, J=4.5, 6.5, 9.0 Hz, 1H; 6-H), 2.09 (dq, J=6.0, 6.9 Hz, 1H; 3″-H), 1.65–1.58 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.56–1.49 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.51 (d, J=7.0 Hz, 3H; 3-CH_3), 1.33 (d, J=7.0 Hz, 3H; 3′-H_3), 1.28–1.17 (complex m, 4H; 6-CH$_2$CH_2CH_2CH$_3$), 0.86 (d, J=6.9 Hz, 3H; 3″-(CH_3)$_2$), 0.85 (d, J=6.9 Hz, 3H; 3″-(CH_3)$_2$), 0.84 ppm (t, J=7.0 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, 1% TFA in D_2O), reference 0–200 ppm. δ=177.7 (C-1″), 177.2 (C-1′), 171.4 (C-2), 168.5 (5-*C*O-), 61.2 (C-2″), 56.8 (C-5), 54.3 (C-3), 53.7 (C-6), 52.5 (C-2′), 33.4 (1C, 6-*C*H$_2$CH$_2$CH$_2$CH$_3$), 32.4 (C-3″), 28.1 (1C, 6-CH$_2$*C*H$_2$CH$_2$CH$_3$), 24.2 (1C, 6-CH$_2$CH$_2$*C*H$_2$CH$_3$), 20.9 (1C, 3″-(CH_3)$_2$), 19.9 (1C, 3″-(CH_3)$_2$), 19.3 (C-3′), 17.2 (1C, 3-CH_3), 15.6 ppm (1C, 6-CH$_2$CH$_2$CH$_2$*C*H$_3$); IR (KBr): $\tilde{\nu}$=3435 (br, -NH), 1672 (C=O, amide), 1566, 1196, 1142, 723 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{18}H_{33}N_4O_5$: 385.2451 [M+H]; found: 385.2436 [M+H]$^+$.

(2*R*,3*S*)-(−)-Ethyl-2,3-epoxyheptanate (24): NaH (55 wt% in mineral oil, 446 mg, 11.1 mmol) was added to a solution of **17** (3.30 g, 10.1 mmol) in EtOH (50.5 mL) at 0°C. After stirring for 20 min, a saturated aqueous solution of NH_4Cl (30 mL) and CH_2Cl_2 (100 mL) was added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (100 mL×2), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=5:1) gave a mixture of *trans*-epoxide **24** and *cis*-epoxide (5.4:1) as a colorless oil (1.70 g, 98%). R_f=0.56 (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{27}=-18.3$ (c=1.00, $CHCl_3$), as a mixture; ^{1}H NMR (270 MHz, $CDCl_3$), major isomer **24** is reported δ=4.23 (dq, J=3.3, 7.3 Hz, 2H; 1-OCH_2CH$_3$), 3.20 (d, J=2.0 Hz, 1H; 2-H), 3.15 (ddd, J=2.0, 5.0, 5.9 Hz, 1H; 3-H), 1.70–1.54 (complex m, 2H; 4-H_2), 1.49–1.35 (complex m, 2H; 5-H_2, 6-H_2), 1.30 (t, J=7.3 Hz, 3H; 1-OCH$_2$CH_3), 0.92 ppm (t, J=6.9 Hz, 3H; 7-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$), major isomer **24** is reported δ=169.3, 61.4, 58.4, 53.0, 31.1, 27.7, 22.3, 14.0, 13.8 ppm; IR (NaCl): $\tilde{\nu}$=1753 (C=O, ester), 1446, 1284 (C-O, epoxide), 1196, 1036, 906 cm^{-1}; MS (FAB, EI): could not be observed.

A mixture of (2*S*,3*S*)-ethyl-2-azido-3-hydroxyheptanate and (2*R*,3*R*)-ethyl-3-azido-2-hydroxyheptanate (56): NH_4Cl (792 mg, 14.8 mmol) and NaN_3 (963 mg, 14.8 mmol) were added to a solution of **24** and *cis*-epoxide mixture (1.70 g, 9.87 mmol) in 1,4-dioxane/H_2O (1:1) (66.0 mL) at RT and warmed to 60°C. After stirring for 40 h, the reaction mixture was cooled to RT, diluted with $CHCl_3$ (100 mL), and the organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=5:1) gave a mixture of **56** as a colorless oil (478 mg, 55%). R_f=0.39 (hexane/EtOAc=3:1); ^{1}H NMR (270 MHz, $CDCl_3$): as a mixture of four compounds δ=4.36–4.10 (complex m, 2H; 1-OCH_2CH$_3$), 3.97–3.88 (complex m, 1H; 2-H), 3.58–3.45 (complex m, 1H; 3-H), 3.07 (br s, 1H; -O*H*), 1.90–1.65 (complex m, 1H; 4-H_2), 1.56–1.23 (complex m, 5H; 4-H_2, 5-H_2, 6-H_2), 1.37–1.27 (complex m, 3H; 1-OCH$_2$CH_3), 0.98–0.86 ppm (complex m, 3H; 7-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): two major isomers were indicated. δ=171.9 and 168.8, 73.3 and 71.7, 66.1 and 64.2, 61.9 and 61.7, 32.4 and 29.3, 28.2 and 27.3, 22.2 and 22.0, 13.8, 13.6 and 13.5 ppm; IR (NaCl) $\tilde{\nu}$=3483 (br, -OH), 2109 (-N=N$^+$=N$^-$), 1739 (-C=O, ester), 1468, 1371, 1265, 1203, 1130, 1095, 1026, 862 cm^{-1}; HRMS (FAB, NBA matrix): m/z: calcd for $C_9H_{17}N_3O_3Na$: 238.1168 [M+Na]; found: 238.1161 [M+Na]$^+$.

(2*S*,3*R*)-Ethyl-2,3-iminoheptanate (25): PPh_3 (1.49 g, 5.70 mmol) was added to a solution of **56** (943 mg, 4.38 mmol) in MeCN (21.9 mL) under argon at RT. After stirring for 30 min, the reaction solution was warmed to 80°C and stirred for 1.5 h. Then the solution was cooled to RT and evaporated under reduced pressure to remove the solvent. Purification by flash chromatography on silica gel (hexane/EtOAc=5:1) gave **25** (667.6 mg, 89%) and *cis*-aziridine **57** (75 mg, 10%) as colorless oils. **25**: R_f=0.46 (silica gel, hexane/EtOAc=3:1); $[\alpha]_D^{25}=+73.8$ (c=0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=4.22 (dq, J=3.2, 7.3 Hz, 2H; 1-OCH_2CH$_3$), 2.26 (d, J=2.3 Hz, 1H; 2-H), 2.21 (m, 1H; 3-H), 1.44–1.32 (complex m, 6H; 4-H_2, 5-H_2, 6-H_2), 1.29 (t, J=7.3 Hz, 3H; 1-OCH$_2$CH_3), 0.90 ppm (t, J=7.3 Hz, 3H; 7-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=172.4, 61.0, 39.2, 35.0, 32.1, 29.0, 22.1, 13.9, 13.6 ppm; IR (NaCl): $\tilde{\nu}$=3288 (br, -NH), 1728 (C=O, ester), 1468, 1431, 1373, 1342, 1209, 1036, 845 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_9H_{18}NO_2$ 172.1338 [M+H]; found: 172.1336 [M+H]$^+$. **57**: R_f=0.25 (silica gel, hexane/EtOAc=3:1); $[\alpha]_D^{23}=-47.6$ (c=1.41, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=4.22 (q, J=7.3 Hz, 2H; 1-OCH_2CH$_3$), 2.63 (br d, J=5.9 Hz, 1H; 2-H), 2.21 (br m, 1H; 3-H), 1.24–1.67 (complex m, 6H; 4-H_2, 5-H_2, 6-H_2), 1.30 (t, J=7.3 Hz, 3H; 1-OCH$_2$CH_3), 0.89 ppm (t, J=6.6 Hz, 3H; 7-H_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=170.8, 61.1, 38.7, 34.5, 29.8, 27.4, 22.2, 14.1, 13.8 ppm; IR (NaCl): $\tilde{\nu}$=3267 (br, NH), 1727 (C=O), 1466, 1408, 1383, 1198, 1034, 827 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_9H_{18}NO_2$: 172.1338 [M+H]; found: 172.1336 [M+H]$^+$.

(2*R*,3*R*)-Ethyl-3-amino-2-azidoheptanate (26) and (2*S*,3*S*)-ethyl-2-amino-3-azidoheptanate (27): TEA (1.63 mL, 11.7 mmol), 2-nitrobenzenesulfonyl chloride (1.29 g, 5.84 mmol), and DMAP (47.5 mg, 389 μmol)

were added to a solution of **25** (666 mg, 3.89 mmol) in CH_2Cl_2 (38.9 mL) at RT under argon. After stirring for 20 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL), the organic layer was separated and aqueous layer was extracted with $CHCl_3$ (30 mL×3). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was roughly purified with silica gel (hexane/EtOAc=5:1) to provide the residue of Ns-aziridine. The residue was dissolved in DMF (38.9 mL), and then NaN_3 (506 mg, 7.78 mmol) was added to the solution at 0 °C under argon, and then the reaction mixture was warmed to RT. After stirring for 30 min, the solution was diluted with EtOAc (40 mL), H_2O (20 mL) was added, and the organic layer was separated. The organic extracts were washed with brine (10.0 mL×3), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to provide a mixture of azido-Ns-amine. The azido-Ns-amine residue was dissolved in MeCN (38.9 mL), and then thiophenol (999 μL, 9.73 mmol), and DIPEA (1.69 mL, 9.73 mmol) were added to the solution at RT under argon. After stirring for 2.5 h, a saturated aqueous solution of $NaHCO_3$ (10 mL) was added to the reaction mixture. Then the mixture was extracted with $CHCl_3$ (30 mL×3). The organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=1:1) gave **26** (385 mg, 53% in 3 steps) and **27** (101.7 mg, 14% in 3 steps) as colorless oils. **26**; R_f=0.24 (hexane/EtOAc=2:1); $[\alpha]_D^{24}$=+60.3 (c=0.50, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=4.25 (dq, J=1.3, 7.3 Hz, 2H; 1-OCH_2CH$_3$), 3.86 (d, J=5.3 Hz, 1H; 2-H), 3.08 (ddd, J=1.6, 5.3, 8.9 Hz, 1H; 3-H), 1.54–1.42 (complex m, 2H; 4-H$_2$), 1.37–1.23 (complex m, 4H; 5-H$_2$, 6-H$_2$), 1.30 (t, J=7.3 Hz, 3H; 1-OCH$_2$CH_3), 0.88 ppm (t, J=7.0 Hz, 3H; 7-H$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=169.0, 67.9, 61.7, 53.1, 33.0, 28.1, 22.5, 14.1, 13.9 ppm; IR (NaCl): $\tilde{\nu}$=2108 (N=N$^+$=N$^-$), 1739 (C=O, ester), 1466, 1265, 1194, 1028, 854 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_9H_{19}N_4O_2$ 215.1508 [M+H]; found: 215.1508 [M+H]$^+$. **27**; R_f=0.35 (hexane/EtOAc=2:1); $[\alpha]_D^{30}$−23.5 (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=4.23 (dq, J=3.3, 6.9 Hz, 2H; 1-OCH_2CH$_3$), 3.61 (d, J=4.6 Hz, 1H; 2-H), 3.52 (ddd, J=4.6, 7.6, 8.9 Hz, 1H; 3-H), 1.80–1.50 (complex m, 2H; 4-H$_2$), 1.51–1.25 (complex m, 4H; 5-H$_2$, 6-H$_2$), 1.30 (t, J=6.9 Hz, 3H; 1-OCH$_2$CH_3), 0.92 ppm (t, J=6.9 Hz, 3H; 7-H$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=171.2, 64.0, 61.8, 57.4, 29.8, 28.3, 22.3, 14.1, 13.8 ppm; IR (NaCl): $\tilde{\nu}$=3302(br, -NH), 2106 (N=N$^+$=N$^-$), 1739 (C=O, ester), 1514, 1468, 1369, 1257, 1234, 1028, 861 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_9H_{19}N_4O_2$: 215.1508 [M+H]; found: 215.1515 [M+H]$^+$.

(2*R*,3*R*,2′*S*)-(+)-Ethyl-2-azido-3-(2′-bromopropanamido)heptanate (58): Compound (*S*)-**10** (85.7 μL, 953 μmol), PyBOP (496 mg, 953 μmol), and DIPEA (204 μL, 1.19 mmol) were added to a solution of **26** (88.7 mg, 476 μmol) in CH_2Cl_2 (4.80 mL) at RT under argon. After stirring for 80 min, a saturated aqueous solution of NH_4Cl (3.0 mL) was added to the reaction solution. The organic layer was separated, then the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=5:1) gave **58** as a yellow powder (156 mg, 94%). R_f=0.44 (hexane/EtOAc=3:1); $[\alpha]_D^{30}$=+61.3 (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=6.51 (d, J=8.3 Hz, 1H; 3-NH-CO-), 4.42 (q, J=7.3 Hz, 1H; 2′-H), 4.37 (m, 1H; 3-H), 4.30 (dq, J=1.0, 6.9 Hz, 2H; 1-OCH_2CH$_3$), 4.24 (d, J=4.0 Hz, 1H; 2-H), 1.90 (d, J=6.9 Hz, 3H; 3′-H$_3$), 1.56–1.43 (complex m, 2H; 4-H$_2$), 1.37–1.20 (complex m, 4H; 5-H$_2$, 6-H$_2$), 1.34 (t, J=7.3 Hz, 3H; 1-OCH$_2$CH_3), 0.88 ppm (3H; t, J=6.9, 7-H$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=169.3, 168.2, 64.4, 62.2, 50.8, 44.7, 29.6, 27.8, 22.9, 22.1, 14.1, 13.7 ppm; IR (NaCl): $\tilde{\nu}$=3300 (br, -NH), 2112 (N=N$^+$=N$^-$), 1743 (C=O, ester), 1658 (C=O, amide), 1541, 1446, 1373, 1269, 1246, 1196, 1026 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{12}H_{22}N_4O_3Br$: 349.0875 [M+H]; found: 349.0890 [M+H]$^+$.

(3*R*,5*R*,6*R*)-(+)-6-Butyl-5-ethoxycarbonyl-3-methyl-2-piperazinone (28): PPh_3 (308 mg, 1.17 mmol) and TEA (164 μL, 1.17 mmol) were added to a solution of **58** (129 mg, 369 μmol) in MeCN (7.37 mL) under argon at RT. After stirring for 1 h, H_2O (730 μL) was added to the reaction solution, it was warmed to 60 °C, and stirred for 1.5 h. Then the solution was cooled to RT and evaporated under reduced pressure to remove the solvent. Purification by flash chromatography on silica gel ($CHCl_3$) gave **28** as a colorless oil (65.0 mg, 73%). R_f=0.37 ($CHCl_3$/MeOH=10:1); $[\alpha]_D^{30}$=+92.9 (c=0.50, $CHCl_3$); ^{1}H NMR (400 MHz, 1% TFA in D_2O): δ=4.22 (q, J=7.0 Hz, 2H; 5-CO-O-CH_2CH$_3$), 4.03 (d, J=4.2 Hz, 1H; 5-H), 3.72 (ddd, J=3.5, 4.2, 10.3 Hz, 1H; 6-H), 3.53 (q, J=6.9 Hz, 1H; 3-H), 1.56 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.36 (m, 1H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.31 (d, J=6.9 Hz, 3H; 3-CH_3), 1.31–1.21 (complex m, 4H; 6-CH$_2$CH_2CH_2CH$_3$), 1.25 (t, J=7.0 Hz, 3H; 5-CO-O-CH$_2$CH_3), 0.83 ppm (t, J=7.0 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (100 MHz, D_2O with TFA): δ=175.1 (C-2), 171.5 (1C, 5-CO-O-CH$_2$CH$_3$), 62.7 (1C, 5-CO-O-CH$_2$CH$_3$), 57.6 (C-5), 52.7 (C-3), 52.6 (C-6), 30.9 (1C, 6-CH$_2$CH$_2$CH$_2$CH$_3$), 27.3 (1C, 6-CH$_2$$CH_2CH_2CH_3$), 21.9 (1C, 6-CH$_2CH_2$$CH_2CH_3$), 16.9 (1C, 3-$CH_3$), 13.4 (1C, 5-CO-O-CH$_2$$CH_3$), 13.2 ppm (1C, 6-CH$_2CH_2CH_2$$CH_3$); IR (NaCl): $\tilde{\nu}$=3330 (br, -NH), 3207 (br, -NH), 1739 (C=O, ester), 1668 (C=O, amide), 1468, 1371, 1329, 1217, 1176, 1041, 1020, 856, 771, 719 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{12}H_{23}N_2O_3$: 243.1709 [M+H]; found: 243.1707 [M+H]$^+$.

(3*R*,5*R*,6*R*)-(+)-4-*tert*-Butoxycarbonyl-6-butyl-5-ethoxycarbonyl-3-methyl-2-piperazinone (29): Di-*tert*-butyl dicarbonate (385 mg, 1.76 mmol) was added to a solution of **28** (85.3 mg, 352 μmol) in EtOAc (3.50 mL) at RT under argon. After stirring for 20 min at 80 °C, the reaction solution was cooled to RT. Then brine (2.0 mL) was added to the reaction mixture, the organic layer was then separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL×2). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=2:1) gave **29** as a yellow powder (88.5 mg, 73%). R_f=0.35 (hexane/EtOAc=1:1); $[\alpha]_D^{30}$=+13.7 (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): as two rotamers. δ=5.73 (br s, 1H; 1-H), 5.04 (br d, J=3.3 Hz, 2/3H; 5-H), 4.78 (br s, 1/3H; 5-H), 4.42 (q, J=6.6 Hz, 1H; 3-H), 4.20 (q, J=7.3 Hz, 4/3H; 5-CO-O-CH_2CH$_3$), 4.19 (q, J=7.3 Hz, 2/3H; 5-CO-O-CH_2CH$_3$), 3.66 (m, 1H; 6-H), 1.75–1.49 (complex m, 2H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.59 (br d, J=6.6 Hz, 3H; 3-CH_3), 1.49 (s, 9H; 4-CO-OC(CH_3)$_3$), 1.46–1.36 (complex m, 4H; 6-CH$_2$CH_2CH_2CH$_3$), 1.28 (t, J=7.3 Hz, 3H; 5-CO-O-CH$_2$CH_3), 0.92 ppm (t, J=6.6 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=171.1, 168.8, 154.0, 81.3, 61.0, 54.0, 52.4, 31.4, 28.2 (3C), 27.5, 22.3, 18.2, 14.0, 13.7 ppm; IR (NaCl): $\tilde{\nu}$=3203 (br, -NH), 3087 (br, -NH), 1747 (C=O, ester), 1695 (C=O, urethane), 1682 (C=O, amide), 1456, 1369, 1327, 1257, 1186, 1169, 1130, 1028, 935, 816, 769 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{17}H_{31}N_2O_5$: 343.2233 [M+H]; found: 343.2232 [M+H]$^+$.

(3*R*,5*R*,6*R*)-(+)-4-*tert*-Butoxycarbonyl-6-butyl-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-analyl)-carbonyl-3-methyl-2-piperazinone (30): Lithium hydroxide (10.5 mg, 438 μmol) was added to a solution of **29** (15.0 mg, 43.8 μmol) in MeOH/THF/H_2O (2:2:1) (880 μL) at RT. After stirring for 85 min, a saturated aqueous solution of NH_4Cl (1.0 mL) was added to the reaction mixture, which was then extracted with $CHCl_3$ (5.0 mL×3). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was used in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (880 μL) and then **19** (12.8 mg, 52.6 μmol), DIPEA (11.2 μL, 65.7 μmol), and PyBOP (27.4 mg, 52.6 μmol) were added at RT under Ar. After stirring for 1 h, the reaction solution was quenched with a saturated aqueous solution of NH_4Cl (1.0 mL), the organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL×2). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH=50:1) gave **30** as a colorless oil (15.9 mg, 67% in 2 steps). R_f=0.47 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{24}$=+29.1 (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=6.96 (d, J=7.3 Hz, 1H; 2′-NH), 6.50 (d, J=8.9 Hz, 1H; 2″-NH), 6.14 (s, 1H; 1-H), 4.69 (d, J=3.6 Hz, 1H; 5-H), 4.48 (q, J=7.3 Hz, 1H; 3-H), 4.46–4.38 (m, 1H; 2′-H), 4.41 (dd, J=4.6, 8.9 Hz, 1H; 2″-H), 3.62 (ddd, J=3.6, 6.9, 6.9 Hz, 1H; 6-H), 2.13 (dqq, J=4.6, 6.6, 6.6 Hz, 1H; 3″-H), 1.82–1.65 (complex m, 2H; 6-CH_2CH$_2$CH$_2$CH$_3$), 1.50–1.24 (complex m, 4H; 6-CH$_2$CH_2CH_2CH$_3$), 1.50 (s, 9H; 4-CO-OC(CH_3)$_3$), 1.45 (s, 9H; 1″-OCH(CH_3)$_3$), 1.44 (d, J=6.9 Hz, 3H; 3-CH_3), 1.36 (d, J=6.9 Hz, 3H; 3′-H$_3$), 0.90 (t, J=7.0 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$CH_3), 0.87, 0.84 ppm (d, J=6.6 Hz, each 3H; 3″-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=171.4, 170.8, 170.2, 168.1,

154.4, 82.0, 81.9, 57.3, 53.5, 53.2, 52.4, 48.6, 31.2, 31.1, 28.3, 28.0, 27.9, 22.4, 18.9, 17.4, 18.6, 18.1, 13.8 ppm; IR (NaCl): $\tilde{\nu}$ = 3315 (br, -NH), 1734 (C=O, ester), 1672 (C=O, amide, urethane), 1535, 1458, 1369, 1331, 1255, 1165, 1132, 1018, 849, 756 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{27}H_{48}N_4O_7Na$: 563.3421 [*M*+Na]; found: 563.3420 [*M*+Na]$^+$.

(3*R*,5*R*,6*R*)-(+)-6-Butyl-5-(L-valinyl-L-alanyl)carbonyl-3-methyl-2-piperazinone (8): After dissolving **30** (15.9 mg, 29.4 μmol) in a solution of TFA/H_2O (3:1) (980 μL), the reaction solution was stirred for 2.5 h at RT. The solution was diluted with H_2O (1.0 mL) and evaporated under reduced pressure. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH = 10:1) gave **8** as a white powder (14.4 mg, 98%). R_f = 0.14 (silica gel, $CHCl_3$/MeOH = 10:1); m.p. 129–131 °C; $[\alpha]_D^{23}$ = +19.8 (*c* = 1.00, MeOH); ^{1}H NMR (400 MHz, 1% TFA in D_2O): δ = 4.53 (d, *J* = 4.5 Hz, 1H; 5-H), 4.35 (q, *J* = 7.2 Hz, 1H; 2′-H), 4.16 (d, *J* = 6.0 Hz, 1H; 2″-H), 4.10 (q, *J* = 7.0 Hz, 1H; 3-H), 3.93 (ddd, *J* = 3.2, 4.2, 10.5 Hz, 1H; 6-H), 2.10 (dq, *J* = 6.0, 6.6 Hz, 1H; 3″-H), 1.52 (m, 1H; 6-C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.50 (d, *J* = 7.0 Hz, 3H; 3-C*H*$_3$), 1.45–1.35 (complex m, 3H; 6-CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.32 (d, *J* = 7.2 Hz, 3H; 3′-H$_3$), 1.30–1.17 (complex m, 2H; 6-CH$_2$CH$_2$C*H*$_2$CH$_3$), 0.88 (d, *J* = 6.6 Hz, 6H; 3″-(C*H*$_3$)$_2$), 0.78 ppm (t, *J* = 6.6 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, 1% TFA in D_2O), reference 0–200 ppm, δ = 177.7 (C-1″), 177.3 (C-1′), 170.7 (C-2), 167.7 (5-*C*O-NH-), 61.2 (C-2″), 59.7 (C-5), 54.8 (C-3), 53.0 (C-6), 52.3 (C-2′), 33.0 (1C, 6-*C*H$_2$CH$_2$CH$_2$CH$_3$), 32.4 (C-3″), 29.5 (1C, 6-CH$_2$*C*H$_2$CH$_2$CH$_3$), 24.0 (1C, 6-CH$_2$CH$_2$*C*H$_2$CH$_3$), 20.9, 20.0 (each 1C, 3″-(*C*H$_3$)$_2$), 19.3 (C-3′), 16.4 (1C, 3-*C*H$_3$), 15.5 ppm (1C, 6-CH$_2$CH$_2$CH$_2$*C*H$_3$); IR (KBr): $\tilde{\nu}$ = 3410 (C=O, -NH), 3278 (C=O, -NH), 1670 (C=O, amide), 1547, 1431, 1394, 1201, 1142, 723 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{18}H_{33}N_4O_5$: 385.2451 [*M*+H]; found: 385.2459 [*M*+H]$^+$.

(3*R*,5*R*,6*R*)-(−)-4-*tert*-Butoxycarbonyl-6-butyl-5-(*O*^{1}-*tert*-butyl-D-valinyl-D-alanyl)-carbonyl-3-methyl-2-piperazinone (59): According to the procedure of the compound **30**, compound **59** (86.0 mg, 74% in 2 steps) was obtained from **29** as a colorless oil (73.5 mg, 215 μmol). R_f = 0.47 (silica gel, $CHCl_3$/MeOH = 10:1); $[\alpha]_D^{22}$ = +69.4 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 6.6 Hz, 1H; 2′-NH), 6.68 (d, *J* = 7.9 Hz, 1H; 2″-NH), 6.08 (brs, 1H; 1-H), 4.66 (brs, 1H; 5-H), 4.49–4.39 (complex m, 2H; 3-H, 2′-H), 4.41 (dd, *J* = 4.3, 7.9 Hz, 1H; 2″-H), 3.61 (dt, *J* = 4.3, 7.3 Hz, 1H; 6-H), 2.15 (dq, *J* = 4.3, 6.9 Hz, 1H; 3″-H), 1.81–1.69 (complex m, 2H; 6-C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.50–1.22 (complex m, 4H; 6-CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.50 (s, 9H; 4-CO-OC(C*H*$_3$)$_3$), 1.47–1.45 (complex m, 3H; 3-C*H*$_3$), 1.45 (s, 9H; 1″-OC(C*H*$_3$)$_3$), 1.31 (d, *J* = 6.9 Hz, 3H; 3′-H$_3$), 0.89 (d, *J* = 6.9 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$C*H*$_3$), 0.89 ppm (d, *J* = 6.9 Hz, 3H; 3″-(C*H*$_3$)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.6 (C-2), 170.8 (C-1′), 170.0 (C-1″), 168.3 (1C, 5-*C*O-NH-), 154.7 (1C, 4-*C*O-OC(CH$_3$)$_3$), 81.9 (1″-O*C*(CH$_3$)$_3$), 81.8 (1C, 4-CO-O*C*(CH$_3$)$_3$), 57.3 (C-2″), 53.5 (C-5), 52.3 (C-3), 52.3 (C-6), 48.4 (C-2′), 31.2 (C-3″), 31.0 (1C, 6-*C*H$_2$CH$_2$CH$_2$CH$_3$), 28.2 (1C, 4-*C*O-OC(CH$_3$)$_3$), 28.0 (1C, 6-CH$_2$*C*H$_2$CH$_2$CH$_3$), 27.9 (1″-O*C*(CH$_3$)$_3$), 22.3 (1C, 6-CH$_2$CH$_2$*C*H$_2$CH$_3$), 18.9, 17.4 (each 1C, 3″-(*C*H$_3$)$_2$), 18.0 (1C, 3-*C*H$_3$), 18.0 (C-3′), 13.8 ppm (1C, 6-CH$_2$CH$_2$CH$_2$*C*H$_3$); IR (KBr) $\tilde{\nu}$ = 3300 (br, -NH), 1728 (C=O, ester), 1689 (C=O, amide), 1531, 1456, 1371, 1331, 1159, 1132, 1070, 849, 756 cm^{-1}; HRMS (FAB, NBA+NaI matrix): *m/z* calcd for $C_{27}H_{49}N_4O_7$: 541.3601 [*M*+Na]; found: 541.33597 [*M*+H]$^+$.

(3*R*,5*R*,6*R*)-(+)-6-Butyl-5-(D-valinyl-D-alanyl)carbonyl-3-methyl-2-piperazinone (31): According to the procedure for **8**, compound **31** (43.0 mg, 93%) was obtained from **59** as a TFA salt (50.1 mg, 45.0 μmol). R_f = 0.14 (silica gel, $CHCl_3$/MeOH = 10:1); $[\alpha]_D^{23}$ = +70.9 (*c* = 1.00, MeOH); ^{1}H NMR (400 MHz, 1% TFA in D_2O): δ = 4.49 (d, *J* = 4.5 Hz, 1H; 5-H), 4.40 (q, *J* = 7.2 Hz, 1H; 2′-H), 4.14 (d, *J* = 5.8 Hz, 1H; 2″-H), 4.09 (q, *J* = 7.2 Hz, 1H; 3-H), 3.89 (ddd, *J* = 3.9, 4.5, 11.2 Hz, 1H; 6-H), 2.09 (dq, *J* = 5.8, 7.0 Hz, 1H; 3″-H), 1.52–1.33 (complex m, 2H; 6-C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.49 (d, *J* = 7.2 Hz, 3H; 3-C*H*$_3$), 1.33–1.10 (complex m, 4H; 6-CH$_2$C*H*$_2$C*H*$_2$CH$_3$), 1.30 (d, *J* = 7.2 Hz, 3H; 3′-H$_3$), 0.86 (d, *J* = 7.0 Hz, 6H; 3″-(C*H*$_3$)$_2$), 0.76 ppm (t, *J* = 7.0 Hz, 3H; 6-CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR (100 MHz, 1% TFA in D_2O), reference 0–200 ppm δ = 177.6 (C-1″), 176.7 (C-1′), 170.6 (C-2), 167.5 (5-*C*O-NH-), 61.0 (C-2″), 59.7 (C-5), 54.8 (C-3), 53.3 (C-6), 52.0 (C-2′), 32.9 (1C, 6-*C*H$_2$CH$_2$CH$_2$CH$_3$), 32.5 (C-3″), 29.6 (1C, 6-CH$_2$*C*H$_2$CH$_2$CH$_3$), 24.2 (1C, 6-CH$_2$CH$_2$*C*H$_2$CH$_3$), 21.0, 19.9 (each 1C, 3″-(*C*H$_3$)$_2$), 19.2 (C-3′), 16.5 (1C, 3-*C*H$_3$), 15.6 ppm (1C, 6-CH$_2$CH$_2$CH$_2$*C*H$_3$); IR (KBr): $\tilde{\nu}$ = 3431 (br, -NH), 3286 (br, -NH), 1668 (C=O, amide), 1552, 1431, 1385, 1203, 1144, 800, 723 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{18}H_{33}N_4O_5$: 385.2451 [*M*+H]; found: 385.2442 [*M*+H]$^+$.

(*R*)-(−)-1-Benzyloxy-2,5-pentanediol (60): BH_3·Me_2S complex (5.16 mL, 48.8 mmol) was slowly added to a solution of **35** (4.70 g, 24.4 mmol) in THF (122 mL) at 0 °C under argon. After stirring for 80 min, the reaction mixture was quenched with 4.0 N aqueous NaOH (65 mL) and 30% aqueous H_2O_2 (65 mL) at 0 °C, then the mixture was warmed up to RT, and stirred for 2 h. The resulting mixture was extracted with EtOAc (200 mL×3), the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel ($CHCl_3$/MeOH = 100:1) gave **60** as a colorless oil (4.50 g, 87%). R_f = 0.20 (silica gel, $CHCl_3$/MeOH = 10:1); $[\alpha]_D^{20}$ = −2.84 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.40–7.26 (complex m, 5H; 1-O-CH$_2$-*Ph*), 4.56 (s, 2H; 1-O-C*H*$_2$-Ph), 3.87 (ddd, *J* = 1.1, 3.3, 7.9 Hz, 1H; 2-H), 3.51 (dd, *J* = 3.3, 9.2 Hz, 1H; 1-*H*$_2$), 3.66 (dt, *J* = 3.9, 5.9 Hz, 2H; 5-H$_2$), 3.36 (dd, *J* = 7.9, 9.2 Hz, 1H; 1-*H*$_2$), 2.06 (brs, 2H; 2-O*H*, 5-O*H*), 1.77–1.64 (complex m, 2H; 3-H$_2$), 1.62–1.43 ppm (complex m, 2H; 4-H$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 138.7, 129.2 (2C), 128.6 (2C), 128.5, 74.9, 73.7, 70.7, 63.0, 30.3, 29.1 ppm; IR (NaCl): $\tilde{\nu}$ = 3365 (OH), 1454, 1093, 1059, 739, 698 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{12}H_{19}O_3$:211.1334 [*M*+H]; found: 211.1342 [*M*+H]$^+$.

(*R*)-(+)-1-Benzyloxy-2,5-di-(*tert*-butyldimethylsiloxy)-pentane (61): Imidazole (6.66 g, 113 mmol) and TBSCl (11.1 g, 73.3 mmol) were added to a solution of **60** (5.14 g, 24.4 mmol) in DMF (48.9 mL) at RT under argon. After stirring for 2 h at RT, the reaction solution was diluted with hexane/EtOAc (2/1) (800 mL), and the solution was washed with H_2O (600 mL×6), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 15:1) gave **61** as a colorless oil (9.16 g, 95%). R_f = 0.76 (silica gel, hexane/EtOAc = 2:1); $[\alpha]_D^{26}$ = +9.40 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.36–7.23 (complex m, 5H; 1-O-CH$_2$-*Ph*), 4.52 (s, 2H; 1-O-C*H*$_2$-Ph), 3.84 (m, 1H; 2-H), 3.63–3.57 (complex m, 2H; 5-H$_2$), 3.41 (dd, *J* = 5.6, 9.6 Hz, 1H; 1-*H*$_2$), 3.36 (dd, *J* = 5.3, 9.6 Hz, 1H; 1-*H*$_2$), 1.65–1.40 (complex m, 4H; 3-H$_2$, 4-H$_2$), 0.89 (s, 9H; 2-OSi[CH$_3$]$_2$C-(C*H*$_3$)$_3$), 0.87 (s, 9H; 5-OSi[CH$_3$]$_2$C(C*H*$_3$)$_3$), 0.05 (s, 3H; 2-OSi[C*H*$_3$]$_2$C-(CH$_3$)$_3$), 0.04 (s, 6H; 5-OSi[C*H*$_3$]$_2$C(CH$_3$)$_3$), 0.04 ppm (s, 3H; 2-OSi-[C*H*$_3$]$_2$C(CH$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 138.4, 128.2 (2C), 127.5 (2C), 127.4, 74.7, 73.2, 71.3, 63.3, 31.0, 28.6, 26.0 (3C), 25.9 (3C), 18.3 (2C), −4.38, −4.78, −5.28 ppm (2C); IR (NaCl) $\tilde{\nu}$ = 1471,1255, 1099, 1051, 835, 775 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{24}H_{47}O_3Si_2$: 439.3064 [*M*+H]; found: 439.3063 [*M*+H]$^+$.

(*R*)-(−)-2,5-Di-(*tert*-butyldimethylsiloxy)pentanol (62): 20 wt% $Pd(OH)_2$/C (791 mg, 1.12 mmol) was added to a solution of **61** (5.10 g, 11.2 mmol) in EtOH (112.6 mL) at RT. After stirring for 20 min under H_2, the reaction solution was filtered through a Celite pad to remove the $Pd(OH)_2$ catalyst, then the pad was washed with EtOAc. The filtrate was washed with a saturated aqueous solution of $NaHCO_3$ (50 mL), dried over Na_2SO_4, filtered, and evaporated to remove the solvent. Purification by flash chromatography on silica gel (hexane/EtOAc = 7:1) gave **62** as a colorless oil (3.77 g, 96%). R_f = 0.43 (silica gel, hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = −13.3 (*c* = 2.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.75 (m, 1H; 2-H), 3.62–3.50 (complex m, 2H; 5-H$_2$), 3.53 (dd, *J* = 5.0, 11.2 Hz, 1H; 1-*H*$_2$), 3.44 (dd, *J* = 5.6, 11.2 Hz, 1H; 1-*H*$_2$), 1.60–1.42 (complex m, 4H; 3-H$_2$, 4-H$_2$), 0.89 (s, 9H; 2-OSi[CH$_3$]$_2$C(C*H*$_3$)$_3$), 0.88 (s, 9H; 5-OSi-[CH$_3$]$_2$C(C*H*$_3$)$_3$), 0.07 (s, 6H; 5-OSi[C*H*$_3$]$_2$C(CH$_3$)$_3$), 0.03 ppm (s, 6H; 5-OSi[C*H*$_3$]$_2$C(CH$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 72.7, 66.2, 63.1, 30.3, 28.5, 25.9 (3C), 25.8 (3C), 18.3, 18.0, −4.5, −4.6, −5.4 ppm (2C); IR (NaCl): $\tilde{\nu}$ = 3435 (-OH), 1473, 1464, 1255, 1099, 1049, 837, 775 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{17}H_{41}O_3Si_2$: 349.2594 [*M*+H]; found: 349.2583 [*M*+H]$^+$.

(3*S*,4*R*)-4,7-Di-(*tert*-butyldimethylsiloxy)-hept-1-ene-3-ol (37): Oxalyl chloride (4.75 mL, 43.6 mmol) was slowly added to a solution of DMSO (7.73 mL, 109 mmol) in CH_2Cl_2 (160 mL) at −78 °C under argon. The solution was stirred for 30 min, then **62** (7.60 g, 21.8 mmol) in CH_2Cl_2

(48.0 mL) was added dropwise at −78 °C. After stirring for 30 min, TEA (18.2 mL, 131 mmol) was added to the solution at −78 °C, then it was warmed to 0 °C. The mixture was stirred for 15 min, and quenched with a saturated aqueous solution of NH_4Cl (60 mL). Then the two layers were separated and the aqueous layer was extracted with hexane/EtOAc (3:1) (60 mL × 2). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl (60 mL), a saturated aqueous solution of $NaHCO_3$ (60 mL), H_2O (60 mL), and brine (60 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give **36**, which was used in the next reaction without further purification. A 1.0 M solution of vinylmagnesium bromide in THF (65.4 mL, 65.4 mmol) was added to a solution of **36** (≈21.8 mmol) in Et_2O (218 mL) at −78 °C under argon. After stirring for 35 min, the reaction mixture was poured through a funnel into a stirred solution of saturated aqueous $NaHCO_3$/hexane (1:1) (200 mL), then the two layers mixture were separated, the organic layer was washed with a saturated aqueous solution of NH_4Cl (60 mL), a saturated aqueous solution of $NaHCO_3$ (60 mL), H_2O (60 mL), and brine (60 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc = 10:1) afforded **37** and the C3-epimer of **37** (5:1) as an inseparable mixture (6.84 g, 84% for 2 steps). R_f = 0.53 (silica gel, hexane/EtOAc = 4:1); ^{1}H NMR (270 MHz, $CDCl_3$), major isomer is indicated. δ = 5.85 (ddd, J = 6.3, 10.6, 16.8 Hz, 1H; 2-H), 5.30 (ddd, J = 1.7, 1.7, 16.8 Hz, 1H; 1-H_2), 5.19 (ddd, J = 1.7, 1.7, 10.6 Hz, 1H; 1-H_2), 4.11 (m, 1H; 3-H), 3.72 (m, 1H; 4-H), 3.65–3.55 (complex m, 2H; 7-H_2), 1.73–1.41 (complex m, 4H; 5-H_2, 6-H_2), 0.91 (s, 6H; 4-OSi[CH_3]$_2$C(CH_3)$_3$), 0.90 (s, 3H; 4-OSi[CH_3]$_2$C-(CH_3)$_3$), 0.89 (s, 9H; 7-OSi[CH_3]$_2$C(CH_3)$_3$), 0.10 (s, 3H; 4-OSi[CH_3]$_2$C-(CH_3)$_3$), 0.09 (s, 3H; 4-OSi[CH_3]$_2$C(CH_3)$_3$), 0.04 ppm (s, 6H; 7-OSi-[CH_3]$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$), major isomer is indicated. δ = 136.6, 116.4, 75.8, 75.2, 63.2, 28.8, 28.1, 26.0 (3C), 25.9 (3C), 18.3, 18.1, −4.4 (2C), −5.3 ppm (2C); IR (NaCl): $\tilde{\nu}$ = 3467 (OH), 1471, 1464, 1255, 1099, 837, 775 cm^{-1}; HRMS (FAB, NBA + NaI matrix): m/z calcd for $C_{19}H_{42}O_3Si_2Na$: 397.2570 [M+Na]; found: 397.2582 [M+Na]$^+$.

(3*S*,4*R*)-Hept-1-ene-3,4,7-triol (63): The 5:1 mixture of **37** was dissolved in a 4 N solution of HCl in dioxane (36.8 mL) and stirred for 20 min at RT. Then the reaction mixture was concentrated under reduced pressure. Flash chromatography on silica gel ($CHCl_3$/MeOH = 20:1) gave **63** as an inseparable mixture of diastereomers (1.61 g, 94%). R_f = 0.13 (silica gel, $CHCl_3$/MeOH = 8:1); ^{1}H NMR (270 MHz, $CDCl_3$), major isomer is reported δ = 5.93 (ddd, J = 6.6, 10.6, 17.2 Hz, 1H; 2-H), 5.35 (ddd, J = 1.3, 1.3, 17.2 Hz, 1H; 1-H_2), 5.28 (ddd, J = 1.3, 1.3, 10.6 Hz, 1H; 1-H_2), 4.12 (ddd, J = 1.3, 4.0, 6.6 Hz, 1H; 3-H), 3.79–3.61 (complex m, 3H; 4-H, 7-H_2), 1.96 (brs, 3H; 3-OH, 4-OH, 7-OH), 1.80–1.69 (complex m, 2H; 5-H_2), 1.65 (m, 1H; 7-H_2), 1.47 ppm (m, 1H; 7-H_2); ^{13}C NMR (67.5 MHz, CD_3OD), major isomer is reported. δ = 139.0, 116.6, 77.3, 75.3, 63.0, 30.0 ppm (2C); IR (NaCl): $\tilde{\nu}$ = 3367 (-OH), 1644, 1429, 1053, 997, 926 cm^{-1}; HRMS (FAB, thioglycerol + glycerol matrix): m/z calcd for $C_7H_{15}O_3$: 147.1021 [M+H]; found: 147.1017 [M+H]$^+$.

(4*R*,5*S*)-4,5-*O*-Isopropylidenehept-6-ene-1-ol (64): 2,2-Dimethoxypropane (1.70 mL, 13.8 mmol) and TsOH·H_2O (131 mg, 690 μmol) were added to a solution of **63** (1.01 g, 6.90 mmol) in acetone (68.9 mL) at RT. After stirring for 15 min, the reaction mixture was quenched with H_2O (4 mL) to remove the acetal on the primary alcohol. The mixture was then diluted with brine (20 mL) and $CHCl_3$ (100 mL), the resulting two layers were separated. The aqueous layer was extracted with $CHCl_3$ (100 mL × 2), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc = 6:1) afforded **64** (1.18 g, 92%) as a diastereomixture (dr ≈ 6:1). R_f = 0.12 (silica gel, hexane/EtOAc = 4:1) for the major isomer and 0.15 (silica gel, hexane/EtOAc = 4:1) for the minor isomer, ^{1}H NMR (270 MHz, $CDCl_3$), major isomer is reported δ = 5.81 (ddd, J = 7.6, 10.2, 17.2 Hz, 1H; 2-H), 5.30 (ddd, J = 1.0, 1.0, 17.2 Hz, 1H; 1-H_2), 5.24 (ddd, J = 1.0, 1.0, 10.2 Hz, 1H; 1-H_2), 4.52 (dd, J = 6.6, 7.6 Hz, 1H; 3-H), 4.16 (dt, J = 6.6, 7.3 Hz, 1H; 4-H), 3.67 (t, J = 5.9 Hz, 2H; 7-H_2), 1.80–1.58 (complex m, 4H; 5-H_2, 6-H_2), 1.49 (s, 3H; 3, 4-*O*-*i*Pr), 1.37 ppm (s, 3H; 3, 4-*O*-*i*Pr); ^{13}C NMR (67.5 MHz, $CDCl_3$), major isomer is reported δ = 133.7, 117.7, 107.6, 79.2, 77.5, 61.6, 28.9, 27.5, 26.5, 25.0 ppm; IR (NaCl): $\tilde{\nu}$ = 3438 (OH), 1379, 1371, 1246, 1217, 1047, 1016, 926, 872 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{10}H_{19}O_3$: 187.1334 [M+H]; found: 187.1337 [M+H]$^+$.

(3*S*, 4*R*)-(+)-7-Benzyloxy-3,4-*O*-isopropylidenehept-1-ene (38) and (3*R*, 4*R*)-(+)-7-Benzyloxy-3,4-*O*-isopropylidenehept-1-ene (C3-epi 38): 55% NaH (1.20 g, 27.4 mmol) was added to a solution of the diastereomixture (ca. 6:1) of **64** (3.40 g, 18.3 mmol) in THF (183 mL) at 0 °C under argon. Then the mixture was warmed to 60 °C and stirred for 30 min and cooled to RT. Then TBAI (8.80 g, 23.7 mmol) and BnBr (2.82 mL, 23.7 mmol) were added to the mixture, and the resulting reaction mixture was heated to 70 °C under stirring. After stirring for 6.5 h, the reaction mixture was cooled to 0 °C and quenched with a saturated aqueous solution of NH_4Cl, then the two layers mixture was separated, the aqueous layer was extracted with EtOAc (200 mL × 4). The organic layers were washed with H_2O (80 mL) and brine (80 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc = 20:1) afforded **38** (4.30 g, 85%; dr = > 20:1) and C3-epi **38** (348 mg, 7%) as colorless oils. Major product **38**: R_f = 0.42 (silica gel, hexane/EtOAc = 4:1); $[\alpha]_D^{27}$ = +1.78 (c = 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.25 (complex m, 5H; 7-O-CH_2-*Ph*), 5.82 (ddd, J = 7.8, 10.2, 18.0 Hz, 1H; 2-H), 5.30 (ddd, J = 1.0, 1.3, 18.0 Hz, 1H; 1-H_2), 5.23 (ddd, J = 1.0, 1.7, 10.2 Hz, 1H; 1-H_2), 4.50 (s, 2H; 7-O-CH_2Ph), 4.49 (dd, J = 7.8, 8.0 Hz, 1H; 3-H), 4.14 (ddd, J = 6.0, 6.2, 8.0 Hz, 1H; 4-H), 3.57–3.44 (complex m, 2H; 7-H_2), 1.80 (m, 1H; 6-H_2), 1.66 (m, 1H; 6-H_2), 1.60–1.48 (complex m, 2H; 5-H_2),1.48 (s, 3H; 3, 4-*O*-*i*Pr), 1.36 ppm (s, 3H; 3, 4-*O*-*i*Pr); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 137.9, 133.8, 127.7 (2C), 127.0 (2C), 126.8, 117.6, 107.5, 79.2, 77.4, 72.1, 69.3, 27.6, 26.5, 25.8, 25.0 ppm; IR (NaCl): $\tilde{\nu}$ = 1454, 1369, 1248, 1215, 1099, 1045, 926, 737, 698 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{17}H_{25}O_3$: 277.1804 [M+H]; found: 277.1811 [M+H]$^+$. Minor product C3-epi **38**: R_f = 0.45 (silica gel, hexane/EtOAc = 4:1); $[\alpha]_D^{26}$ = +0.52 (c = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.37–7.22 (complex m, 5H; 7-O-CH_2-*Ph*), 5.80 (ddd, J = 7.3, 10.2, 17.2 Hz, 1H; 2-H), 5.36 (ddd, J = 1.3, 1.3, 17.2 Hz, 1H; 1-H_2), 5.24 (ddd, J = 1.3, 1.6, 10.2 Hz, 1H; 1-H_2), 4.50 (s, 2H; 7-O-CH_2Ph), 4.00 (dd, J = 7.3, 8.3 Hz, 1H; 3-H), 3.69 (ddd, J = 4.0, 7.6, 8.3 Hz, 1H; 4-H), 3.56–3.44 (complex m, 2H; 7-H_2), 1.88–1.53 (complex m, 4H; 5-H_2, 6-H_2), 1.41 (s, 3H; 3, 4-*O*-*i*Pr), 1.40 ppm (s, 3H; 3, 4-*O*-*i*Pr); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 138.5, 135.4, 128.3, 128.3, 127.6 (2C), 127.5, 118.9, 108.5, 82.7, 80.4, 72.8, 70.0, 28.4, 27.3, 26.9, 26.2 ppm; IR (NaCl): $\tilde{\nu}$ = 1454, 1369, 1242, 1217, 1097, 1053, 928, 885,737, 698 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{17}H_{25}O_3$: 277.1804 [M+H]; found: 277.1796 [M+H]$^+$.

(3*S*,4*R*)-7-Benzyloxy-3,4-*O*-isopropylideneheptanol (65): BH_3·Me_2S complex (656 μL, 6.77 mmol) was slowly added to a solution of **38** (1.70 g, 6.15 mmol) in THF (61.5 mL) at 0 °C under argon. After stirring for 30 min, the reaction mixture was warmed to RT and stirred for a further 2 h. The reaction was quenched with H_2O (65 mL), $NaBO_3$·4H_2O (3.12 g, 20.3 mmol) and NaOH (271 mg, 6.77 mmol), then the mixture was warmed to 50 °C with stirring for 90 min. The resulting two layers were separated, and the aqueous layer was extracted with EtOAc (200 mL × 2), the combined organic layers were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel ($CHCl_3$/MeOH = 100:1) afforded **65** as a colorless oil (1.25 g, 69%). R_f = 0.41 (silica gel, $CHCl_3$/MeOH = 10:1); $[\alpha]_D^{27}$ = −17.8 (c = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.38–7.26 (complex m, 5H; 7-O-CH_2*Ph*), 4.50 (s, 2H; 7-O-CH_2Ph), 4.25 (ddd, J = 3.0, 5.9, 10.6 Hz, 1H; 3-H), 4.10 (dt, J = 5.9, 7.9, 1H; 4-H), 3.82 (dt, J = 3.3, 5.6 Hz, 2H; 7-H_2), 3.59–3.44 (complex m, 2H; 1-H_2), 1.91–1.70 (complex m, 4H; 2-H_2, 5-H_2), 1.70–1.50 (complex m, 2H; 6-H_2), 1.45 (s, 3H; 3, 4-*O*-*i*Pr), 1.33 ppm (s, 3H; 3, 4-*O*-*i*Pr); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 138.3, 128.2 (2C), 127.5 (2C), 127.4, 107.7, 77.5, 76.5, 72.7, 69.7, 60.6, 31.9, 28.3, 26.3, 26.3, 25.7 ppm; IR (NaCl): $\tilde{\nu}$ = 3429 (-OH), 1367, 1246, 1217, 1093, 1057, 739, 698 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{17}H_{27}O_4$: 295.1909 [M+H]; found: 295.1919 [M+H]$^+$.

(3*S*,4*R*)-(−)-7-(*tert*-Butyldiphenylsiloxy)-3,4-*O*-isopropylideneheptanol (66): Imidazole (429 mg, 6.32 mmol) and TBDPSCl (1.29 mL, 5.05 mmol) were added to a solution of **65** (1.24 g, 4.21 mmol) in DMF (8.4 mL) at RT under argon. After stirring for 40 min at RT, the reaction was

quenched with H_2O (10 mL) and extracted with EtOAc (20 mL×3). The combined extracts were washed with 1 N aqueous HCl (20 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL×2), H_2O (50 mL), and brine (50 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford the crude product, which was used in the next reaction without further purification. 20 wt% $Pd(OH)_2$/C (296 mg, 421 μmol) was added to a solution of crude product in EtOAc (42.1 mL) at RT. After stirring for 2.5 h under H_2, the reaction solution was filtered through a Celite pad to remove the $Pd(OH)_2$ catalyst, then the pad was washed with EtOAc. The filtrate was concentrated, and purified by flash chromatography on silica gel (hexane/EtOAc=4:1) to give **66** as a colorless oil (1.45 g, 78% for 2 steps). R_f=0.22 (hexane/EtOAc=2:1); $[\alpha]_D^{23}=-7.80$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.80–7.63 (complex m, 4H; 7-OSi(*Ph*)$_2$C(CH$_3$)$_3$), 7.46–7.33 (complex m, 6H; 7-OSi(*Ph*)$_2$C-(CH$_3$)$_3$), 4.30 (dd, J=6.3, 10.6 Hz, 1H; 5-H), 4.08 (ddd, J=5.0, 6.0, 10.6 Hz, 1H; 4-H), 3.81 (t, J=6.3 Hz, 2H; 1-H$_2$), 3.67 (dt, J=1.7, 6.0 Hz, 2H; 7-H$_2$), 1.79–1.60 (complex m, 4H; 2-H$_2$, 6-H$_2$), 1.59–1.44 (complex m, 2H; 3-H$_2$), 1.39 (s, 3H; 4,5-*O*-*i*Pr), 1.33 (s, 3H; 4,5-*O*-*i*Pr), 1.05 ppm (s, 9H; 7-OSi(Ph)$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=135.4 (4C), 133.7, 133.6, 129.5, 127.7, 127.5 (4C), 107.4, 77.8, 74.6, 62.5, 60.9, 32.6, 29.6, 28.4, 26.8 (3C), 25.8, 20.9, 19.1 ppm; IR (NaCl): $\tilde{\nu}$=3404 (-OH), 1375, 1219, 1099, 1018, 743, 700, 611 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for $C_{26}H_{39}O_4Si$ 443.2618 [M+H]; found: 443.2617 [M+H]$^+$.

(4*S*,2′*S*,3′*R*,6′*R*,7′*S*)-(+)-3-[9′-(*tert*-Butyldiphenylsilyloxy)-2′-chloro-3′-hydroxy-6′,7′-*O*-isopropylidenenonanoyl]-4-benzyloxazolidinone (67): Oxalyl chloride (1.07 mL, 12.3 mmol) was slowly added to a solution of DMSO (1.74 mL, 24.5 mmol) in CH_2Cl_2 (50.0 mL) at −78 °C under Ar. The solution was stirred for 20 min, then **66** (2.70 g, 6.12 mmol) in CH_2Cl_2 (11.2 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, TEA (4.27 mL, 30.6 mmol) was added to the solution, and then it was warmed to 0 °C. The mixture was stirred for 10 min, and quenched with a saturated aqueous solution of NH_4Cl (20 mL). Then the two layers were separated, and the aqueous layer was extracted with hexane/EtOAc (1/1) (40 mL×2). The combined organic extracts were washed with H_2O (60 mL), saturated aqueous NH_4Cl (60 mL), saturated aqueous $NaHCO_3$ (60 mL), and brine (60 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give *anti*-**33**, which was used in the next reaction without further purification. Et_3N (2.13 mL, 15.3 mmol) was added to a solution of (*S*)-**16** (3.11 g, 12.3 mmol) in CH_2Cl_2 (75.5 mL) at −78 °C, followed by *n*Bu$_2$BOTf (1.0 M in CH_2Cl_2, 12.6 mL, 12.6 mmol). The solution was stirred for 1 h at −78 °C and for 1 h at RT. After the solution was cooled to −78 °C, crude *anti*-**33** in CH_2Cl_2 (12.1 mL) was added. After stirring for 10 min at −78 °C, the reaction mixture was warmed to 0 °C, stirred for 80 min, and then quenched with phosphate buffer (Ph 7.2, 20 mL), 30% aqueous H_2O_2/MeOH (1:2; 10 mL), and stirred for a further 1 h at RT. The resulting mixture was extracted with $CHCl_3$ (80 mL×3) and the combined extracts were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc=2:1) gave **67** as a colorless oil (2.77 g, 65% for 2 steps). R_f=0.35 (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{28}=+24.5$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.70–7.63 (complex m, 4H; 9′-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.43–7.29 (complex m, 9H; 4-CH$_2$*Ph*, 9′-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.26–7.21 (complex m, 2H; 4-CH$_2$*Ph*), 5.68 (d, J=3.3 Hz, 1H; 2′-H), 4.72 (dddd, J=3.3, 3.6, 6.9, 9.6 Hz, 1H; 4-H), 4.32 (ddd, J=3.3, 5.9, 7.2 Hz, 1H; 3′-H), 4.26 (d, J=6.9 Hz, 1H; 4-C*H*$_2$Ph), 4.26 (d, J=3.6 Hz, 1H; 4-C*H*$_2$Ph), 4.15 (m, 1H; 6′-H), 4.07 (m, 1H; 7′-H), 3.81 (t, J=6.9 Hz, 2H; 9′-H$_2$), 3.33 (dd, J=3.3, 13.5 Hz, 1H; 5-*H*$_2$), 2.83 (dd, J=9.6, 13.5 Hz, 1H; 5-*H*$_2$), 1.89–1.57 (complex m, 6H; 4′-H$_2$, 5′-H$_2$, 8′-H$_2$), 1.38 (s, 3H; 6′, 7′-*O*-*i*Pr), 1.32 (s, 3H; 6′, 7′-*O*-*i*Pr), 1.05 ppm (s, 9H; 9-O-Si(Ph)$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=167.8, 152.5, 135.5 (2C), 135.3 (2C), 134.5, 133.6, 133.5, 129.4 (2C), 129.2 (2C), 128.8 (2C), 127.6, 127.4 (2C), 127.2, 107.4, 77.2, 74.3, 71.0, 66.3, 60.7, 59.8, 55.2, 36.9, 32.4, 30.6, 28.3, 26.8, 26.7 (3C), 26.0, 25.8, 18.9 ppm; IR (NaCl): $\tilde{\nu}$=3558 (-OH), 3431 (-NH), 1782 (C=O, imide), 1711 (C=O, amide), 1389, 1213, 1111, 1084, 760, 742, 702 cm^{-1}; HRMS (FAB, NBA+NaI matrix): m/z calcd for $C_{38}H_{49}NO_7SiClNa$: 716.2796 [M+Na]; found: 716.2786 [M+Na]$^+$.

(*S*)-(−)-5-*tert*-Butyldimethylsiloxy-1,2-pentanediol (68): Nitrosobenzene (13.1 g, 122 mmol) was added to a solution of D-proline (2.81 g, 24.4 mmol) in $CHCl_3$ (250 mL). A solution of **39** (31.8 g, 147 mmol) in $CHCl_3$ (44.0 mL) was added dropwise to the reaction mixture over 10 min at 0 °C under argon, and stirred for 105 min. Then a solution of $NaBH_4$ (10.9 g, 294 mmol) in EtOH (118 mL) was added to the reaction solution. After stirring for 30 min at 0 °C, a saturated aqueous solution of $NaHCO_3$ (100 mL) was poured into the reaction solution. The organic layer was separated, washed with brine (100 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product of **40** was dissolved in EtOAc (735 mL) and 10% wt Pd/C (15.6 g, 14.7 mmol) was added. After stirring for 4 h under H_2, the reaction solution was filtered through a Celite pad to remove the Pd catalyst, then the pad was washed with EtOAc. The filtrate solution was evaporated to remove the solvent. Purification by flash chromatography on silica gel (hexane/EtOAc=1:1) gave **68** as a colorless oil (13.7 g, 40% for 2 steps). R_f=0.10 (silica gel, hexane/EtOAc=1:1); $[\alpha]_D^{27}=-4.29$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=3.76–3.58 (complex m, 4H; 1-*H*$_2$, 2-H, 5-H$_2$), 3.45 (dd, J=7.3, 9.9 Hz, 1H; 1-*H*$_2$), 1.76–1.56 (complex m, 3H; 3-H$_2$, 4-*H*$_2$), 1.48 (m, 1H; 4-*H*$_2$), 0.89 (s, 9H; 5-OSi[CH$_3$]$_2$C(C*H*$_3$)$_3$), 0.05 ppm (s, 6H; 5-OSi[C*H*$_3$]$_2$C(CH$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=71.9, 66.9, 63.6, 31.0, 29.1, 25.9 (3C), 18.3, −5.4 ppm (2C); IR (NaCl): $\tilde{\nu}$=3363 cm^{-1} (OH); HRMS (FAB, NBA matrix): m/z calcd for $C_{11}H_{27}O_3Si$: 235.1729 [M+H]; found: 235.1732 [M+H]$^+$.

(4*S*)-4-(1′-*tert*-Butyldimethylsiloxypropane-3′-yl)-2-(*p*-methoxyphenyl)-1,3-dioxolane (69): *p*-Anisaldehyde dimethylacetal (3.92 mL, 23.0 mmol) and PPTS (386 mg, 1.53 mmol) were added to a solution of **68** (3.60 g, 15.3 mmol) in CH_2Cl_2 (153 mL) at 0 °C. After stirring for 100 min, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (70 mL), and the resulting two layers were separated. The aqueous layer was extracted with $CHCl_3$ (100 mL×), the combined organic layers were washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was diluted with EtOH (40 mL) and treated with $NaBH_4$ (1.5 g, 39.7 mmol) under stirring for 10 min. H_2O (100 mL) was added to the resulting mixture, and it was extracted with $CHCl_3$ (120 mL×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on NH-silica(NH, 100≈200 μm; purchased from Fuji Silysia; hexane/EtOAc=200:1) afforded **69** as a colorless oil (5.00 g, 92%). R_f=0.64 (silica gel, hexane/EtOAc=1:1); ^{1}H NMR (270 MHz, $CDCl_3$), as a mixture of two diastereomers δ=7.41 (t, J=6.6 Hz, 4/5H; 2-O-*Ph*-CH$_3$), 7.40 (t, J=5.0 Hz, 6/5H; 2-O-*Ph*-CH$_3$), 6.90 (d, J=8.3 Hz, 2H; 2-O-*Ph*-CH$_3$), 5.87 (s, 2/5H; 2-H), 5.76 (s, 3/5H; 2-H), 4.36–4.15 (m, 7/5H; 5-H$_2$), 4.09 (t, J=6.9 Hz, 3/5H; 5-H$_2$), 3.81 (s, 3H; 2-CH-Ph-OC*H*$_3$), 3.75–3.54 (complex m, 1H; 4-H), 3.75–3.54 (complex m, 2H; 1′-H$_2$), 1.85–1.53 (complex m, 2H; 2′-H$_2$), 1.85–1.53 (complex m, 2H; 3′-H$_2$), 0.90 (s, 9H; 1′-OSi[CH$_3$]$_2$C(C*H*$_3$)$_3$), 0.05 ppm (s, 6H; 1′-OSi[C*H*$_3$]$_2$C(CH$_3$)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$), as a mixture of two diastereomers δ=161.0, 131.0 (3/5C), 130.0 (2/5C), 128.0, 127.8, 113.7 (2C), 104.0 (3/5C), 102.9 (2/5C), 76.3, 70.8 (3/5C), 70.0 (2/5C), 62.8, 55.2, 30.0 (3/5C), 29.8 (2/5C), 29.0, 25.9 (3C), 18.3, −5.3 ppm (2C); HRMS (FAB, NBA matrix): m/z calcd for $C_{19}H_{33}O_4Si$: 353.2148 [M+H]; found: 351.1995 [M+H]$^+$.

(*S*)-(+)-5-(*tert*-Butyldimethylsiloxy)-2-(*p*-methoxybenzyloxy)-1-pentanol (70): DIBAL-H solution (0.94 M in hexane, 45.3 mL, 42.5 mmol) was added dropwise over 20 min to a solution of **69** (5.00 g, 14.1 mmol) in CH_2Cl_2 (141 mL) at −78 °C under argon. After stirring for 1 h, the solution was quenched by the addition of a saturated aqueous solution of Rochelle's salt (100 mL) and stirred for 1 h at RT. The organic layer was then separated, and the aqueous layer was extracted with $CHCl_3$ (150 mL×3). The combined organic extracts were washed with a saturated aqueous solution of Rochelle's salt (75 mL×3), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=5:1) gave **70** as colorless oil (4.69 g, 93%; >99% *ee*). R_f=0.15 (silica gel, hexane/EtOAc=1:1); $[\alpha]_D^{27}=+16.0$ (c=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ=7.27 (d, J=8.6 Hz, 2H; 2-O-CH$_2$-*Ph*-OCH$_3$), 6.88 (d, J=8.6 Hz, 2H; 2-O-CH$_2$-*Ph*-OCH$_3$), 4.56 (d, J=11.2 Hz, 1H; 2-O-C*H*$_2$-Ph-OCH$_3$), 4.46 (d, J=11.2 Hz, 1H; 2-O-C*H*$_2$-Ph-OCH$_3$), 3.80 (s, 3H; 2-O-CH$_2$-Ph-OC*H*$_3$), 3.61

(t, $J=5.9$ Hz, 2H; 5-H), 3.73–3.48 (complex m, 3H; 1-H_2, 2-H), 1.70–1.51 (complex m, 4H; 3-H_2, 4-H_2), 0.89 (s, 9H; 5-OSi[CH_3]$_2$C(CH_3)$_3$), 0.05 ppm (s, 6H; 5-OSi[CH_3]$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=159.3$, 130.5, 129.4 (2C), 113.9 (2C), 79.2, 71.1, 64.2, 63.0, 55.3, 28.5, 27.0, 26.0 (3C), 18.3, −5.3 ppm (2C); IR (NaCl): $\tilde{\nu}=3437$ cm^{-1} (-OH); HRMS (FAB, NBA matrix): *m/z* calcd for $C_{19}H_{35}O_4Si$: 355.2305 [*M*+H]; found: 355.2312 [*M*+H]$^+$.

(3*S*,4*S*)-(+)-S-Ethyl-7-*tert*-butyldimethylsiloxy-3-hydroxy-4-(*p*-methoxybenzyloxy)thioheptanate (42): Oxalyl chloride (0.956 mL, 10.9 mmol) was slowly added over 5 min to a solution of DMSO (1.55 mL, 21.9 mmol) in CH_2Cl_2 (50.0 mL) at −78 °C under argon. The solution was stirred over 15 min, then **70** (1.94 g, 5.48 mmol) in CH_2Cl_2 (4.8 mL) was added dropwise at −78 °C. After stirring for 30 min at −78 °C, TEA (3.82 mL, 27.4 mmol) was added to the solution, and then it was warmed to 0 °C. The mixture was stirred for 15 min, and quenched with H_2O (20 mL). Then the two layers were separated, and the aqueous layer was extracted with hexane/EtOAc (1/1; 100 mL). The combined organic extracts were washed with H_2O (30 mL×2), saturated aqueous NH_4Cl (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (10 mL×2), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude aldehyde **41**, which was used in the next reaction without further purification. $TiCl_4$ (1.0 M in CH_2Cl_2; 4.52 mL, 4.52 mmol) was added to a solution of Ti(O-*i*Pr)$_4$ (441 μL, 1.51 mmol) in CH_2Cl_2 (14.8 mL) at 0 °C. After stirring for 30 min, the mixture, as a solution of $TiCl_3$(O-*i*Pr), was then cooled to −78 °C. Crude aldehyde **41** in CH_2Cl_2 (40 mL) was added by using a cannula to a solution of $TiCl_3$(O-*i*Pr) in CH_2Cl_2 at −78 °C, and the resulting mixture was stirred for 10 min. 1-Ethylthio-1-trimethylsilyloxyethene (1.95 mL, 9.90 mmol) was then added to the mixture. After stirring for 2 h, the cooled mixture was added to a saturated aqueous solution of $NaHCO_3$ (60 mL)by using a cannula with stirring at RT over 30 min. The resulting mixture was extracted with $CHCl_3$ (80 mL) and the extracts was washed with a saturated aqueous solution of $NaHCO_3$ (60 mL) and brine (60 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (hexane/EtOAc=5:1) gave **42** as a colorless oil (1.61 g, 64% for 2 steps; >99% *ee*). $R_f=0.5$ (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{25}=+1.93$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=7.27$–7.20 (complex m, 2H; 4-OCH$_2$-*Ph*-OCH$_3$), 6.91–6.85 (complex m, 2H; 4-OCH$_2$-*Ph*-OCH$_3$), 4.57 (d, $J=10.9$ Hz, 1H; 4-OCH_2-Ph-OCH$_3$), 4.45 (d, $J=10.9$ Hz, 1H; 4-OCH_2-Ph-OCH$_3$), 4.12 (ddd, $J=2.3$, 6.3, 10.6 Hz, 1H; 3-H), 3.81 (s, 3H; 4-OCH$_2$-Ph-OCH_3), 3.61 (t, $J=5.6$ Hz, 2H; 7-H_2), 3.37 (dd, $J=$ 4.6, 8.9 Hz, 1H; 4-H), 2.90 (q, $J=7.6$ Hz, 2H; 1-SCH_2CH$_3$), 2.74 (apparent d, $J=7.0$ Hz, 2H; 2-H_2), 1.76–1.54 (complex m, 2H; 5-H_2), 1.76–1.54 (complex m, 2H; 6-H_2), 1.25 (t, $J=7.3$ Hz, 3H; 1-SCH$_2$CH_3), 0.90 (s, 9H; 7-OSi[CH_3]$_2$C(CH_3)$_3$), 0.05 ppm (s, 6H; 7-OSi[CH_3]$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=198.5$, 159.3, 130.2, 129.5 (2C), 113.8 (2C), 80.1, 71.8, 69.4, 63.0, 55.2, 47.4, 28.6, 26.0, 25.9 (3C), 23.4, 14.5, 18.3, −5.3 ppm (2C); IR (NaCl): $\tilde{\nu}=3425$ cm^{-1} (-OH), 1685 (C=O, ester); HRMS (FAB, NBA matrix): *m/z* calcd for $C_{23}H_{40}O_5SSiNa$: 479.2263 [*M*+Na]; found: 479.2245 [*M*+Na]$^+$.

(3*S*,4*S*)-(+)-7-(*tert*-Butyldimethylsiloxy)-3-hydroxy-4-(*p*-methoxybenzyloxy)heptanol (71): The solution of **42** (4.06 g, 8.90 mmol) in THF (44.5 mL) was treated with $LiBH_4$ (0.969 g, 44.5 mmol) under stirring for 2 h at −10 °C. A saturated aqueous solution of $NaHCO_3$ (20 mL), then H_2O (20 mL), and EtOAc (200 mL) were added to the resulting mixture. The two layers mixture was separated, and the aqueous layer was extracted with EtOAc (200 mL×4). The combined organic layers were washed with H_2O (80 mL) and brine (80 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc=1:1) afforded **71** as a colorless oil (3.11 g, 88%). $R_f=$ 0.10 (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{25}=+12.4$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=7.28$–7.20 (complex m, 2H; 4-O-CH$_2$-*Ph*-OCH$_3$), 7.00–6.83 (complex m, 2H; 4-O-CH$_2$-*Ph*-OCH$_3$), 4.43 (d, 1H; $J=10.9$ Hz, 4-O-CH_2-Ph-OCH$_3$), 4.42 (d, $J=10.9$ Hz, 1H; 4-O-CH_2-Ph-OCH$_3$), 3.89–3.74 (complex m, 3H; 1-H_2, 3-H), 3.81 (s, 3H; 4-O-CH$_2$-Ph-OCH_3), 3.62 (t, $J=5.6$ Hz, 2H; 7-H_2), 3.34 (apparent dd, $J=4.9$, 5.9 Hz, 1H; 4-H), 1.75–1.68 (complex m, 2H; 2-H_2), 1.63–1.52 (complex m, 4H; 5-H_2, 6-H_2), 0.90 (s, 9H; 7-OSi[CH_3]$_2$C(CH_3)$_3$), 0.05 ppm (s, 6H; 7-OSi-[CH_3]$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=159.3$, 130.2, 129.5 (2C), 113.9 (2C), 81.1, 72.7, 71.9, 63.0, 61.3, 55.2, 34.7 (C-2), 28.0, 26.1, 25.9 (3C), 18.3, −5.3 ppm (2C); IR (NaCl): $\tilde{\nu}=3425$ cm^{-1} (OH); HRMS (FAB, NBA matrix): *m/z* calcd for $C_{21}H_{39}O_5Si$: 399.2567 [*M*+H]; found: 399.2561 [*M*+H]$^+$.

(3*S*,4*S*)-(+)-7-(*tert*-Butyldiphenylsiloxy)-1,4,5-heptanetriol (72): DMAP (93.9 mg, 768 μmol), TEA (1.61 mL, 11.5 mmol) and TBDPSCl (2.36 mL, 9.22 mmol) were added to a solution of **71** (3.06 g, 7.68 mmol) in CH_2Cl_2 (76.8 mL) at 0 °C under argon. After stirring for 3 h, the mixture was warmed to RT and stirred for a further 3.5 d. The reaction was quenched with a saturated aqueous solution of NH_4Cl (30 mL) and extracted with $CHCl_3$ (80 mL×3). The combined extracts were washed with brine (80 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford crude product, which was used in the next reaction without further purification. 20 wt% Pd(OH)$_2$/C (539 mg, 768 μmol) was added to a solution of crude product in EtOAc (76.8 mL) at RT. After stirring for 2 h under H_2, the reaction solution was filtered through a Celite pad to remove the Pd(OH)$_2$ catalyst, then the pad was washed with EtOAc. The filtrate was concentrated, and purification by flash chromatography on silica gel ($CHCl_3$/MeOH=10:1) gave **72** as a colorless oil (2.80 g, 90% for 2 steps). $R_f=0.70$ (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{26}=-1.22$ ($c=1.00$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) $\delta=7.70$–7.62 (complex m, 4H; 7-OSi(*Ph*)$_2$C(CH_3)$_3$), 7.50–7.34 (complex m, 6H; 7-OSi(*Ph*)$_2$C-(CH_3)$_3$), 3.90 (d, $J=5.3$ Hz, 1H; 1-H_2), 3.88 (d, $J=4.6$ Hz, 1H; 1-H_2), 3.76 (m, 1H; 5-H), 3.73–3.60 (complex m, 2H; 7-H_2), 3.50 (m, 1H; 4-H), 1.89–1.47 (complex m, 2H; 6-H_2), 1.89–1.47 (complex m, 4H; 3-H_2, 2-H_2), 1.04 ppm (s, 9H; 7-OSi(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=135.4$ (4C), 132.9 (2C), 129.8 (2C), 127.7 (4C), 74.3, 73.5, 62.6, 60.4, 35.1, 30.4, 29.1, 26.7 ppm (3C); IR (NaCl) $\tilde{\nu}=3425$ cm^{-1} (-OH), 1513 (Ar-C); HRMS (FAB, NBA PEG 200+400+NaI matrix): *m/z* calcd for $C_{23}H_{34}O_4SiNa$: 425.2124 [*M*+Na]; found: 425.2126 [*M*+Na]$^+$.

(3*S*,4*S*)-(−)-7-(*tert*-Butyldiphenylsiloxy)-3,4-*O*-isopropylideneheptanol (73): 2,2-Dimethoxypropane (1.60 mL, 13.0 mmol) and TsOH•H_2O (124 mg, 651 μmol) were added to a solution of **72** (2.62 g, 6.51 mmol) in acetone (65.1 mL) at RT. After stirring for 5 min, the reaction mixture was quenched with a saturated aqueous solution of $NaHCO_3$ (20 mL). The resulting two layers were separated, and the aqueous layer was extracted with $CHCl_3$ (60 mL×3), the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography on silica gel (hexane/EtOAc=2:1) afforded **73** as a colorless oil (2.80 g, 97%). $R_f=0.30$ (silica gel, hexane/EtOAc=3:1); $[\alpha]_D^{25}=$ −19.1 ($c=1.00$, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta=7.69$–7.64 (complex m, 4H; 7-OSi(*Ph*)$_2$C(CH_3)$_3$), 7.46–7.34 (complex m, 6H; 7-OSi(*Ph*)$_2$C(CH_3)$_3$), 3.83 (m, 1H; 5-H), 3.88–3.78 (complex m, 2H; 1-H_2), 3.71–3.61 (complex m, 2H; 7-H_2), 3.66 (m, 1H; 4-H), 1.87–1.64 (complex m, 6H; 2-H_2, 3-H_2, 6-H_2), 1.38 (s, 3H; 3,4-*Oi*Pr), 1.36 (s, 3H; 3,4-*Oi*Pr), 1.05 ppm (s, 9H; 1-OSi(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): $\delta=$ 135.5 (4C), 133.6 (2C), 129.6 (2C), 127.6 (4C), 108.1, 80.8, 77.6, 62.6, 60.6, 35.5, 29.5, 29.2, 27.2, 27.1, 26.8 (3C), 19.1 ppm; IR (NaCl): $\tilde{\nu}=$ 3425 cm^{-1} (OH); HRMS (FAB, NBA matrix): *m/z* calcd for $C_{26}H_{39}O_4Si$: 443.2618 [*M*+H]; found: 443.2626 [*M*+H]$^+$.

(4*S*,2′*S*,3′*R*,6′*S*,7′*S*)-(−)-3-[9′-(*tert*-Butyldiphenylsilyloxy)-2′-chloro-3′-hydroxy-6′,7′-*O*-isopropylidenenonanoyl]-4-benzyloxazolidinone (74): According to the procedure for **67**, compound **74** (2.69 g, 62% for 2 steps) was obtained from **73** (2.69 g, 6.08 mmol). $R_f=0.39$ (silica gel, hexane/EtOAc=2:1); $[\alpha]_D^{25}=-6.0$ ($c=1.26$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.70$–7.66 (complex m, 4H; 9′-O-Si(*Ph*)$_2$C(CH_3)$_3$), 7.43–7.29 (complex m, 3H; 4-CH$_2$*Ph*), 7.43–7.29 (complex m, 6H; 9′-O-Si(*Ph*)$_2$C-(CH_3)$_3$), 7.26–7.21 (complex m, 2H; 4-CH$_2$*Ph*), 5.70 (d, $J=3.2$ Hz, 1H; 2′-H), 4.73 (dddd, $J=3.2$, 3.5, 7.0, 9.1 Hz, 1H; 4-H), 4.27 (dd, $J=7.0$, 9.0 Hz, 1H; 4-CH_2Ph), 4.23 (dd, $J=3.5$, 9.0 Hz, 1H; 4-CH_2Ph), 4.17 (ddd, $J=3.2$, 5.0, 8.7 Hz, 1H; 3′-H), 3.86 (ddd, $J=5.0$, 8.5, 9.0 Hz, 1H; 7′-H), 3.84 (t, $J=6.0$ Hz, 2H; 9′-H_2), 3.68 (ddd, $J=2.7$, 8.5, 8.5 Hz, 1H; 6′-H), 3.35 (dd, $J=3.2$, 13.5 Hz, 1H; 5-H_2), 2.84 (dd, $J=9.1$, 13.5 Hz, 1H; 5-H_2), 1.88 (m, 1H; 8′-H_2), 1.87 (m, 1H; 5′-H_2), 1.86–1.78 (complex m, 2H; 4′-H_2), 1.75 (m, 1H; 8′-H_2), 1.58 (m, 1H; 5′-H_2), 1.39 (s, 3H; 6′, 7′-*O*-*i*Pr), 1.36 (s, 3H; 6′, 7′-*O*-*i*Pr), 1.06 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (75.0 MHz, $CDCl_3$): $\delta=168.2$ (C-1′), 152.6 (C-2), 135.5 (2C, 9′-O-Si(*Ph*)$_2$C(CH_3)$_3$), 135.5 (2C, 9′-O-Si(*Ph*)$_2$C(CH_3)$_3$), 134.6 (1C, 4-CH$_2$*Ph*), 133.8 (1C, 9′-O-Si(*Ph*)$_2$C(CH_3)$_3$), 133.7 (1C, 9′-O-Si(*Ph*)$_2$C-

(CH_3)$_3$), 129.6 (1C, 9′-O-Si(Ph)$_2$C(CH_3)$_3$), 129.5 (1C, 9′-O-Si(Ph)$_2$C-(CH_3)$_3$), 129.4 (2C, 4-CH_2Ph), 129.0 (2C, 4-CH_2Ph), 127.6 (2C, 9′-O-Si(Ph)$_2$C(CH_3)$_3$), 127.6 (2C, 9′-O-Si(Ph)$_2$C(CH_3)$_3$), 127.5 (1C, 4-CH_2Ph), 108.1 (1C, 6′,7′-*O*-*i*Pr), 80.6 (C-6′), 77.5 (C-7′), 71.3 (C-3′), 66.5 (C-5), 60.6 (C-9′), 59.8 (C-2), 55.4 (C-4), 37.2 (1C, 4-CH_2Ph), 35.5 (C-8), 30.6 (C-4′), 28.3 (C-5′), 27.3 (1C, 6′,7′-*O*-*i*Pr), 27.2 (1C, 6′,7′-*O*-*i*Pr), 26.8 (3C, 9′-O-Si(Ph)$_2$C(CH_3)$_3$), 19.1 ppm (1C, 9′-O-Si(Ph)$_2$$C$($CH_3$)$_3$); IR (KBr): $\tilde{\nu}$ = 3444 (-OH), 1782 (C=O, imide), 1711 cm^{-1} (C=O, amide); HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{38}H_{49}NO_7SiCl$: 694.2967 [*M*+H]; found: 694.2987 [*M*+H]$^+$.

(2*S*,3*R*,6*R*,7*S*)-Ethyl-9-(*tert*-butyldiphenylsilyloxy)-2,3-epoxy-6,7-*O*-isopropylidenenonanate (major) and (2*R*,3*R*,6*R*,7*S*)-ethyl-9-(*tert*-butyldiphenylsilyloxy)-2,3-epoxy-6,7-*O*-isopropylidenenonanate (minor) (75): NaH (60 wt% in mineral oil, 176 mg, 4.39 mmol) was added to a solution of chlorohydrin **74** (2.77 g, 3.99 mmol) in EtOH (20.0 mL) at 0°C. After stirring for 20 min, a saturated aqueous solution of NH_4Cl (15 mL) and $CHCl_3$ (80 mL) were added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (40 mL × 2), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 10:1) gave a mixture of *trans*- and *cis*-**75** (5.8:1) as a colorless oil (1.85 g, 88%). R_f = 0.58 (silica gel, hexane/EtOAc = 2:1); $[\alpha]_D^{25}$ = +11.2 (*c* = 1.00, $CHCl_3$) as mixture of *trans* and *cis* (5.8:1); ^{1}H NMR (270 MHz, $CDCl_3$), major isomer is indicated. δ = 7.70–7.63 (complex m, 4H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 7.47–7.33 (complex m, 6H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 4.32–4.11 (complex m, 2H; 1-OCH_2CH$_3$), 4.27 (m, 1H; 7-H), 4.07 (ddd, *J* = 3.6, 5.3, 9.2 Hz, 1H; 6-H), 3.81 (t, *J* = 6.6 Hz, 2H; 9-H$_2$), 3.23 (d, 1.7 Hz, 1H; 2-H), 3.21 (m, 1H; 3-H), 1.92–1.42 (complex m, 6H; 4-H$_2$, 5-H$_2$, 8-H$_2$), 1.37 (s, 3H; 6,7-*O*-*i*Pr), 1.32 (s, 3H; 6,7-*O*-*i*Pr), 1.30 (t, *J* = 7.3 Hz, 3H; 1-OCH$_2$CH_3), 1.5 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$), major isomer is indicated. δ = 168.8, 135.3 (2C), 135.2 (2C), 133.4, 133.3, 129.3 (2C), 127.4 (2C), 127.4 (2C), 107.3, 76.5, 74.3, 61.1, 60.7, 57.5, 52.7, 32.3, 28.2, 27.8, 26.6 (3C), 25.8, 25.6, 18.9, 13.8 ppm; IR (NaCl): $\tilde{\nu}$ = 1751 (C=O, ester), 1736, 1429, 1369, 1248, 1196, 1111, 1086, 1030, 823, 741, 702, 615 cm^{-1}; HRMS (FAB, NBA + NaI matrix): *m*/*z* calcd for $C_{30}H_{42}O_6SiNa$: 549.2648 [*M*+Na]; found: 549.2659 [*M*+Na]$^+$.

(2*R*,3*R*,6*R*,7*S*)-Ethyl-2-azido-9-(*tert*-butyldiphenylsilyloxy)-3-hydroxy-6,7-*O*-isopropylidenenonanate (major) and (2*S*,3*S*,6*R*,7*S*)-ethyl-3-azido-9-(*tert*-butyldiphenylsilyloxy)-2-hydroxy-6,7-*O*-isopropylidenenonanate (minor) (76): NH_4Cl (282 mg, 5.27 mmol) and NaN_3 (343 mg, 5.27 mmol) were added to a solution of mixture of **75** (1.85 g, 3.52 mmol) in EtOH/H_2O (20:1) (35.2 mL) at RT and the reaction mixture was warmed to 60°C. After stirring for 38 h, the reaction mixture was cooled to RT and diluted with EtOAc (200 mL). The resulting single layer was washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 8:1) gave a 3:1 mixture of **76** as a inseparable mixture (1.08 g, 56%). R_f = 0.59 (silica gel, hexane/EtOAc = 2:1); IR (NaCl) $\tilde{\nu}$ = 3458 (-OH), 2110 (-N=N$^+$=N$^-$), 1739 (C=O, ester), 1473, 1429, 1369, 1248, 1219, 1111, 1088, 1026, 823, 740, 704, 613 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{30}H_{44}N_3O_6Si$: 570.2999 [*M*+H]; found: 570.2999 [*M*+H]$^+$.

(2*R*,3*S*,6*R*,7*S*)-(−)-Ethyl-9-(*tert*-butyldiphenylsilyloxy)-2,3-imino-6,7-*O*-isopropylidenenonanate (major) and (2*S*,3*S*,6*R*,7*S*)-(+)-ethyl-9-(*tert*-butyldiphenylsilyloxy)-2,3-imino-6,7-*O*-isopropylidenenonanate (minor) (77): PPh_3 (1.03 g, 3.93 mmol) was added to a solution of the mixture of **76** (1.72 g, 3.02 mmol) in MeCN (30.2 mL) under Ar at RT. After stirring for 30 min, the reaction solution was warmed to 80°C and stirred for 21 h. Then the solution was cooled to RT and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 8:1) gave *trans*-**77** (1.21 g, 76%; single isomer) and *cis*-**77** (157 mg, 13%; single isomer) as colorless oils. *trans*-**77**: R_f = 0.39 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{26}$ = −35.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.70–7.62 (complex m, 4H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 7.46–7.33 (complex m, 6H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 4.25 (dq, *J* = 6.3, 12.5 Hz, 2H; 1-OCH_2CH$_3$), 4.18 (m, 1H; 7-H), 4.03 (ddd, *J* = 5.6, 5.6, 8.3 Hz, 1H; 6-H), 3.81 (t, *J* = 6.3 Hz, 2H; 9-H$_2$), 2.34 (d, *J* = 2.3 Hz, 1H; 2-H), 2.28 (br m, 1H; 3-H), 1.82–1.65 (complex m, 4H; 5-H$_2$, 8-H$_2$), 1.60–1.33 (complex m, 2H; 4-H$_2$), 1.37 (s, 3H; 6,7-*O*-*i*Pr), 1.31 (s, 3H; 6,7-*O*-*i*Pr), 1.31 (t, *J* = 7.3 Hz, 3H; 1-OCH$_2$CH_3), 1.05 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 172.4, 135.4 (4C), 133.6, 133.5, 129.4 (2C), 127.5 (2C), 127.5 (2C), 107.4, 77.5, 74.4, 61.3, 60.8, 39.2, 35.2, 32.5, 29.6, 28.4, 27.5, 26.7 (3C), 25.8, 19.0, 14.0 ppm; IR (NaCl): $\tilde{\nu}$ = 3286 (NH), 1741 (C=O, ester), 1462, 1429, 1369, 1217, 1111, 1088, 823, 702, 688, 613 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{30}H_{44}NO_5Si$: 526.2989 [*M*+H]; found: 526.2993 [*M*+H]$^+$. *cis*-**77**: R_f = 0.23 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{26}$ = +14.6 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.75–7.62 (complex m, 4H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 7.46–7.30 (complex m, 6H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 4.26 (m, 1H; 7-H), 4.21 (dq, *J* = 2.3, 6.9 Hz, 2H; 1-OCH_2CH$_3$), 4.05 (dd, *J* = 5.9, 12.9 Hz, 1H; 6-H), 3.81 (t, *J* = 6.3 Hz, 2H; 9-H$_2$), 2.65 (br d, *J* = 5.6 Hz, 1H; 2-H), 2.28–2.18 (br m, 1H; 3-H), 1.82–1.45 (complex m, 6H; 4-H$_2$, 5-H$_2$, 8-H$_2$), 1.36 (s, 3H; 6,7-*O*-*i*Pr), 1.31 (s, 3H; 6,7-*O*-*i*Pr), 1.29 (t, *J* = 6.9 Hz, 2H; 1-OCH$_2$CH_3), 1.05 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); IR (NaCl): $\tilde{\nu}$ = 3446 (-NH), 1728 (C=O, ester), 1653, 1462, 1423, 1379, 1248, 1217, 1198, 1111, 1086, 1032, 823, 741, 704 cm^{-1}; HRMS (FAB, NBA + NaI matrix): *m*/*z* calcd for $C_{30}H_{44}NO_5Si$: 548.2808 [*M*+Na]; found: 548.2784 [*M*+Na]$^+$.

(2*S*,3*S*,6*R*,7*S*)-(−)-Ethyl-2-azido-9-(*tert*-butyldiphenylsilyloxy)-3-(*p*-nitrobenzensulfonylimino)-6,7-*O*-isopropylidenenonanate (78): TEA (327 μL, 2.35 mmol), 4-nitrobenzenesulfonyl chloride (312 mg, 1.41 mmol), and DMAP (28.7 mg, 235 μmol) were added to a solution of *trans*-**77** (247 mg, 470 μmol) in CH_2Cl_2 (9.40 mL) under argon at 0°C, and then warmed to RT. After stirring for 4 h at RT, the reaction solution was quenched with a saturated aqueous solution of NH_4Cl (7.0 mL), the organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (10 mL × 3). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), a saturated aqueous solution of NH_4Cl (10 mL × 2), H_2O (10 mL), and brine (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was roughly purified with silica gel (hexane/EtOAc = 2:1) to provide the residue of Ns-aziridine. The residue was dissolved in DMF (4.70 mL), and then NaN_3 (61.2 mg, 0.940 mmol) was added to the solution at 0°C under argon, and then the reaction mixture was warmed to RT. After stirring for 1 h, the solution was diluted with hexane/EtOAc (2:1; 20 mL). The mixture was washed with H_2O (10 mL × 6), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to provide a crude mixture. Flash chromatography on silica gel (hexane/EtOAc = 6:1) gave **78** as a colorless oil (331 mg, 93% for 2 steps; >20:1 = α-/β-N$_3$). R_f = 0.62 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{27}$ = −24.1 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$): δ = 8.34 (ddd, *J* = 2.2, 2.2, 8.6 Hz, 2H; *N*″-S(O$_2$)-*Ph*-NO$_2$), 8.08 (ddd, *J* = 2.2, 2.2, 8.6 Hz, 2H; *N*″-S(O$_2$)-*Ph*-NO$_2$), 7.70–7.62 (complex m, 4H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 7.48–7.34 (complex m, 6H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 5.44 (d, *J* = 9.5 Hz, 1H; 3-N*H*), 4.26 (m, 1H; 7-H), 4.24 (q, *J* = 7.0 Hz, 2H; 1-OCH_2CH$_3$), 4.14 (d, *J* = 4.3 Hz, 1H; 2-H), 3.87 (ddd, *J* = 5.7, 9.7, 15.1 Hz, 1H; 6-H), 3.78 (m, 1H; 3-H), 3.76 (t, *J* = 8.6 Hz, 2H; 9-H$_2$), 1.72–1.38 (complex m, 6H; 4-H$_2$, 5-H$_2$, 8-H$_2$), 1.34 (s, 3H; 6,7-*O*-*i*Pr), 1.30 (s, 3H; 6,7-*O*-*i*Pr), 1.30 (t, *J* = 7.0 Hz, 3H; 1-OCH$_2$CH_3), 1.05 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 167.7, 149.8, 146.6, 135.4 (4C), 133.6, 133.4, 129.5 (2C), 128.1 (2C), 127.6 (4C), 124.2 (2C), 107.5, 74.1, 65.3, 62.3, 60.6, 60.2, 55.3, 36.5, 28.1, 27.4, 26.7 (3C), 26.5, 25.6, 19.1, 14.0 ppm; IR (NaCl) $\tilde{\nu}$ = 3292 (-NH), 2114 (-N=N$^+$=N$^-$), 1741 (C=O, ester), 1533 (NO$_2$), 1427, 1350 (SO$_2$), 1217, 1167 (N-SO$_2$), 1111, 1092, 854, 737, 704, 687 cm^{-1}; HRMS (FAB, NBA + NaI matrix): *m*/*z* calcd for $C_{36}H_{47}N_5O_9SiSNa$: 776.2761 [*M*+Na]; found: 776.2771 [*M*+Na]$^+$.

(2*S*,3*S*,6*R*,7*S*)-(−)-Ethyl-3-amino-2-azido-9-(*tert*-butyldiphenylsiloxy)-6,7-*O*-isopropylidenenonanate (43): Compound **78** (331 mg, 439 μmol) was dissolved in MeCN (4.39 mL), and then thiophenol (226 μL, 2.20 mmol) and DIPEA (382 μL, 2.20 mmol) were added to the solution at RT under Ar. After stirring for 6 h, the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). Then the mixture was extracted with $CHCl_3$ (20 mL × 3). The organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 2:1) gave **43** as a colorless oil (161 mg, 65%). R_f = 0.24 (silica gel, hexane/EtOAc = 1:1); $[\alpha]_D^{25}$ = −22.4 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (270 MHz, CD_2Cl_2): δ = 7.70–

7.62 (complex m, 4H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.47–7.33 (complex m, 6H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 4.26 (m, 1H; 7-H), 4.25 (dq, J=1.0, 6.9 Hz, 2H; 1-OC*H*$_2$CH$_3$), 4.02 (ddd, J=3.3, 5.9, 9.3 Hz, 1H; 6-H), 3.87 (d, J=5.3 Hz, 1H; 2-H), 3.82 (d, J=5.6 Hz, 1H; 9-*H*$_2$), 3.79 (d, J=5.6 Hz, 1H; 9-*H*$_2$), 3.12 (ddd, J=4.0, 5.3, 8.9 Hz, 1H; 3-H), 1.78–1.32 (complex m, 6H; 4-H$_2$, 5-H$_2$, 6-H$_2$), 1.34 (s, 3H; 6,7-*O*-*i*Pr), 1.29 (s, 3H; 6,7-*O*-*i*Pr), 1.30 (t, J=7.3 Hz, 3H; 1-OCH$_2$C*H*$_3$), 1.04 ppm (s, 9H; 9-O-Si(Ph)$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (67.5 MHz, CDCl$_3$): δ=168.8, 135.4 (3C), 135.4, 133.6, 133.6, 129.5, 129.4, 127.5 (4C), 107.4, 77.9, 74.5, 67.7, 61.7, 60.9, 53.2, 32.5, 30.2, 28.4, 26.7 (3C), 26.7, 25.8, 19.1, 14.1 ppm; IR (NaCl): $\tilde{\nu}$=3394 (-NH), 2108 (-N=N$^+$=N$^-$), 1739 (C=O, ester), 1379, 1367, 1246, 1217, 1194, 1169, 1111, 1088, 1028, 823, 741, 702, 615 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for C$_{30}$H$_{45}$N$_4$O$_5$Si: 569.3159 [M+H]; found: 569.3149 [M+H]$^+$.

(2*S*,3*S*,6*R*,7*S*,2′*R*)-(−)-Ethyl-2-azido-3-(2′-bromopropanamido)-9-(*tert*-butyldiphenylsilyloxy)-6,7-*O*-isopropylidenenonanate (79): Compound (*R*)-**10** (50.5 μL, 562 μmol), PyBOP (292 mg, 562 μmol), and DIPEA (120 μL, 0.703 mmol) were added to a solution of **43** (160 mg, 281 μmol) in CH$_2$Cl$_2$ (9.37 mL) at RT under argon. After stirring for 60 min, a saturated aqueous solution of NH$_4$Cl (3.0 mL) was added to the reaction mixture. Then, the organic layer was separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ (7.0 mL×3). The combined organic extracts were washed with a saturated aqueous solution of NaHCO$_3$ (20 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=15:1) gave **79** as a colorless oil (188 mg, 95%). R_f=0.52 (silica gel, hexane/EtOAc=1:1); $[\alpha]_D^{23}=-21.1$ (c=1.00, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$): δ=7.70–7.61 (complex m, 4H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.47–7.34 (complex m, 6H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 6.56 (d, J=8.6 Hz,1H; 3-N*H*), 4.37 (m, 1H; 3-H), 4.32 (q, J=7.3 Hz, 1H; 2′-H), 4.29 (q, J=6.9 Hz, 2H; 1-OC*H*$_2$CH$_3$), 4.27 (m, 1H; 7-H), 4.26 (d, J=4.3 Hz, 1H; 2-H), 3.99 (dd, J=5.6, 12.5 Hz, 1H; 6-H), 3.80 (t, J=5.9 Hz, 2H; 9-H$_2$), 1.85 (d, J=7.3 Hz, 3H; 3′-H$_3$), 1.84 (m, 1H; 8-*H*$_2$), 1.77–1.62 (complex m, 3H; 5-H$_2$, 8-*H*$_2$,), 1.61–1.28 (complex m, 2H; 4-H$_2$), 1.37 (s, 3H; 6,7-*O*-*i*Pr), 1.31 (s, 3H; 6,7-*O*-*i*Pr), 1.33 (t, J=6.9 Hz, 3H; 1-OCH$_2$C*H*$_3$), 1.05 ppm (s, 9H; 9-O-Si(Ph)$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (67.5 MHz, CDCl$_3$): δ=169.4, 168.1, 135.4 (2C), 135.4 (2C), 133.7, 133.5, 129.5 (2C), 127.6 (4C), 107.5, 77.4, 74.5, 64.1, 62.2, 60.9, 51.1, 44.4, 32.3, 30.8, 28.3 (2C), 26.8 (3C), 25.8, 22.6, 19.1, 14.1 ppm; IR (NaCl): $\tilde{\nu}$=3296 (-NH), 2112 (-N=N$^+$=N$^-$), 1741 (C=O, ester), 1658 (C=O, amide), 1379, 1369, 1248, 1217, 1111, 1086, 1026, 823, 740, 702 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for C$_{33}$H$_{48}$N$_4$O$_6$BrSi: 703.2527 [M+H]; found: 703.2532 [M+H]$^+$.

(3*S*,5*S*,6*S*,3′*S*,4′*R*)-(+)-4-(*tert*-Butoxycarbonyl)-6-[1′-(*tert*-butyldiphenylsiloxy)-3′,4′-*O*-isopropylidenehexane-6′-yl]-5-ethyloxycarbonyl-3-metyl-2-piperazinone (81): PPh$_3$ (197 mg, 1.02 mmol) and TEA (143 μL, 1.02 mmol) were added to a solution of **79** (239 mg, 339 μmol) in MeCN (3.39 mL) under argon at RT. After stirring for 1 h, H$_2$O (730 μL) was added to the reaction mixture. The resulting mixture was warmed to 60°C and stirred for 7 h. Then the solution was cooled to RT and evaporated under reduced pressure. The crude product was roughly purified by flash chromatography on silica gel (CHCl$_3$/MeOH=120:1) to provide piperazinone **80**. Di-*tert*-butyl dicarbonate (519 mg, 2.37 mmol) was added to a solution of crude **80** in EtOAc (3.39 mL) at RT under argon. After stirring for 60 min at 80°C, the reaction solution was cooled to RT. Then the reaction mixture was diluted with CHCl$_3$ (20 mL), the mixture was washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=10:1) gave **81** as a colorless oil (160 mg, 68% for 2 steps). R_f=0.29 (silica gel, hexane/EtOAc=1:1); $[\alpha]_D^{26}=+2.77$ (c=0.50, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$), as two rotamers. δ=7.70–7.62 (complex m, 4H; 1′-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.47–7.32 (complex m, 6H; 1′-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 5.92 (brs, 1H; 1-H), 5.02 (brs, 5/6H; 5-H), 4.75 (brs, 1/6H; 5-H), 4.52–4.36 (brm, 1H; 3-H), 3.80 (dd, J=6.3, 12.9 Hz, 1H; 3′-H), 4.19 (q, J=7.3 Hz, 2H; 1-OC*H*$_2$CH$_3$), 4.02 (brm, 1H; 4′-H), 3.81 (t, J=5.9 Hz, 2H; 1′-H$_2$), 3.64 (brm, 1H; 6-H), 1.98–1.85 (brm, 1H; 2′-*H*$_2$), 1.69 (dd, J=6.6, 13.2 Hz, 1H; 2′-*H*$_2$), 1.70–1.38 (complex m, 4H; 5′-H$_2$, 6′-H$_2$), 1.59 (d, J=6.9 Hz, 3H; 3-C*H*$_3$), 1.50 (s, 9H; 4-CO-OC(C*H*$_3$)$_3$), 1.38 (s, 3H; 3′,4′-*O*-*i*Pr), 1.33 (s, 3H; 3′,4′-*O*-*i*Pr), 1.28 (t, J=7.3 Hz, 3H; 1-OCH$_2$C*H*$_3$), 1.05 ppm (s, 9H; 1′-O-Si(Ph)$_2$C(C*H*$_3$)$_3$); ^{13}C NMR (67.5 MHz, CDCl$_3$): δ=171.0, 168.6, 154.0, 135.5 (2C), 135.4 (2C), 133.7, 133.5, 129.5, 129.5, 127.5 (2C), 127.5 (2C), 107.6, 81.3, 77.1, 74.3, 61.1, 60.8, 54.1, 54.0, 52.3, 32.5, 28.6, 28.3, 28.2 (3C), 26.7 (3C), 26.5, 25.7, 19.1, 18.2, 14.0 ppm; IR (NaCl): $\tilde{\nu}$=3205 (-NH), 1745 (C=O, ester), 1699 (C=O, urethane), 1676 (C=O, amide), 1473, 1429, 1369, 1329, 1186, 1171, 1111, 1092, 1028, 823, 742, 669 cm^{-1}; HRMS (FAB, NBA matrix): m/z calcd for C$_{38}$H$_{57}$N$_2$O$_8$Si: 697.3884 [M+H]; found: 697.3909 [M+H]$^+$.

(3*S*,5*S*,6*S*,3‴*S*,4‴*R*)-(−)-4-(*tert*-Butoxycarbonyl)-6-[1‴-(*tert*-butyldiphenylsiloxy)-3‴,4‴-*O*-isopropylidenehexane-6‴-yl]- 5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-3-metyl-2-piperazinone (82): Lithium hydroxide (49.9 mg, 2.08 mmol) was added to a solution of **81** (145 mg, 208 μmol) in MeOH/THF/H$_2$O (2:2:1; 4.16 mL) was added at RT. After stirring for 60 min, a saturated aqueous solution of NH$_4$Cl (6.0 mL) was added to the reaction mixture and then it was extracted with CHCl$_3$ (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next reaction without further purification. The residue was dissolved in CH$_2$Cl$_2$ (2.08 mL) and then **19** (102 mg, 416 μmol), DIPEA (72.5 μL, 416 μmol), HOBt (28.1 mg, 208 μmol), and PyBOP (163 mg, 312 μmol) were added at 0°C under Ar. After stirring for 1 h at 0°C, the reaction mixture was warmed to RT, and stirred for further 4 h. Then, the reaction solution was quenched with a saturated aqueous solution of NH$_4$Cl (4.0 mL), the organic layer was separated and the aqueous layer was extracted with CHCl$_3$ (10 mL×3). The combined organic extracts were washed with a saturated aqueous solution of NH$_4$Cl (10 mL), a saturated aqueous solution of NaHCO$_3$ (10 mL), and brine (10 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc=3:1) gave **82** as a colorless oil (131 mg, 70% for 2 steps). R_f=0.25 (silica gel, hexane/EtOAc=1:2); $[\alpha]_D^{26}=-31.0$ (c=1.00, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$) δ=7.72–6.84 (complex m, 4H; 1‴-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.44–7.32 (complex m, 6H; 1‴-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 6.92 (brd, J=6.3 Hz, 1H; 2′-N*H*), 6.53 (brd, J=8.6 Hz, 1H; 2″-N*H*), 6.36 (brs, 1H; 1-H), 4.67 (brs, 1H; 5-H), 4.53–4.35 (complex m, 3H; 3-H, 2′-H, 2″-H), 4.30 (dd, J=6.6, 12.9 Hz, 1H; 3‴-H), 3.99 (dd, J=6.3, 12.9 Hz, 1H; 4‴-H), 3.80 (t, J=5.9 Hz, 2H; 1‴-H$_2$), 3.60 (dd, J=6.3, 12.6 Hz, 1H; 6-H), 2.17 (m, 1H; 3″-H), 1.93–1.82 (complex m, 2H; 6‴-*H*$_2$, 2‴-*H*$_2$), 1.72–1.62 (complex m, 2H; 6‴-*H*$_2$, 2‴-*H*$_2$), 1.55–1.45 (complex m, 2H; 5‴-*H*$_2$), 1.52 (s, 9H; 4-CO-OC(C*H*$_3$)$_3$), 1.46 (d, J=7.2 Hz, 3H; 3-C*H*$_3$), 1.46 (s, 9H; 1″-OC(C*H*$_3$)$_3$), 1.36 (s, 3H; 3‴,4‴-*O*-*i*Pr), 1.30 (s, 3H; 3‴,4‴-*O*-*i*Pr), 1.33 (d, J=6.9 Hz, 3H; 3′-H$_3$), 1.04 (s, 9H; 1‴-O-Si(Ph)$_2$C-(C*H*$_3$)$_3$), 0.90 (d, J=6.6 Hz, 3H; 3″-(C*H*$_3$)$_2$), 0.88 ppm (d, J=6.9 Hz, 3H; 3″-(C*H*$_3$)$_2$); ^{13}C NMR (67.5 MHz, CDCl$_3$): δ=171.5, 170.8, 170.0, 168.1, 154.6, 135.5 (2C), 135.4 (2C), 133.7, 133.6, 129.5, 129.5, 127.5, (2C), 127.5 (2C), 107.6, 81.9, 81.8, 76.9, 74.3, 60.9, 57.4, 53.5, 53.2, 52.1, 48.4, 32.6, 31.1, 28.4, 28.2 (3C), 28.1, 28.0 (6C), 26.8 (2C), 25.7, 19.1, 18.9, 18.1, 18.0, 17.5 ppm; IR (NaCl) $\tilde{\nu}$=3317 (-NH), 1732 (C=O, ester), 1672 (C=O, urethane), 1656 (C=O, amide), 1539, 1369, 1155, 1111, 1086, 756, 704 cm^{-1}; HRMS (FAB, NBA+NaI matrix): m/z calcd for C$_{48}$H$_{74}$N$_4$O$_{10}$SiNa: 917.5072 [M+Na]; found: 917.5096 [M+Na]$^+$.

(3*S*,5*S*,6*S*,3‴*S*,4‴*R*)-(−)-4-(*tert*-Butoxycarbonyl)-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-6-[1‴-hydroxy-3‴,4‴-*O*-isopropylidenehexane-6‴-yl]-3-metyl-2-piperazinone (83): Compound **82** (129 mg, 145 μmol) was dissolved in THF (1.45 mL) and TBAF (1.0 M THF solution, 362 μL, 362 μmol) was added at RT. After stirring for 3 h, a saturated aqueous solution of NH$_4$Cl (5.0 mL) and CHCl$_3$ (5.0 mL) were added, then the two layers were separated, and the aqueous phase was extracted with CHCl$_3$ (10 mL×3). The combined organic layers were washed with brine (20 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (CH$_3$Cl/MeOH=10:1) gave **83** as a colorless oil (75 mg, 79%). R_f=0.30 (silica gel, CHCl$_3$/MeOH=10:1); $[\alpha]_D^{21}=-47.5$ (c=2.00, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$): δ=7.04 (brs, 1H; 2′-N*H*), 6.95 (brs, 1H; 1-H), 6.82 (brd, J=7.0 Hz, 1H; 2″-N*H*), 4.72 (brs, 1H; 5-H), 4.63–4.43 (complex m, 2H; 3-H, 2′-H), 4.30 (dd, J=4.6, 8.9 Hz, 1H; 2″-H), 4.24 (ddd, J=4.9, 5.3, 10.2 Hz, 1H; 3‴-H), 4.05 (ddd, J=3.0, 5.3, 9.6 Hz, 1H; 4‴-H), 3.89–3.71 (complex m, 2H; 1‴-H), 3.68 (dd, J=6.6, 10.9 Hz, 1H; 6-H), 2.88 (brs, 1H; 1‴-O*H*), 2.15 (m, 1H; 3″-H), 1.94–1.78 (complex m, 2H; 6‴-H$_2$), 1.81–1.60 (complex m, 3H; 2‴-H$_2$, 5‴-*H*$_2$), 1.51 (m, 1H; 5‴-*H*$_2$), 1.51 (s,

9H; 1″-OC(CH_3)$_3$), 1.45 (s, 9H; 4-CO-OC(CH_3)$_3$), 1.44 (d, J=7.3 Hz, 3H; 3-CH_3), 1.32 (s, 6H; 3‴,4‴-*O*-*i*Pr), 1.30 (d, J=7.0 Hz, 3H; 3′-H$_3$), 0.90 (d, J=6.9 Hz, 3H; 3″-(CH_3)$_2$), 0.70 ppm (d, J=6.9 Hz, 3H; 3″-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ=171.8, 170.8, 170.4, 168.3, 154.6, 107.8, 83.9, 82.3, 81.9, 76.3, 60.4, 57.4, 53.4, 52.0, 49.9, 48.3, 32.3, 31.2, 28.3 (2C), 28.2 (3C), 28.0 (3C), 26.7, 25.7, 18.9, 18.3, 17.9, 17.5 ppm; IR (NaCl): $\tilde{\nu}$=3327 (NH), 1732 (C=O, ester), 1686 (C=O, urethane), 1666 (C=O, amide), 1539, 1456, 1369, 1315, 1219, 1157, 850, 789 cm^{-1}; HRMS (FAB, NBA+NaI matrix): *m*/*z* calcd for $C_{32}H_{56}N_4O_{10}Na$: 679.3894 [*M*+Na]; found: 679.3920 [*M*+Na]$^+$.

(3*S*,5*S*,6*S*,2′*S*,4′*S*,5′*R*)-(−)-4-(*tert*-Butoxycarbonyl)-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-6-[2′-hydroxy-4′,5′-*O*-isopropylidene-1′-nitrohexane-7′-yl]-3-methyl-2-piperazinone (46): DMSO (73.0 μL, 1.03 mmol), TEA (72.3 μL, 515 μmol), and SO_3·Py (41.0 mg, 2.57 mmol) were added to a solution of **83** (67.7 mg, 103 μmol) in CH_2Cl_2 (2.58 mL) at 0 °C under argon. After stirring for 5 min, then the reaction mixture was warmed to RT and stirred for further 1 h. Then the reaction was quenched with a saturated aqueous solution of NH_4Cl (5 mL), diluted with EtOAc (10 mL), and the two layers were separated. The aqueous layer was extracted with EtOAc (10 mL×3). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl (20 mL×2), H_2O (20 mL), and brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give crude aldehyde **44**, which was used in the next reaction without further purification. Compound (*R*,*R*)-**45** (31.0 mg, 52 μmol) and $MeNO_2$ (167 μL, 3.09 mmol) were added to a solution of **44** in CH_2Cl_2 (2.58 mL) at room temperature. Then the solution was cooled to −40 °C and DIPEA (44.9 μL, 257 μmol) was added. After stirring for 46 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (3.0 mL), then the aqueous layer was extracted with $CHCl_3$ (10 mL×3). The combined organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH= 20:1) gave **46** as a colorless oil (38.9 mg, 53% for 2 steps; 90% *de*). The *de* was determined by HPLC (CHIRALCEL OD 4.6ϕ×250 mm, hexane/2-propanol=99:1, 0.9 mL min^{-1}, 25 °C, 210 nm). R_f=0.50 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{22}$=−52.0 (*c*=1.00, $CHCl_3$); ^{1}H NMR (270 MHz, CD_2Cl_2): δ=6.83 (brs, 1H; 2‴-N*H*), 6.70 (brs, 1H; 2″-N*H*), 6.60 (brs, 1H; 1-H), 4.58 (brs, 1H; 5-H), 4.52–4.33 (complex m, 2H; 3-H, 2′-H), 4.46 (d, J=9.3 Hz, 1H; 1′-H_2), 4.33 (d, J=9.3 Hz, 1H; 1′-H_2), 4.25 (dd, J=4.3, 7.9 Hz, 1H; 2‴-H), 4.19 (dd, J=5.9, 13.5 Hz, 1H; 4′-H), 3.96 (m, 1H; 5′-H), 3.96 (m, 1H; 6-H), 2.04 (m, 1H; 3‴-H), 1.79–1.60 (complex m, 2H; 3′-H_2, 7′-H_2), 1.59–1.36 (complex m, 4H; 3′-H_2, 6′-H$_2$, 7′-H_2), 1.38 (s, 9H; 1‴-OC(CH_3)$_3$), 1.34 (s, 9H; 4-CO-OC(CH_3)$_3$), 1.27 (d, J=6.8 Hz, 3H; 3-CH_3), 1.19 (s, 3H; 4′,5′-*O*-*i*Pr), 1.15 (d, J=6.8 Hz, 3H; 3″-H$_3$), 1.14 (s, 3H; 4′,5′-*O*-*i*Pr), 0.78 (d, J=6.9 Hz, 3H; 3‴-(CH_3)$_2$), 0.74 ppm (d, J=6.9 Hz, 3H; 3‴-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, CD_2Cl_2): δ=171.9, 171.0, 170.7, 168.4, 154.7, 108.1, 82.1, 81.9, 81.4, 77.6, 77.0, 74.2, 67.2, 57.7, 52.8, 52.3, 48.2, 34.5, 31.3, 29.7, 28.2, 28.1 (3C), 27.9, 27.8 (3C), 27.1, 18.9, 18.7, 18.1, 17.4 ppm; IR (NaCl): $\tilde{\nu}$=3327 (-OH, -NH), 1728 (C=O, ester), 1687 (C=O, urethane), 1665 (C=O, amide), 1554 (NO_2), 1520, 1381, 1369, 1315, 1219, 1157, 1074, 877, 847, 756 cm^{-1}; HRMS (FAB, NBA+NaI matrix): *m*/*z* calcd for $C_{33}H_{57}N_5O_{12}Na$: 738.3901 [*M*+Na]; found: 738.3908 [*M*+Na]$^+$.

(3*S*,5*S*,6*S*,2′*S*,4′*S*,5′*R*)-(−)-4-(*tert*-Butoxycarbonyl)-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-6-{1′-[*N*,*N*-di-(*tert*-butoxycarbonyl)guanidino]-2′-hydroxy-4′,5′-*O*-isopropylidenehexane-7′-yl}-3-methyl-2-piperazinone (48): 10% Pd/C (54.4 mg, 51.1 μmol) and ammonium formate (34.3 mg, 544 μmol) were added to a solution of **46** (38.9 mg, 54.4 μmol) in MeOH (1.09 mL) under Ar at RT. After stirring for 2 h, the reaction mixture was filtered through a Celite pad, and the pad was washed with MeOH. The solvent was removed and the residue was dissolved in $CHCl_3$ (30 mL), washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to afford crude amine, which was used in the next reaction without further purification. The crude amine was dissolved in CH_3CN (1.09 mL) and then added **47** (25.3 mg, 81.6 μmol) and *i*PrNEt (14.2 μL, 81.6 μmol) were added at RT. After stirring for 60 min, the solution was evaporated under reduced pressure. Purification by flash chromatography on silica gel ($CHCl_3$/MeOH=100:1) gave **48** as a colorless amorphous solid (28.9 g, 57% for 2 steps). R_f=0.32 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{22}$=−25.6 (*c*=1.00, $CHCl_3$) ^{1}H NMR (300 MHz, CD_2Cl_2): δ=11.48 (s, 1H; 1′-NH-C[N*H*CO-OC(CH_3)$_3$][NCO-OC(CH_3)$_3$]), 8.64 (t, J=5.5 Hz, 1H; 1′-N*H*-C[NHCO-OC(CH_3)$_3$][NCO-OC(CH_3)$_3$]), 7.00 (brs, 1H; 1-H), 6.81 (d, J=8.0 Hz, 1H; 2″-N*H*), 6.57 (brs, 1H; 2‴-N*H*), 5.02–4.86 (brs, 1H; 5-H), 4.71 (brs, 1H; 2″-H), 4.60–4.46 (brm, 1H; 3-H), 4.40 (m, 1H; 2‴-H), 4.31 (m, 1H; 2′-H), 4.05 (ddd, J=3.0, 5.8, 9.2 Hz, 1H; 4′-H), 3.88 (m, 1H; 5′-H), 3.66 (m, 1H; 6-H), 3.61 (ddd, J=2.5, 6.0, 13.8 Hz, 1H; 1′-H_2), 3.34 (ddd, J=5.0, 7.2, 13.8 Hz, 1H; 1′-H_2), 2.15 (m, 1H; 3‴-H), 1.72–1.48 (complex m, 4H; 3′-H_2, 7′-H$_2$, 7′-H_2), 1.51 (s, 9H; 1′-NH-C[NHCO-OC-(CH_3)$_3$][NCO-OC(CH_3)$_3$]), 1.45 (s, 18H; 1′-NH-C[NHCO-OC(CH_3)$_3$]-[NCO-OC(CH_3)$_3$], 4-CO-OC(CH_3)$_3$), 1.42 (d, J=7.0 Hz, 3H; 3-CH_3), 1.40 (s, 9H; 1‴-OC(CH_3)$_3$), 1.31 (s, 6H; 4′,5′-*O*-*i*Pr), 1.28 (d, J=7.0 Hz, 3H; 3″-H$_3$), 0.92 (d, J=7.0 Hz, 3H; 3‴-(CH_3)$_2$), 0.89 ppm (d, J=7.0 Hz, 3H; 3‴-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, CD_2Cl_2): δ=171.7, 170.9, 170.0, 168.4, 163.0, 157.3, 154.4, 153.0, 107.9, 83.3, 81.9, 81.8, 81.6, 79.1, 77.0, 74.7, 69.1, 57.7, 52.8, 52.2, 48.5, 47.8, 35.0, 31.3, 29.7, 28.3, 28.1 (3C), 28.0 (3C), 27.8 (3C), 27.8 (3C), 26.9, 25.6, 18.9, 18.2, 18.0, 17.5 ppm; IR (NaCl): $\tilde{\nu}$=3329 (-NH), 3298 (-OH), 1726 (C=N, guanidyl), 1726 (C=O, ester), 1664 (C=O, urethane), 1654 (C=O, amide), 1620, 1568, 1369, 1327, 1157, 1142, 1055, 877, 849, 810 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{44}H_{78}N_7O_{14}$: 928.5607 [*M*+H]; found: 928.5644 [*M*+H]$^+$.

(3*S*,5*S*,6*S*,2′*S*,3′*R*,4″*R*)-(−)-6-{1′-[*N*,3″-Di-(*tert*-butoxycarbonyl)-2″-imino-imidazolidin-4″-yl]-2′,3′-*O*-isopropylidenehexan-5′-yl}-4-(*tert*-butoxycarbonyl)-5-(*O*^{1}-*tert*-butyl-L-valinyl-L-alanyl)carbonyl-3-methyl-2-piperazinone (50): Pyridine (4.90 μL, 60.3 μmol), methanesulfonic anhydride (34.0 mg, 0.197 mmol), and DMAP (one crystal) were added to a solution of **48** (5.6 mg, 6.03 μmol) in CH_2Cl_2 (0.603 mL) at 0 °C under argon. After stirring for 30 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (2.0 mL). Then the mixture was extracted with $CHCl_3$ (5 mL×3). The combined organic extracts were washed with a saturated aqueous solution of NH_4Cl (5.0 mL), a saturated aqueous solution of $NaHCO_3$ (5.0 mL), and brine (5.0 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next reaction without further purification. The crude mesylate was dissolved in MeCN (603 μL), DIPEA (2.60 μL) was added, and the mixture was heated to 65 °C and stirred for 4 h. The reaction mixture was then cooled to RT and concentrated to afford the crude material, which was purified by preparative TCL ($CHCl_3$/MeOH=10:1) to give **50** as a colorless amorphous solid (4.5 mg, 82% for 2 steps).

Alternative method: PPh_3 (14.8 mg, 56.4 μmol), imidazole (4.82 mg, 70.5 μmol), and I_2 (6.3 mg, 49.4 μmol) were added to a solution of **48** (13.1 mg, 14.1 μmol) in CH_2Cl_2 (0.282 mL) 0 °C. After stirring for 60 min at 0 °C, the reaction mixture was warmed to RT and stirred for further 2 h. Then the reaction mixture was diluted with $CHCl_3$ (5.0 mL). The mixture was washed with a saturated aqueous solution of NH_4Cl (3.0 mL) and brine (3.0 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash column chromatography ($CHCl_3$/MeOH=90:1) gave **50** as an amorphous solid (11.3 mg, 88%). R_f=0.32 (silica gel, $CHCl_3$/MeOH=10:1); $[\alpha]_D^{20}$=−27.4 (*c*=0.75, $CHCl_3$); ^{1}H NMR (300 MHz, CD_2Cl_2): δ=6.90 (brd, J=7.3 Hz, 1H; 2‴-N*H*), 6.54 (brd, J=8.6 Hz, 1H; 2⁗-N*H*), 6.20 (brs, 1H; 1-H), 4.69 (brs, 1H; 5-H), 4.43 (dq, J=6.8, 7.3 Hz, 1H; 2‴-H), 4.42 (q, J=6.8 Hz, 1H; 3-H), 4.38 (m, 1H; 4″-H), 4.35 (dd, J=4.2, 8.6 Hz, 1H; 2⁗-H), 4.15–4.03 (complex m, 2H; 2′-H, 3′-H), 3.74 (dd, J=8.5, 10.5 Hz, 1H; 5″-H_2), 3.66 (ddd, J=4.5, 5.5, 8.2 Hz, 1H; 6-H), 3.50 (dd, J=3.5, 10.5 Hz, 1H; 5″-H_2), 2.15 (dqq, J=6.5, 6.5, 8.6 Hz, 1H; 3⁗-H), 1.86 (m, 1H; 1′-H_2), 1.95–1.85 (complex m, 2H; 5′-H$_2$), 1.72–1.48 (complex m, 3H; 1′-H_2, 4′-H$_2$), 1.52 (s, 9H; 2″-*N*-CO-O-C(CH_3)$_3$), 1.48 (s, 9H; 3″-CO-O-C(CH_3)$_3$), 1.47 (s, 9H; 1⁗-O-C(CH_3)$_3$), 1.42 (d, J=7.3 Hz, 3H; 3-CH_3), 1.42 (s, 9H; 4-CO-O-C-(CH_3)$_3$), 1.41 (s, 3H; 2′,3′-*O*-*i*Pr), 1.30 (d, J=7.3 Hz, 3H; 3‴-H$_3$), 1.29 (s, 3H; 2′,3′-*O*-*i*Pr), 0.92 (d, J=6.5 Hz, 3H; 3⁗-(CH_3)$_2$), 0.90 ppm (d, J=6.5 Hz, 3H; 3⁗-(CH_3)$_2$); ^{13}C NMR (75.0 MHz, CD_2Cl_2): δ=171.5 (C-1‴), 170.8 (C-1⁗), 169.8 (C-2), 168.5 (1C, 5-*C*O-NH-), 155.7 (C-2″), 154.9 (1C, 4-*C*O-O-C(CH_3)$_3$), 152.5 (1C, *N*-*C*O-O-C(CH_3)$_3$), 152.0 (1C, 3″-CO-O-C(CH_3)$_3$), 108.5 (1C, 2′,3′-*O*-*i*Pr), 83.0 (1C, 2″-*N*-CO-O-*C*(CH_3)$_3$), 82.0 (1C, 1⁗-O-*C*(CH_3)$_3$), 82.0 (1C, 3″-CO-O-*C*(CH_3)$_3$), 82.0 (1C, 4-CO-O-*C*(CH_3)$_3$), 77.0 (C-3′), 73.6 (C-2′), 57.8 (C-2⁗), 54.3 (C-4″), 54.2 (C-

5″), 53.4 (C-6), 53.2 (C-5), 52.3 (C-3), 48.8 (C-2‴), 33.5 (C-1′), 31.4 (C-3‴), 29.9, 27.1 (each 1C, 2′,3′-*O*-*i*Pr), 28.4 (C-5′), 28.3 (C-4′), 28.1 (3C, 2″-*N*-CO-O-C(CH_3)$_3$), 28.1 (3C, 4-CO-O-C(CH_3)$_3$), 28.0 (3C, 3″-CO-O-C(CH_3)$_3$), 27.9 (3C, 1‴-O-C(CH_3)$_3$), 18.9 (1C, 3‴-(CH_3)$_2$), 18.0 (C-3‴), 17.9 (1C, 3-CH_3), 17.6 ppm (1C, 3‴-(CH_3)$_2$); IR (NaCl): $\tilde{\nu}$ = 3319 (-OH; -NH), 1761 (C=N, guanidyl), 1732 (C=O, carboxylic acid), 1668 (C=O, amide), 1608 (C=O, amide), 1531, 1379, 1369, 1317, 1254, 1146, 999, 849, 769 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{44}H_{76}N_7O_{13}$: 910.5501 [*M*+H]; found: 910.5538 [*M*+H]$^+$.

(3*S*,5*S*,6*S*,2′*S*,3′*R*,4″*R*)-(−)-5-(L-Valinyl-L-alanyl)carbonyl-6-[2′,3′-dihydroxy-1′-(1″-carbamoyl-2″-iminoimidazolidinyl)heptan-5′-yl]-3-methyl-2-piperazinone ((3′*R*)-4): *p*-Methoxyphenyl isocyanate (2.21 μL, 16.9 μmol) was added to a solution of **50** (13.1 mg, 14.1 μmol) in PhH (0.470 mL) at RT under argon. After stirring for 10 min, the reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (1.0 mL). Then the mixture was extracted with $CHCl_3$ (5.0 mL×3). The combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next reaction without further purification. Cerium(IV) ammonium nitrate (15.8 mg, 28.2 μmol) was added to a solution of the crude material in CH_3CN/H_2O (1:1; 470 μL) at 0 °C. After stirring for 2.5 h, the reaction mixture was diluted with $CHCl_3$ (6.0 mL) and a saturated aqueous solution of $NaHCO_3$ (3.0 mL). The mixture was extracted with $CHCl_3$ (10 mL×3), the combined organic extracts were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next reaction without further purification. The crude material was dissolved in TFA/H_2O (3:1) (470 μL) and the reaction mixture was stirred for 5 h at RT. The reaction mixture was then concentrated and purified by preparative HPLC (Develosil C30 UG-5, 20φ×250 mm, 15% MeOH in H_2O/with 0.1% TFA, 8.0 mL min^{-1}, UV at 210 nm) to give (3′*R*)-**4** as a colorless oil (7.3 mg, 60% for 3 steps). t_R = 9.71 min (Analytical HPLC, Develosil C30 UG-5, 4.6 φ×250 mm, 0.1% TFA/15% MeOH/H_2O, 1.0 mL min^{-1}, 210 nm); $[\alpha]_D^{27} = -25.7$, ≈−13.8 (*c* = 0.10, MeOH), $[\alpha]_D^{20} = -10.7$ (*c* = 0.10, 1% TFA in MeOH) (natural: $[\alpha]_D^{26} = -7.8$ (*c* = 0.10, MeOH)}; ^{1}H NMR (400 MHz, D_2O with TFA): δ = 4.52 (d, *J* = 4.5 Hz, 1H; 5-H), 4.44 (q, *J* = 7.2 Hz, 1H; 2‴-H), 4.25 (dddd, *J* = 5.8, 5.8, 6.0, 8.4 Hz, 1H; 4″-H), 4.21 (dd, *J* = 8.4, 8.4 Hz, 1H; 5″-H_2), 4.10 (q, *J* = 7.2 Hz, 1H; 3-H), 4.08 (d, *J* = 6.0 Hz, 1H; 2‴-H), 3.99 (ddd, *J* = 2.5, 4.5, 11.2 Hz, 1H; 6-H), 3.78 (dd, *J* = 5.8, 8.4 Hz, 1H; 5″-H_2), 3.61 (ddd, *J* = 2.1, 5.8, 10.0 Hz, 1H; 2′-H), 3.48 (ddd, *J* = 3.0, 5.8, 10.0 Hz, 3′-H), 2.12 (dsep, *J* = 6.0, 6.8 Hz, 1H; 3‴-H), 1.92 (ddd, *J* = 2.1, 6.0, 14.0 Hz, 1H; 1′-H_2), 1.75 (ddd, *J* = 5.8, 10.0, 14.0 Hz, 1H; 1′-H_2), 1.74 (m, 1H; 4′-H_2), 1.70 (m, 1H; 5′-H_2), 1.59 (m, 1H; 5′-H_2), 1.58 (q, *J* = 7.2 Hz, 3H; 3-CH_3), 1.43 (m, 1H; 4′-H_2), 1.38 (d, *J* = 7.2 Hz, 3H; 3‴-H_3), 0.92 ppm (d, *J* = 6.8 Hz, 6H; 3‴-(CH_3)$_2$); ^{13}C NMR (100 MHz, D_2O with TFA), reference (0 and 200 ppm): δ = 177.8 (C-1‴), 177.1 (C-1‴), 170.8 (C-2), 167.5 (1C, 5-*C*O-NH), 159.0 (C-2″), 158.4 (1C, 1″-*C*O-NH_2), 76.7 (C-3′), 74.2 (C-2′), 61.4 (C-2‴), 59.7 (C-5), 54.8 (C-3), 54.0 (C-4″), 53.4 (C-6), 53.1 (C-5″), 52.1 (C-2‴), 38.7 (C-1′), 32.3 (C-3‴), 30.4 (C-5′), 30.1 (C-4′), 20.9 (1C, 3‴-(*C*H$_3$)$_2$), 20.1 (1C, 3‴-(*C*H$_3$)$_2$), 19.2 (C-3‴), 16.5 ppm (1C, 3-*C*H$_3$); IR (KBr): $\tilde{\nu}$ = 3427 (-OH), 3217 (-NH), 1730 (C=O, carboxylic acid), 1672 (C=O, amide), 1562, 1427, 1201, 1138, 841, 800, 723 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{23}H_{41}N_8O_8$: 557.3047 [*M*+H]; found: 557.3036 [*M*+H]$^+$; see the Supporting Information for the NMR spectra.

Compound (3′*S*)-4: See the Supporting Information for details.

(2*S*,3*S*,6*R*,7*S*)-(+)-Ethyl-2,3-bis(*tert*-butoxycarbonylamino)-9-(*tert*-butyldiphenylsiloxy)-6,7-*O*-isopropylidenenonanate (84): 10% Pd/C (146 mg, 137 μmol) was added to a solution of **43** (156 mg, 274 μmol) in EtOAc (5.48 mL) under H_2 at RT. After stirring for 1 h, the reaction solution was filtered through a Celite pad to remove the catalyst, and the pad was washed with EtOAc. The solvent was removed to give crude diamine compound, which was used in the next reaction without further purification. The crude diamine was dissolved in EtOAc (5.48 mL), and then Boc_2O (598 mg, 2.74 mmol) was added, and the mixture was heated to 60 °C with stirring. After 45 min, the reaction solution was cooled to RT and diluted with EtOAc (50 mL). The mixture was washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 10:1) gave **84** as a colorless oil (185 mg, 91% in 2 steps). R_f = 0.55 (silica gel, hexane/EtOAc = 2:1); $[\alpha]_D^{27} = +1.29$ (*c* = 0.75, $CHCl_3$); ^{1}H NMR (270 MHz, CD_2Cl_2): δ = 7.70–7.61 (complex m, 4H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.47–7.34 (complex m, 6H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 5.37 (m, 1H; 2-N*H*), 4.77 (br d, *J* = 7.9 Hz, 1H; 3-N*H*), 4.44–4.27 (br m, 1H; 2-H), 4.27 (m, 1H; 7-H), 4.20 (q, *J* = 6.9 Hz, 2H; 1-OCH_2CH$_3$), 3.99–3.88 (br m, 1H; 3-H), 3.98 (dd, *J* = 5.9, 12.5 Hz, 1H; 6-H), 3.80 (t, *J* = 5.6 Hz, 2H; 9-H_2), 1.82–1.61 (complex m, 3H; 4-H_2, 8-H_2), 1.59–1.32 (complex m, 3H; 5-H_2, 8-H_2), 1.44 (s, 9H; 3-CO-OC(CH_3)$_3$), 1.43 (s, 9H; 2-CO-OC(CH_3)$_3$), 1.34, (s, 3H; 6,7-*O*-*i*Pr), 1.29 (s, 3H; 6,7-*O*-*i*Pr), 1.26 (t, *J* = 6.9 Hz, 3H; 1-OCH$_2$CH_3), 1.04 ppm (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$); ^{13}C NMR (67.5 MHz, CD_2Cl_2): δ = 170.9, 155.8, 155.5, 135.6 (2C), 135.6 (2C), 134.0, 133.9, 129.7 (2C), 127.7 (4C), 107.8, 79.9, 79.5, 77.8, 74.6, 74.4, 61.6, 61.2, 60.3, 57.2, 32.7, 28.5, 28.2 (3C), 28.1 (3C), 27.0, 26.7 (3C), 25.8, 20.9, 19.1, 14.1 ppm; IR (NaCl): $\tilde{\nu}$ = 3365 (-NH), 1741 (C=O, ester), 1707 (C=O, urethane), 1512, 1367, 1248, 1219, 1169, 1111, 1086, 1022, 868, 823, 756, 704 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{40}H_{62}N_2O_9SiNa$: 765.4122 [*M*+Na]; found: 765.4144 [*M*+Na]$^+$.

(2*S*,3*S*,6*R*,7*S*,)-(−)-(*O*^{1}-*tert*-Butyl-L-valinyl-L-alanyl)-2,3-bis(*tert*-butoxycarbonylamino)-9-(*tert*-butyldiphenylsiloxy)-6,7-*O*-isopropylidenenonanate (51): Lithium hydroxide monohydrate (105 mg, 2.50 mmol) was added to a solution of **84** (185 mg, 250 μmol) in MeOH/THF/H_2O (2:2:1; 4.99 mL) at RT. After stirring for 30 min, a saturated aqueous solution of NH_4Cl (5.0 mL) was added to the reaction mixture and then it was extracted with $CHCl_3$ (10 mL×3). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next reaction without further purification. The residue was dissolved in CH_2Cl_2 (4.99 mL) and then **19** (91.4 mg, 374 μmol), ADIPEA (69.4 μL, 399 μmol), and PyBOP (208 mg, 399 μmol) were added at RT under Ar. After stirring for 3 h, the reaction was then quenched with a saturated aqueous solution of NH_4Cl (5.0 mL). The organic layer was separated and aqueous layer was extracted with $CHCl_3$ (10 mL×2). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Purification by flash chromatography on silica gel (hexane/EtOAc = 4:1) gave **51** as a colorless solid (210 mg, 89% for 2 steps). R_f = 0.61 (silica gel, hexane/EtOAc = 1:1); m.p. 133–137 °C ($CHCl_3$); $[\alpha]_D^{26} = -22.3$ (*c* = 1.00, $CHCl_3$; ^{1}H NMR (270 MHz, $CDCl_3$ δ = 7.70–7.63 (complex m, 4H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.46–7.32 (complex m, 6H; 9-O-Si(*Ph*)$_2$C(CH$_3$)$_3$), 7.17 (m, 1H; 2′-N*H*), 6.62 (br d, *J* = 8.6 Hz, 1H; 2″-N*H*), 5.70 (br d, *J* = 5.9 Hz, 1H; 2-N*H*), 5.39 (br d, *J* = 7.9 Hz, 1H; 3-N*H*), 4.40 (dd, *J* = 4.6, 8.9 Hz, 1H; 2″-H), 4.37 (m, 1H; 2′-H), 4.27 (m, 1H; 2-H), 4.25 (apparent t, *J* = 5.9 Hz, 1H; 7-H), 3.97 (dd, *J* = 5.6, 12.9 Hz, 1H; 6-H), 3.86–3.77 (br m, 1H; 3-H), 3.80 (t, *J* = 6.3 Hz, 2H; 9-H_2), 2.15 (m, 1H; 3″-H), 1.82 (m, 1H; 8-H_2), 1.71–1.58 (complex m, 3H; 5-H_2, 8-H_2), 1.52–1.40 (complex m, 2H; 4-H_2), 1.46 (s, 9H; 3-CO-OC-(CH_3)$_3$), 1.44 (s, 9H; 2-CO-OC(CH_3)$_3$), 1.43 (s, 9H; 1″-OC(CH_3)$_3$), 1.39 (d, *J* = 7.6 Hz, 3H; 3′-H_3), 1.35 (s, 3H; 6,7-*O*-*i*Pr), 1.29 (s, 3H; 6,7-*O*-*i*Pr), 1.04 (s, 9H; 9-O-Si(Ph)$_2$C(CH_3)$_3$), 0.91 (d, *J* = 6.6 Hz, 3H; 3″-(CH_3)$_2$), 0.88 ppm (d, *J* = 6.9 Hz, 3H; 3″-(CH_3)$_2$); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 171.5, 170.8, 170.4, 156.4, 155.7, 135.4 (2C), 135.3 (2C), 133.6, 133.5, 129.4, 129.4, 127.5 (2C), 127.4 (2C), 107.4, 81.7, 80.0, 79.4, 77.6, 74.2, 60.8, 60.2, 57.3, 53.6, 49.2, 32.6, 31.2, 29.3, 28.4, 28.4 (3C), 28.2 (3C), 27.9 (3C), 26.9, 26.7 (3C), 25.7, 19.0, 18.8, 17.7, 17.5 ppm; IR (NaCl): $\tilde{\nu}$ = 3329 (-NH), 1720 (C=O,ester), 1691 (C=O, urethane), 1643 (C=O, amide), 1523, 1454, 1392, 1367, 1248, 1221, 1169, 1113, 1088, 872, 823, 702 cm^{-1}; HRMS (FAB, NBA matrix): *m*/*z* calcd for $C_{50}H_{81}N_4O_{11}Si$: 941.5671 [*M*+H]; found: 941.5662 [*M*+H]$^+$.

(2*S*,3*S*,6*R*,7*S*,4′*R*)-(−)-(L-Valinyl-L-alanyl)-2,3-diamino-8-(1′-carbamoyl-2′-iminoimidazolidin-4′-yl)-6,7-dihydroxy-octanate (2): t_R = 16.8 min (Analytical HPLC, Develosil C30 UG-5, 4.6 φ×250 mm, 0.1% TFA/10% MeOH/H_2O, 1.0 mL min^{-1}, 210 nm); $[\alpha]_D^{28} = +8.5$ (*c* = 0.10, 1% TFA in MeOH), {natural: $[\alpha]_D^{27} = +13.7$ (*c* = 0.10, 1% TFA in MeOH)}; ^{1}H NMR (400 MHz, 1% TFA in D_2O): δ = 4.41 (q, *J* = 7.3 Hz, 1H; 2″-H), 4.26 (d, *J* = 3.5 Hz, 1H; 2-H), 4.19 (dddd, *J* = 5.9, 6.0, 6.0, 8.9 Hz, 1H; 4′-H), 4.16 (dd, *J* = 8.9, 14.5 Hz, 1H; 5′-H_2), 4.12 (d, *J* = 5.9 Hz, 1H; 2‴-H), 3.78 (ddd, *J* = 3.5, 5.2, 8.6 Hz, 1H; 3-H), 3.72 (dd, *J* = 6.0, 14.5 Hz, 1H; 5′-H_2), 3.56 (ddd, *J* = 2.2, 6.0, 10.0 Hz, 1H; 7-H), 3.46 (ddd, *J* = 2.0, 5.5, 9.5 Hz,

1H; 6-H), 2.11 (dsep, $J=5.9$, 6.9 Hz, 1H; 3‴-H), 1.98 (dddd, $J=4.5$, 5.2, 10.0, 14.5 Hz, 1H; 4-H_2), 1.87 (ddd, $J=2.2$, 5.9, 14.0 Hz, 1H; 8-H_2), 1.76 (ddt, $J=5.0$, 8.6, 14.5 Hz, 1H; 4-H_2), 1.72 (dddd, $J=2.0$, 5.0, 10.0, 14.5 Hz, 1H; 5-H_2), 1.71 (ddd, $J=6.0$, 10.2, 14.0 Hz, 1H; 8-H_2), 1.44 (ddt, $J=4.5$, 9.5, 14.5 Hz, 1H; 5-H_2), 1.35 (d, $J=7.3$ Hz, 3″-H_3), 0.89 ppm (d, $J=6.9$ Hz, 6H; 3‴-(CH_3)$_2$); ^{13}C NMR (100 MHz, 1% TFA in D_2O): $\delta=$ 177.7 (C-1‴), 177.3 (C-1″), 167.9 (C-1), 159.0 (C-2′), 158.4 (1C, 1′-*C*O-NH_2), 76.2 (C-6), 74.3 (C-7), 61.5 (C-2‴), 56.2 (C-2), 54.7 (C-3), 54.0 (C-4′), 53.1 (C-5′), 52.5 (C-2″), 38.8 (C-8), 32.3 (C-3‴), 29.8 (C-5), 28.5 (C-4), 20.9 (1C, 3‴-(*C*H$_3$)$_2$), 20.0 (1C, 3‴-(*C*H$_3$)$_2$), 19.3 ppm (C-3″); IR (KBr): $\tilde{\nu}=$3365 (-OH, -NH), 1734 (C=N, guanidyl), 1732 (C=O, carboxylic acid), 1672 (C=O, amide), 1608 (C=O, amide), 1531, 1379, 1369, 1317, 1254, 1146, 999, 849, 769 cm^{-1}; HRMS (FAB, NBA matrix): *m/z* calcd for $C_{20}H_{39}N_8O_7$: 503.2942 [*M*+H]; found: 503.2944 [*M*+H]$^+$; see the Supporting Information for detailed procedures, data (for intermediates) and NMR spectra for synthetic **2**.

Acknowledgements

This work was supported by the Grant for the 21st Century COE Program, Ministry of Education Culture, Sports, Science and Technology (18790022). We also thank A. Nakagawa, C. Sakabe, N. Sato, and Y. Kawauchi (all Kitasato University) for various instrumental analyses.

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Received: May 28, 2008
Published online: July 24, 2008

