

Novel Synthesis of the Main Central 2,3,6-Trisubstituted Pyridine Skeleton [Fragment A-B-C] of a Macrobicyclic Antibiotic, Cyclothiazomycin

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The useful synthesis of the main central 2,3,6-trisubstituted pyridine skeleton [the protected Fragment A-B-C] of a macrobicyclic antibiotic, cyclothiazomycin, was first accomplished. First, the 2-[2-(2-substituted thiazol-4-yl)]-4,5-dihydrothiazole-4-carboxylate [Fragment A derivative], attached to the 6-substituent of the main pyridine skeleton, was synthesized by two consecutive thiazolations of the protected Ser thioamide derivative with 3-bromopyruvate, and then thiazolination of the C-terminal Ser residue of the sequence. Secondly, an efficient synthesis of the central 2-(2-{2-[(1*R*)-1-aminoethyl]pyridin-6-yl}thiazol-4-yl)-4,5-dihydrothiazole-4-carboxylate [Fragment B derivative] was also achieved by thiazolation of the formyl group of the 2-(1-aminoethyl)-6-formylpyridine derivative, and then thiazolination. Thirdly, a convenient synthesis of the protected dehydrotetrapeptide [Fragment C derivative], which is bound to the 2-substituent of the pyridine skeleton, was attained by the usual stepwise elongation of the appropriate α-amino acids and β-elimination of a Thr residue of the sequence. Finally, the facile fragment condensation of the three Fragments thus obtained gave the protected Fragment A-B-C derivative via Fragment A-B. Furthermore, the configurational structures of the three Fragments (A, B, and C) were also investigated.

Cyclothiazomycin (**1**),[1] isolated from a culture of *Streptomyces NR0516*, is a very interesting thiostrepton-type macrobicyclic antibiotic. So far, many structurally similar thiostrepton antibiotics, such as GE 2270 A,[2] micrococcins P and P_1,[3] have also been isolated from various kinds of strains. However, no total synthesis of any similar antibiotic has yet been reported, except for the recent syntheses of micrococcin P and P_1.[4–6] The cyclothiazomycin features a very unique structure and interesting bioactivities,[1] which attracted our attention and prompted us to investigate its total synthesis and structure-bioactivity relationship. The natural product **1** includes a characteristic main central and long chain 2,3,6-trisubstituted pyridine skeleton, called Fragment A-B-C **2**, which is constituted of an (*S*)-2-{2-[2-(1-aminoethenyl)thiazol-4-yl]thiazol-4-yl}thiazoline-4-carboxylate segment called Fragment A **4**, a central (4*S*)-2-(2-{2-[(1*R*)-1-aminoethyl]-3-carboxypyridin-6-yl}thiazol-4-yl)-4,5-dihydrothiazole-4-carboxylate skeleton, called Fragment B **5**, and L-Thr-Gly-(*Z*)-ΔAbu-L-Pro (ΔAbu = 2-amino-2-butenoic acid residue) sequence, called Fragment C **6**, as shown in Fig. 1. Moreover, interestingly, many 4,5-dihydrothiazole-4-carboxylate moieties, which are unusual in thiostrepton-type antibiotics, are involved.

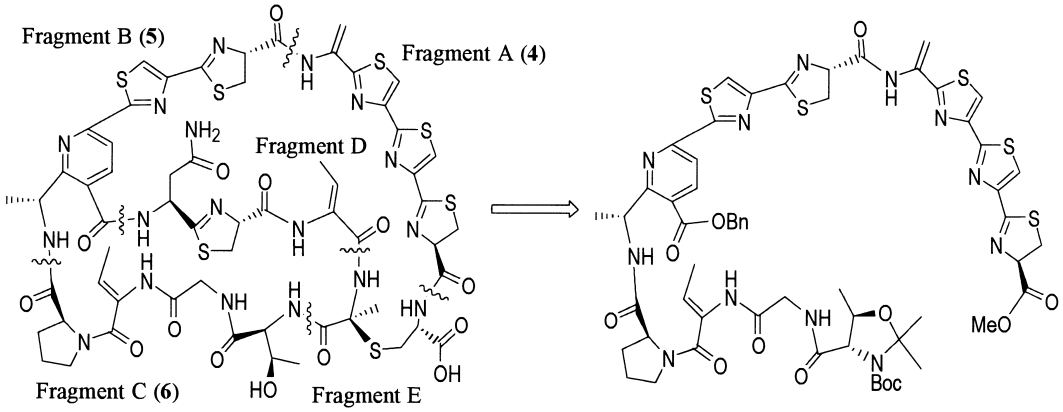


Fig. 1. Retrosynthesis of **1**.

In connection with the total synthesis of **1**, we have already briefly reported a novel synthesis of the protected Fragment A derivative **(P)-4**[7] by two consecutive thiazolations, and then thiazolination of the protected Ser thioamide derivative with 3-bromopyruvate by the Hantzsch method.[8] More recently,[9] a useful synthesis of the protected Fragment B derivative **(P)-5** by successive thiazolination and thiazolation of a 2,3-disubstituted 6-formylpyridine derivative[10] with H-Cys-OMe was achived by the Shioiri method.[11] Furthermore, the facile synthesis of the protected Fragment A-B drivative **(P)-3** by the coupling of Fragment A with Fragment B, mentioned above, has also been briefly reported.[9]

In this paper, we wish to report in detail on versatile synthetic methods for all of the Fragment derivatives [**(P)-4**, **5**, and **6**], the protected Fragment [A-B **(P)-3**], and Fragment A-B-C derivatives [**(P)-2**], derived by coupling of **(P)-3** with **(P)-6**. Furthermore, in order to determine which of the two synthetic stereoisomers, 2-(1′*R*)- and 2-(1′*S*)-**(P)-5**, is identical to the configuration of natural **1**, the structures of the two isomers were thoroughly examined by comparing the circular dichroism (CD) spectra and the specific rotations ($[\alpha]_D$) with those of an independently prepared structurally similar 2-(1-aminoethyl)pyridine derivative.

Results and Discussion

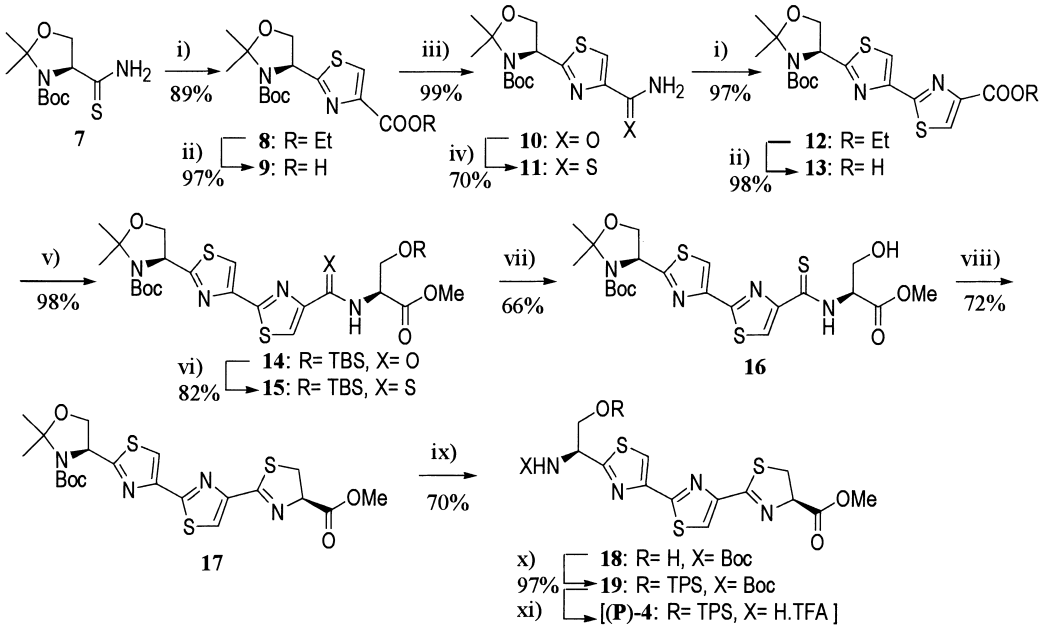
The novel syntheses of the protected Fragment A, B, and C derivatives and their couplings for the formations of the protected Fragments A-B and A-B-C derivatives were accomplished as follows. In particular, with regard to the synthesis of the Fragment A **(P)-4**, since the previous synthetic method[7] was found to be slightly difficult, and the overall yield from Ser is very low (2%), an alternative revised method was adopted. First of all, to synthesize the protected 3,4-bithiazolylthiocarbonyl-Ser-OMe derivative **16** as the precursor of **(P)-4**, the synthesis of the desired thiazolylthiazole sequence **13** by the stepwise thiazolations of thioamides was successfully tried. Initially, the thiazolation of the 3-*t*-butoxycarbonyl(Boc)-2,2-dimethyloxazolidine-4-thiocarboxamide (**7**),[4] derived from Boc-L-Cys-OH and acetone, with ethyl 3-bromopyruvate in the presence of $KHCO_3$, and then with trifluoroacetic anhydride (TFAA) and pyridine, proceeded to give 2-substituted thiazole-4-carboxylate derivative **8** by the Hantzsch method.[8] After ester hydrolysis with 1 M LiOH (1 M = 1 mol dm^{-3}), amidation of the formed free carboxylic acid **9** with ClCOOEt and then a 28% NH_3 aqueous solution gave the corresponding thiazole-4-carboxamide derivative **10**. Similarly to the case of **8**, thioamidation with Lawesson's reagent, followed by thiazolation of the formed thiazole-4-thioamide **11** with ethyl 3-bromopyruvate, gave the corresponding 2-substituted 2-(thiazol-4-yl)thiazole-4-carboxylate derivative **12**. The ester was again hydrolyzed with 1 M LiOH to give the corresponding free acid **13**.

Subsequently, the coupling of **13** with H-L-Ser(TBS)-OMe (TBS = *t*-butyldimethylsilyl) by using DPPA (DPPA = diphenyl phosphorazidate)[12] as the condensing agent, followed by thioamidation of the formed peptide derivative **14** with Lawesson's reagent gave 2,4-bithiazole-4-thiocarbonyl-Ser-(TBS)-OMe **15**. Deprotection of the TBS group with TBAF (tetrabutylammonium fluoride) was then performed to give the corresponding thiocarbonyl-Ser-OMe derivative **16**, which was treated with triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DEAD) by the Mitsunobu reaction[13] to give the expected 2-(2,4′-bithiazol-4-yl)-4,5-dihydrothiazole-4-carboxylate **17**.

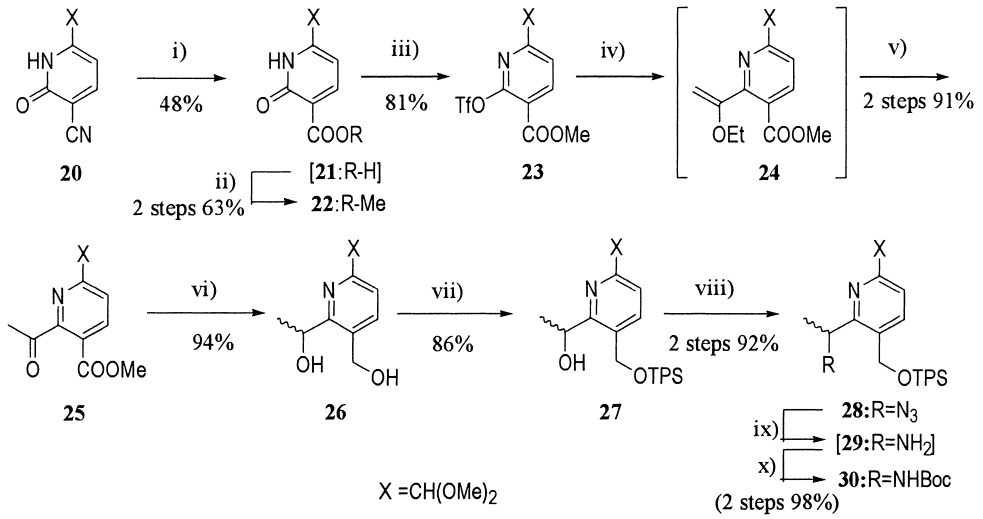
Finally, deprotection of only the isopropylidene (Isop) group of the 2,2-dimethyloxazolidine ring with a mixture of trifluoroacetic acid (TFA) and $CHCl_3$ (4:96 v/v) gave the corresponding 2-[2′-(1-amino-2-hydroxyethyl)-2,4′-bithiazol-4-yl]-4,5-dihydrothiazole derivative **18**. Subsequent protection of the formed hydroxy group of **18** with *t*-butyldiphenylsilyl chloride (TPS-Cl) in the presence of imidazole gave the corresponding 2-(*O*-TPS)ethyl derivative **19** as the protected Fragment A derivative, as shown in Scheme 1. As a result, a convenient synthesis of **19** was achieved by two consecutive thiazolations and thiazolination from **7**; the overall yield was found to attain to 19% from Ser. Later, after deprotection of the Boc group of **19** with TFA, without isolation, the obtained amino group free amino-2-(2,4′-bithiazol-4-yl)-4,5-dihydrothiazole derivative **(P)-4** was intact utilized to the next coupling with **(P)-5**.

The structure of **19** was determined by the ^1H NMR spectral data and satisfactory elemental analysis. In particular, the appearances of two protons of the thiazole rings as a singlet at δ 8.03 and 8.04, the methylene protons as a double doublet at δ 3.68 (J = 5.8 and 9.2 Hz) and the methine proton of thiazoline (4,5-dihydrothiazole) ring as a triplet at δ 5.32 supported the formation of **19**.

On the other hand, to synthesize the Fragment B derivative, as was already reported,[9] first, the starting 3-cyano-6-dimethoxymethyl-2-pyridone (**20**)[10] was converted to the corresponding 2-oxo-1,2-dihydropyridine-3-carboxylic acid **21** by hydrolysis of the cyano group with 6 M KOH. Without the isolation of **21**, one-pot esterification with MeOH gave the methyl ester **22**, the carbonyl group of which was then triflated with trifluoromethanesulfonic (triflic) anhydride (Tf_2O) to give the corresponding 2-(trifluoromethylsulfonyloxy)pyridine derivative **23**. The 2-TfO group was then treated with ethyl vinyl ether in the presence of $Pd(OAc)_2$ and dppp [1,3-bis(diphenylphosphino)propane] to give the 2-(1-ethoxyvinyl)pyridine derivative **24**. Without the purification of **24**, the conversion of the ethoxyvinyl group to an acetyl group by using 70% AcOH afforded the corresponding 2-acetyl-3-methoxycarbonyl derivative **25**, which was then subjected to reduction. That is, the simultaneous reductions of both the acetyl and methoxycarbonyl groups with $NaBH_4$ in the presence of $CaCl_2$ gave the (*RS*)-2-(1-hydroxyethyl)-3-(hydroxymethyl)pyridine derivative **26** as a racemate. Subsequently, the formed primary hydroxy group of **26** was protected by TPS-Cl to give the 3-(*O*-TPS-hydroxymethyl)pyridine derivative **27**, and the secondary hydroxy group was mesylated with methanesulfonyl (mesyl) chloride (Ms-Cl) in the presence of Et_3N and then azidated with NaN_3 in one-pot to give the corresponding 2-(1-azidoethyl)pyridine derivative **28**. The hydrogenolysis of the azido group with 10% Pd–C/H_2 gave the 2-(1-aminoethyl)pyridine derivative **29**, the amino group of which was in situ protected with Boc_2O (di-*t*-butyl dicarbonate) to give the expected 6-dimethoxymethyl-2-[1-(*N*-Boc)aminoethyl]pyridine derivative **30**, as shown in Scheme 2.



Scheme 1. Reagents and conditions: i) a) $KHCO_3$, ethyl 3-bromopyruvate, DME, 0 °C, 30 min, rt, 2 h, b) TFAA, pyridine, DME, 0 °C, 1 h, ii) 1 M LiOH, H_2O–dioxane (1:1 v/v), 0 °C, 30 min, rt, 3 h, iii) a) ClCOOEt, Et_3N, THF, 0 °C, 30 min, b) 28% aq NH_3, THF, 0 °C, 5 min, iv) Lawesson's reagent, DME, rt, 10 h, v) H-Ser(TBS)-OMe, DPPA, Et_3N, DMF, 0 °C, 30 min, rt, 9 h, vi) Lawesson's reagent, 50 °C 16 h, vii) TBAF, THF, 0 °C 1 h, viii) Ph_3P, DEAD, THF, 0 °C, 1 h, ix) TFA–$CHCl_3$ (4:96 v/v), rt, 2 h, x) TPSCl, imidazole, $CHCl_3$, 0 °C, rt, 12 h, xi) THF–$CHCl_3$ (2:3 v/v), rt, 30 min.



Scheme 2. Reagents and conditions: i) 6 M KOH, EtOH, reflux, 8 h, 0 °C, 30 min, rt, 2 h, ii) H^+, MeOH, reflux, overnight, iii) Tf_2O, DMAP, pyridine, 0 °C, 30 min, iv) $Pd(OAc)_2$, dppp, ethyl vinyl ether, v) 70% AcOH, THF, rt, overnight, vi) $NaBH_4$, $CaCl_2$, EtOH, 0 °C, 30 min, rt, 3 h, vii) TPS-Cl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 30 min, rt, 2 h, viii) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min, b) NaN_3, DMF, rt, 1 h, ix) H_2, 10% Pd–C, EtOH, rt, 30 min, x) Boc_2O, Et_3N, $CHCl_3$, 0 °C, 30 min, rt, 4 h.

Secondly, in order to construct the thiazolylthiazoline-4-carboxylate segment to the 6-position of the pyridine ring of **30**, in the first place, the 6-dimethoxymethyl group was hydrolyzed. That is, the hydrolysis of the 6-dimethoxymethyl group with 2 M HCl, followed by one-pot thiazolation of the formed 6-formylpyridine derivative **31** with H-L-Cys-OMe and then oxidation with MnO_2,[11] gave the 2-(pyridin-6-yl)thiazole-4-carboxylate derivative **32**. The subsequent ester hydrolysis of **32** with 1 M LiOH gave the free acid **33**, without purification, the carboxyl group of which was again esterified with phenacyl bromide (Pac-Br) to give the corresponding Pac ester **34**. On the other hand, deprotection of the 3-(*O*-TPS)hydroxymethyl group by using TBAF was followed by oxidation of the formed 3-(hydroxymethyl)pyridine derivative **35** with Jones' reagent. As a result, unexpectedly, the formed labile 2-[1-(*N*-Boc)aminoethyl]pyridine-3-carboxylic acid was immediately intramolecularly cyclized to give the corresponding γ-lactam derivative **36**. Fortunately, it was found that the formation of the γ-lactam ring resulted in the effective protection of the 2 and 3-positions of **36**. Consequently, after hydrolysis of the

Pac ester with K_2CO_3 aqueous solution, without isolation, the formed free acid **37** was in situ coupled with H-L-Ser(TBS)-OBu^t by the DPPA method to give the 2-(pyridin-6-yl)thiazoloyl-Ser-OBu^t derivative **38** as a diastereomeric mixture. Furthermore, the γ-lactam ring was easily clevaged with 1 M LiOH to give the corresponding 3-carboxyl-pyridine derivative **39**, which was utilized in the next reaction without isolation.

Later, to differentiate the carboxy (C-) terminal *t*-butyl ester from another ester, the carboxyl group of **39** was esterified with benzyl bromide (Bn-Br) to give the corresponding 3-benzyl ester derivative **40**. Similarly to the case of **15**, the thioamidation of **40** with Lawesson's reagent gave the expected thiocarbonyl-Ser(TBS) derivative **41**. Although compound **41** was obtained as a diastereomeric mixture, the separation was tried very successfully. That is, after the deprotection of the TBS group with 2 M HCl, the product was chromatographed intact on a silica-gel column using a mixture of $CHCl_3$ and acetone (50:1 v/v) to give the corresponding 2-[(1*R*)- and (1*S*)-1-aminoethyl]pyridine derivatives **42** from the last eluate and **43** from the first eluate, respectively.

Lastly, one of the diastereomers **42** was thiazolinated with Mitsunobu reagent[13] to give only the corresponding 2-[2-(pyridin-6-yl)thiazol-4-yl]-4,5-dihydrothiazole derivative **44**. On the other hand, in the case of another diastereomer **43**, interestingly, although similar thiazolination proceeded, it was found that a mixture of the thiazolylthiazoline derivative **46** and thiazolylithiazole derivative **47** was obtained in 67% yield in a 1:2.5 ratio. The obtained mixture could be readily separated by the chromatogram method on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v). Subsequently, oxidation of the thiazoline ring of **44** with MnO_2 in toluene gave the corresponding bithiazole derivatives **45**, similar to **47**, as shown in Scheme 3. As a result, the physical (IR and ^{1}H NMR) and chemical constants (mp and elemental analysis) of **45** and **47** were found to be completely identical, but only the sign of the specific rotations were reversed. These facts clearly indicate that compounds **44** and **46** as well as **42** and **43** are diastereomers; further, **45** and **47** are enantiomers to each other.

Naturally, it is neccessary to examine which of the two configurational structures of **44** and **46** is identical with that of the natural product (**1**). Accordingly, in order to determine the configuration of the 2-(1-aminoethyl) moiety of the synthetic **44** and **46**, both (*R*)- and (*S*)-configurational 2-[1-(*N*-Boc)aminoethyl]pyridines (**51**) were independently synthesized, and their CD spectra were compared with those of **44** and **46**. That is, the well-known asymmetric reduction of 2-acetylpyridine (**48**) with Baker's Yeast afforded the authentic (*S*)-2-(1-hydroxyethyl)pyridine **49**,[14] which was further converted to (*R*)-**51** via (*R*)-2-(1-azidoethyl)pyridine **50**. The specific rotation value of **49** thus obtained was $[\alpha]_D^{26}$ $-55.5°$ (*c* 1.6, EtOH) {lit.[14] $[\alpha]_D$ $-55.5°$ (*c* 1.5, EtOH)}, showing high optical purity (96% ee). Similarly, (*S*)-**51** was also obtained from (*S*)-**49** via successive (*R*)-**49** and (*S*)-**50**, as shown in Scheme 4. Moreover, the CD spectra of optically active **44** and (*R*)-**51** showed strong negative Cotton effects at 373 and 270 nm, respectively, while those of **46** and (*S*)-**51** showed positive Cotton effects in the same region. Furthermore, from the ^{1}H NMR spectrum of **44**, the appearances of the chemical shifts of the pyridine ring protons at δ 8.17 and 8.34 as a doublet (2H, J = 8.3 Hz), the thiazole ring protons at δ 8.20 as a singlet (1H), and the thiazoline ring protons at δ 3.63 as a doublet (2H, J = 9.2 Hz) and at δ 5.22 as a triplet (1H, J = 9.2 Hz) definitely support the Fragment B skeleton structure. Therefore, it could be completely determined that the absolute structure of **44** was the (1′*R*,4*S*)-configuration and identical with that of the natural **1**. As a result, the compound **(P)-5** (**44**) was found to be first synthesized.

In addition, to synthesize the protected Fragment C derivative **(P)-6**, the condensation of *N*-Boc-*N*,*O*-Isop-L-Thr-OH (**52**) with H-Gly-OMe by the usual DCC and *N*-hydroxysuccinimide (HOSu) method gave the corresponding dipeptide methyl ester **53**, the methyl ester of which was hydrolyzed with 1 M LiOH to give the free carboxylic acid **54**. Similarly, compound **54** was elongated by coupling with H-L-Thr(TBS)-OMe to give the protected tripeptide methyl ester **55**, the TBS group of which was then deprotected with TBAF to give the protected L-Thr-Gly-L-Thr-OMe derivative **56**. Subsequently, to synthesize the expected Δ^3-dehydrotripeptide,[15] the β-elimination of **56** with successive Ms-Cl in the presence of Et_3N and with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) was performed to give the protected Δ^3-dehydrotripeptide derivative (*N*-Boc-*N*,*O*-Isop-L-Thr-Gly-(*Z*)-ΔAbu-OMe) **57**, by a previously reported method.[16] After ester hydrolysis with 1 M LiOH, the obtained free acid **58** was further elongated with H-L-Pro-OMe by the DCC method to give Δ^3-dehydrotetrapeptide methyl ester **59**, the methyl ester of which was finally hydrolyzed to give the corresponding hydrolyzate derivative **(P)-6** as the protected Fragment C, as shown in Scheme 5. The geometry of the ΔAbu residue was readily determined to be the (*Z*)-configurational structure by a comparison with the extensive ^{1}H NMR data of the authentic samples previously reported by us.[17]

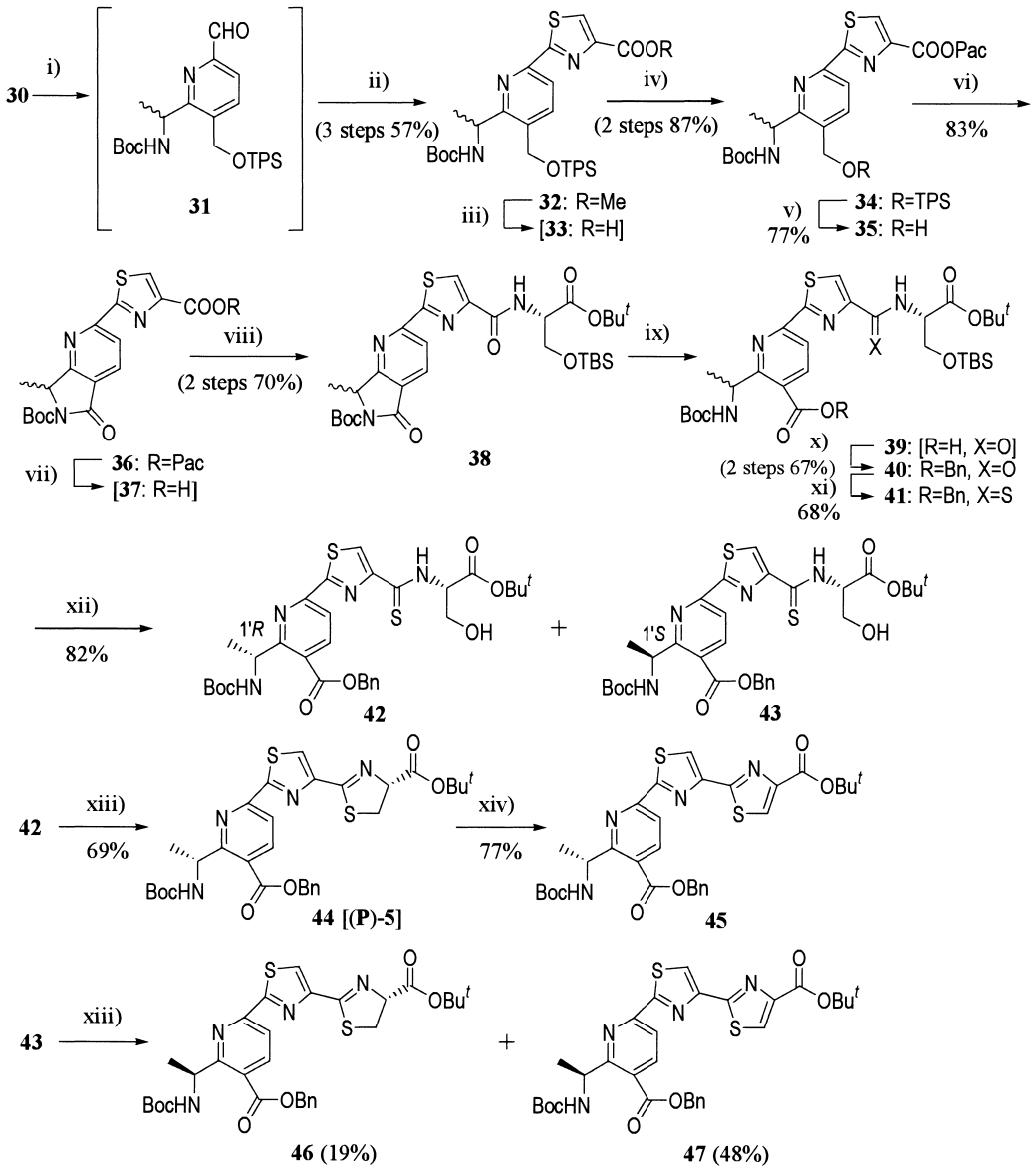
Finally, the hydrolysis of the *t*-butyl ester of (1′*R*,4*S*)-**(P)-5** with a mixture of TFA and $CHCl_3$ (3:2 v/v), accompanying deprotection of the Boc group, gave the corresponding free intermediate of both the amino and carboxyl groups. The amino group of the yielded intermediate was protected intact again with Boc_2O to give the corresponding *N*-Boc-4,5-dihydrothiazole-4-carboxylic acid derivative **60**. Without isolating **60**, one-pot coupling with **(P)-4** gave the protected Fragment A-B derivative **(P)-3**, by the BOP method.[18] Lastly, deprotection of the Boc group of **(P)-3** with a mixture of TFA and $CHCl_3$ (2:3 v/v), followed by similar coupling with **(P)-6** gave first the expected Fragment A-B-C **(P)-2**, as shown in Scheme 6.

The structures of all the thus-obtained new products were confirmed by the spectral data (^{1}H NMR , IR, and specific rotation) and satisfactory elemental analyses.

In conclusion, a useful synthetic method for the main central Fragment A-B-C skeleton of cyclothiazomycin (**1**) was successfully developed. A further investigation of the total synthesis of **1** is currently under way in our laboratory.

Experimental

The melting points were measured using a Yamato (Model Mp-21) micro-melting point apparatus, and are uncorrected. The IR spectra were recorded using an EPI-G2 spectrometer in KBr. The ^{1}H NMR spectra were measured with JEOL EX 90, EX 200, and JNE 500 spectrometers in $CDCl_3$ or DMSO-d_6 solution with tet-



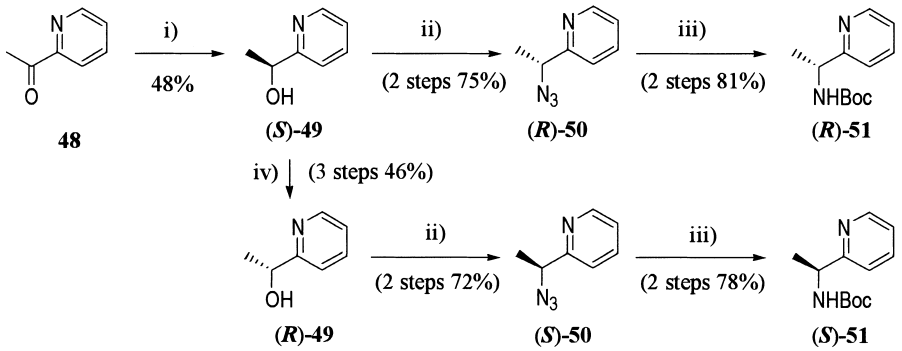
Scheme 3. Reagents and conditions: i) 2 M HCl, rt, overnight, ii) a) HCl·H-L-Cys-OMe, Et_3N, toluene, rt, 10 h, b) MnO_2 , toluene, rt, overnight, iii) 1 M LiOH, H_2O–dioxane (1:1 v/v), 0 °C, 30 min, rt, 8 h, iv) PacBr, Et_3N, DMF, 0 °C, 30 min, rt, 6 h, v) TBAF, THF, 0 °C, 30 min, vi) Jones reagent, acetone, 0 °C, 30 min, vii) K_2CO_3, THF, H_2O, 0 °C, 30 min, rt, 8 h, viii) H-L-Ser(TBS)-OBu^t, DPPA, Et_3N, DMF, 0 °C, 30 min, rt, overnight, ix) 1 M LiOH, THF, H_2O, 0 °C, 30 min, rt, 1 h, x) BnBr, Et_3N, DMF, 0 °C, 30 min, rt, 12 h. xi) Lawesson's, reagent, DMF, 50 °C, 12 h, xii) 2 M HCl, THF, rt, xiii) Ph_3P, EDAD, THF, 0 °C, 30 min, xiv) MnO_2, toluene, rt, 20 h.

ramethylsilane used as the internal standard. The specific rotations were measured in a 0.5 dm tube using a JASCO DIP-4 polarimeter in MeOH. Thin-layer chromatography (TLC) was performed with Merck silica-gel 60Art 5554 plates, and column chromatography was carried out with Merck silica-gel 60 or Wakogel C-300.

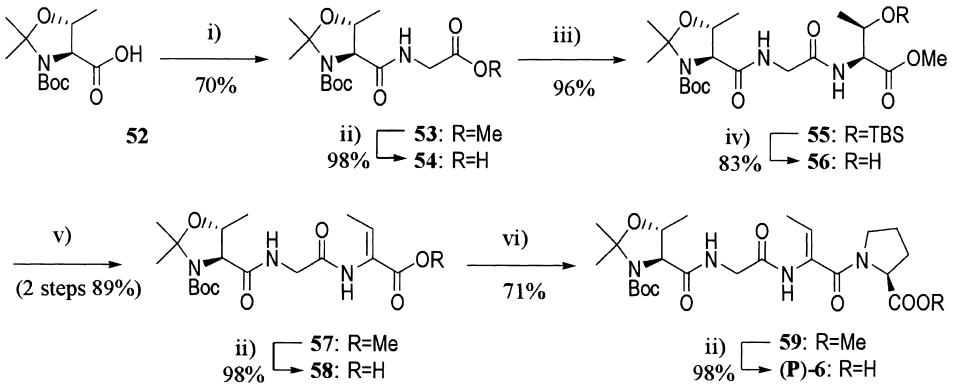
Starting Materials. H-Gly-OH, H-L-Ser-OH, and H-L-Thr-OH were purchased from Nippon Rikagakuyakuhin Co., Ltd.

(*S*)-3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidine-4-thiocarboxamide (7). A solution of (*S*)-3-*t*-butoxycarbonyl-2,2-dimethyloxazolidine-4-carboxamide[4] (1.51 g, 6.19 mmol) and Lawesson's reagent (1.38 g, 3.40 mmol) in DME (100 mL) was stirred at room temperature for 18 h. The reaction mixture was concentrated in vacuo to give a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give a solid material. Recrystallization from a hexane–EtOAc gave **7** as colorless prisms. Yield 80% (1.29 g). Mp 114–115 °C. $[\alpha]_D^{25}$ +14.9° (*c* 1.01, MeOH). IR 3346, 3275, 3182, 3006, 2982, 2943, 2885, 1479, 1438 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.49 (s, 9H, Boc), 1.54 and 1.74 (each s, 6H, Isop's CH_3 × 2), 3.95, 3.99 and 4.27, 4.30 (each dd, 2H, CH_2, J = 3.6, 7.6, 8.9 Hz), 4.67 and 4.69 (dd, 1H, CH, J = 3.6, 7.6 Hz), 8.75 and 9.50 (each br s, 2H, NH_2). Found: C, 50.86; H, 7.66; N, 10.51%. Calcd for $C_{11}H_{20}N_2O_3S$: C, 50.75; H, 7.74; N, 10.76%.

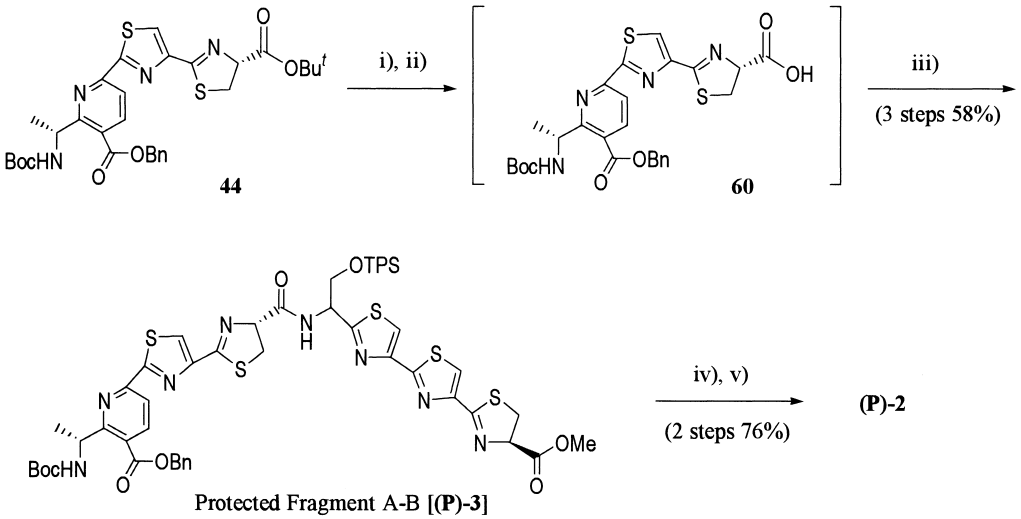
Ethyl (*S*)-2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazole-4-carboxylate (8). To a solution of **7** (533 mg, 2.05 mmol) in DME (20 mL) in the presence of $KHCO_3$ (410 mg, 4.10 mmol) was added, with stirring, $BrCH_2COCOOEt$ (0.51 mL, 4.10



Scheme 4. Reagents and conditions: i) Baker's Yeast, D-Glucose, H_2O, 48 h, ii) a) MsCl, Et_3N, $CHCl_3$, 0 °C, 30 min, b) NaN_3, DMF, rt, overnight, iii) a) H_2, 10% Pd–C, EtOH, rt, 30 min, b) Boc_2O, Et_3N, $CHCl_3$, 0 °C, 30 min, rt, 3 h, iv) a) MsCl, Et_3N, 0 °C, 30 min, b) NaOAc, 15-crown-5-ether, DMF, rt, 24 h, c) K_2CO_3, MeOH, H_2O, 0 °C, 30 min, rt, 3 h.



Scheme 5. Reagents and conditions: i) DCC, HOSu, HCl·H-Gly-OMe, CH_2Cl_2, 0 °C, 30 min, rt, 6 h, ii) 1 M LiOH, H_2O–dioxane (1:1 v/v), 0 °C, 30 min, rt, 1 h, iii) H-L-Thr(TBS)-OMe, DCC, HOBt, 0 °C, 30 min, rt, 6 h, iv) TBAF, THF, 0 °C, 30 min, v) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, b) DBU, CH_2Cl_2, 0 °C, 10 min, rt, 6 h, vi) H-Pro-OMe, DCC, HOBt, DMF, 0 °C, 30 min, rt, 6 h.



Scheme 6. Reagents and conditions: i) THF–$CHCl_3$ (3:2 v/v), rt, 5 h, ii) Boc_2O, Et_3N, $CHCl_3$, 0 °C, 30 min, 5 h, iii) **(P)-4**, BOP, $(i\text{-Pr})_2$NEt, DMF, 0 °C, 30 min, rt, 4 h, iv) TFA–$CHCl_3$ (2:3 v/v), rt, 30 min, v) **(P)-6**, BOP, $(i\text{-Pr})_2$NEt, DMF, 0 °C, 30 min, rt, 12 h.

mmol) at 0 °C. After stirring for 2 h, to the mixture were further added, with stirring, TFAA (0.85 mL, 6.15 mmol) and pyridine (1.07 mL, 13.33 mmol) at 0 °C. The reaction mixture was stirred continuously for 1 h and then concentrated in vacuo to give a residual substance, which was dissolved in EtOAc (30 mL). The resulting solution was washed successively with 10% citric acid (30 mL × 3), saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give

colorless crystals. Recrystallization from a hexane-EtOAc gave **8** as colorless prisms. Yield 89% (647 mg). Mp 131–132 °C. $[\alpha]_D^{28}$ +6.2° (*c* 1.00, MeOH). IR 3127, 3001, 2982, 2937, 2900, 1731, 1698, 1377, 1364 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.32 (t, 3H, CH_2CH_3, J = 6.9 Hz), 1.36 (s, 9H, Boc), 1.54 and 1.67 (each s, 6H, Isop's CH_3 × 2), 4.04–4.10 and 4.27–4.37 (each m, 4H, CH_2O, CH_2CH_3), 5.25 (dd, 1H, CHN, J = 2.0, 6.6 Hz), 8.38 (s, 1H, thiazole's H). Found: C, 53.42; H, 6.31; N, 7.61%. Calcd for $C_{16}H_{24}N_2O_5S$: C, 53.91; H, 6.79; N, 7.86%.

(*S*)-2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazole-4-carboxylic Acid (9). A solution of **8** (1.38 g, 3.87 mmol) and 1 M LiOH (5.81 mL) in a mixture of water and dioxane (50 mL, 1:1 v/v) was stirred at 0 °C. After stirring for 30 min and at room temperature for 3 h, the reaction mixture was washed with diethyl ether (30 mL × 3). The aqueous layer was acidified with citric acid hydrate to pH 4 and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from a hexane–EtOAc to give **9** as colorless crystals. Yield 97% (1.26 g). Mp 230–232 °C. $[\alpha]_D^{25}$ +12.0° (*c* 0.05, acetone). IR 3179, 3086, 2992, 2979, 1786, 1673, 1475, 1404, 1370 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.37 (s, 9H, Boc), 1.54 and 1.67 (each s, 6H, Isop's CH_3 × 2), 4.01–4.13 and 4.25–4.40 (each m, 2H, CH_2O), 5.19–5.28 (m, 1H, CHN), 8.31 (s, 1H, thiazole's H). Found: C, 51.19; H, 6.19; N, 8.21%. Calcd for $C_{14}H_{20}N_2O_5S$: C, 51.21; H, 6.14; N, 8.53%.

(*S*)-2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazole-4-carboxamide (10). A solution of **9** (1.27 g, 3.87 mmol) and ethyl chloroformate (0.41 mL, 4.26 mmol) in THF (30 mL) in the presence of Et_3N (0.59 mL, 4.26 mmol) was strried at 0 °C for 30 min. To the resulting solution was added 28% aq NH_3 (0.42 mL, 5.81 mmol) and, after stirring for 5 min, the aqueous layer was removed. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo to give crude crystals. Recrystallization from a hexane–EtOAc gave **10** as colorless crystals. Yield 99% (1.26 g). Mp 157–159 °C. $[\alpha]_D^{24}$ +1.8° (*c* 1.00, MeOH). IR 3450, 2982, 1704, 1681, 1596 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.37 (s, 9H, Boc), 1.54 and 1.67 (each s, 6H, Isop's CH_3 × 2), 4.05–4.38 (m, 2H, CH_2O), 5.15–5.27 (m, 1H, CHN), 7.33 (br s, 2H, NH_2), 8.14 (s, 1H, thiazole's H). Found: C, 51.30; H, 6.28; N, 12.83%. Calcd for $C_{14}H_{21}N_3O_4S$: C, 51.36; H, 6.47; N, 12.83%.

(*S*)-2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazole-4-thiocarboxamide (11). A solution of **10** (1.26 g, 3.85 mmol) and Lawesson's reagent (856 mg, 2.12 mmol) in DME (30 mL) was stirred at room temperature for 10 h. The reaction mixture was concentrated in vacuo to give a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give yellow crystals. Recrystallization from a hexane–EtOAc gave **11** as yellow prisms. Yield 70% (924 mg). Mp 178–179 °C. $[\alpha]_D^{25}$ −0.2° (*c* 1.00, MeOH). IR 3389, 3298, 3215, 2979, 1684, 1627 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.38 (s, 9H, Boc), 1.54 and 1.66 (each s, 6H, Isop's CH_3 × 2), 4.15–4.37 (m, 2H, CH_2O), 5.20–5.24 (m, 1H, CHN), 8.14 (s, 1H, thiazole's H), 9.10 and 9.68 (each br s, NH_2). Found: C, 49.28; H, 5.98; N, 12.51%. Calcd for $C_{14}H_{21}N_3O_3S_2$: C, 48.96; H, 6.16; N, 12.23%.

Ethyl (*S*)-2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazol-4-yl]thiazole-4-carboxylate (12). A solution of **11** (810 mg, 2.36 mmol) and $BrCH_2COCOOEt$ (0.59 mL, 4.72 mmol) in the presence of $KHCO_3$ (472 mg, 4.72 mmol) in DME (30 mL) were stirred at 0 °C for 2 h. To the resulting solution was added, with stirring, TFAA (0.98 mL, 7.08 mmol) and pyridine (1.23 mL, 15.34 mmol) and, after stirring for 1 h, the reaction mixture was concentrated in vacuo to give a residual substance. The residue was dissolved in EtOAc (30 mL) and the resultant solution was washed successively with 10% citric acid (30 mL × 3), saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **12** as colorless crystals. Yield 98% (1.03 g). Mp 134–136 °C. $[\alpha]_D^{26}$ +2.4° (*c* 1.01, MeOH). IR 3100, 2978, 2935, 2872, 1699, 1366, 1239 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.35 (t, 3H, CH_2CH_3, J = 7.3 Hz), 1.36 (s, 9H, Boc), 1.55 and 1.71 (each s, 6H, Isop's CH_3 × 2), 4.11 and 4.36 (each dd, 2H, CH_2O, J = 1.9, 6.5, 9.2 Hz), 4.36 (q, 2H, CH_2CH_3, J = 7.3 Hz), 5.30 (dd, 1H, CHN, J = 1.9, 6.5 Hz), 8.26 and 8.47 (each s, 2H, thiazole's H). Found: C, 51.44; H, 5.50; N, 9.13%. Calcd for $C_{19}H_{25}N_3O_5S_2$: C, 51.92; H, 5.73; N, 9.56%.

(*S*)-2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-thiazol-4-yl]thiazole-4-carboxylic Acid (13). A solution of **12** (1.01 g, 2.30 mmol) and 1 M LiOH (3.45 mL) in a mixture of H_2O and dioxane (30 mL, 1:1 v/v) was stirred at 0 °C for 30 min and then at room temperature for 3 h. After washing with diethyl ether (30 mL × 3), the aqueous layer was acidified to pH 4 with citric acid hydrate. The reaction mixture was extracted with EtOAc (30 mL × 3) and the combined extracts were washed with brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from a hexane–EtOAc to give **13** as colorless needles. Yield 98% (945 mg). Mp 203–205 °C. $[\alpha]_D^{23}$ +4.8° (*c* 1.01, MeOH). IR 3446, 3133, 2979, 1694, 1363 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.36 (s, 9H, Boc), 1.55 and 1.71 (each s, 6H, Isop's CH_3 × 2), 4.11 and 4.36 (each dd, 2H, CH_2O, J = 1.7, 6.3, 9.2 Hz), 5.30 (dd, 1H, CHN, J = 1.7, 6.3 Hz), 8.22 and 8.38 (each s, 2H, thiazole's H × 2). Found: C, 48.45; H, 5.09; N, 10.10%. Calcd for $C_{17}H_{21}N_3O_5S_2 \cdot 0.5H_2O$: C, 48.56; H, 5.27; N, 9.99%.

(*S*,*R*)-2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-thiazol-4-yl]thiazole-4-carbonyl-L-Ser(TBS)-OMe (14). To a solution of **13** (392 mg, 0.95 mmol) and H-Ser(TBS)-OMe (357 mg, 1.53 mmol) in the presence of Et_3N (0.24 mL, 1.71 mmol) in DMF (20 mL) was added, with stirring, DPPA (0.27 mL, 1.24 mmol) at 0 °C. The resulting solution was stirred for 30 min and continuously at room temperature for 9 h and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with 10% citric acid (30 mL × 3), saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **14** as a pale-yellow syrup. Yield 98% (595 mg). $[\alpha]_D^{24}$ +26.0° (*c* 1.00, MeOH). IR 2953, 2932, 2884, 2857, 1749, 1706, 1375 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.06 and 0.08 (each s, 6H, TBS's CH_3 × 2), 0.88 (s, 9H, TBS's Bu^t), 1.36 (s, 9H, Boc), 1.56 and 1.71 (each s, 6H, Isop's CH_3 × 2), 3.72 (s, 3H, OCH_3), 3.94–4.42 (m, 4H, CH_2OC, Ser's β-H), 4.65–4.77 (m, 1H, Ser's α-H), 5.26–5.34 (m, 1H, CHN), 8.03–8.15 (m, 1H, Ser's NH), 8.12 and 8.32 (each s, 2H, thiazole's H × 2). Found: C, 51.48; H, 6.67; N, 8.80%. Calcd for $C_{27}H_{42}N_4O_7S_2Si$: C, 51.73; H, 6.73; N, 8.94%.

(*S*,*R*)-2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-

thiazol-4-yl]thiazole-4-thiocarbonyl-L-Ser(TBS)-OMe (15). Similarly to the case of **11**, a solution of **14** (592 mg, 0.94 mmol) and Lawesson's reagent (209 mg, 0.52 mmol) in DME (10 mL) was woked up at 50 °C for 16 h. The reaction mixture was concentrated in vacuo to give a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **15** as a yellow syrup. Yield 82% (495 mg). $[\alpha]_D^{24}$ +60.2° (*c* 1.00, MeOH). IR 2952, 2931, 1778, 1706, 1521 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.07 and 0.08 (each s, 6H, TBS's CH_3 × 2), 0.88 (s, 9H, TBS's Bu^t), 1.37 (s, 9H, Boc), 1.56 and 1.72 (each s, 6H, Isop's CH_3 × 2), 3.75 (s, 3H, OCH_3), 4.05–4.42 (m, 4H, CH_2OC, Ser's β-H), 5.23–5.38 (m, 2H, CHN, Ser's α-H), 8.11 and 8.51 (each s, 2H, thiazole's H × 2), 9.90 (br d, 1H, Ser's NH, J = 6.6 Hz). Found: C, 50.69; H, 6.37; N, 8.62%. Calcd for $C_{27}H_{42}N_4O_7S_2Si$: C, 50.44; H, 6.58; N, 8.71%.

(*S*,*R*)-2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)-thiazol-4-yl]thiazole-4-thiocarbonyl-L-Ser-OMe (16). A solution of **15** (486 mg, 0.76 mmol) and TBAF (1.13 mL, 1 M in THF) in THF (10 mL) was stirred at 0 °C for 1 h. Evaporation of THF gave a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **16** as a yellow amorphous material. Yield 66% (264 mg). $[\alpha]_D^{24}$ +31.2° (*c* 1.00, MeOH). IR 3335, 2979, 1744, 1704, 1523, 1366 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.14–1.47 (m, 10H, Boc, OH), 1.56 and 1.72 (each s, 6H, Isop's CH_3 × 2), 3.73 (s, 3H, OCH_3), 3.90–4.42 (m, 4H, CH_2OC, Ser's β-H), 5.17–5.38 (m, 2H, CHN, Ser's α-H), 8.28 and 8.50 (each s, 2H, thiazole's H × 2), 9.90–10.01 (m, 1H, Ser's NH). Found: C, 47.96; H, 5.39; N, 10.43%. Calcd for $C_{21}H_{28}N_4O_6S_3$: C, 47.71; H, 5.34; N, 10.60%.

Methyl (*S*,*R*)-2-{2-[2-(3-*t*-Butoxycarbonyl-2,2-dimethyloxazolidin-4-yl)thiazol-4-yl]thiazol-4-yl}-4,5-dihydrothiazole-4-carboxylate (17). To a solution of **16** (249 mg, 0.47 mmol) in THF (10 mL) were added, with stirring, Ph_3P (185 mg, 0.71 mmol) and DEAD (40% in toluene; 0.28 mL, 0.71 mmol) at 0 °C. After stirring for 1 h, evaporation of THF gave a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **17** as a colorless amorphous material. Yield 72% (173 mg). $[\alpha]_D^{24}$ +3.7° (*c* 1.02, MeOH). IR 2980, 1743, 1704 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 1.36 (s, 9H, Boc), 1.55 and 1.71 (each s, 6H, Isop's CH_3 × 2), 3.76 (s, 3H, OCH_3), 3.60–4.40 (m, 4H, thiazoline's CH_2, CH_2O), 5.27–5.42 (m, 2H, CHN, thiazoline's CH), 8.20 and 8.29 (each s, 2H, thiazole's H). Found: C, 49.37; H, 5.51; N, 10.92%. Calcd for $C_{21}H_{26}N_4O_5S_3$: C, 49.39; H, 5.13; N, 10.97%.

Methyl (*S*,*R*)-2-{2-[2-(1-*t*-Butoxycarbonylamino-2-hydroxyethyl)thiazol-4-yl]thiazol-4-yl}-4,5-dihydrothiazole-4-carboxylate (18). A solution of **17** (173 mg, 0.34 mmol) in a mixture of TFA and $CHCl_3$ (10 mL, 4:96 v/v) was stirred at room temperature for 2 h. The reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution and the organic layer was washed with brine (10 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **18** as colorless crystals. Yield 70% (112 mg). Mp 207–209 °C. $[\alpha]_D^{23}$ +1.3° (*c* 0.31, MeOH). IR 3439, 3336, 1732, 1700, 1586, 1524 cm^{-1}. ^1H NMR δ 1.48 (s, 9H, Boc), 178–2.04 (m, 1H, OH), 3.68 (dd, 2H, thiazoline's CH_2, J = 5.2, 9.4 Hz), 3.84 (s, 3H, OCH_3), 3.93–4.18 (m, 2H, CH_2O), 5.02–5.15 (m, 1H, CHN), 5.32 (t, 1H, thiazoline's CH, J = 9.4 Hz), 6.70–6.80 (m, 1H, NH), 8.03 and 8.04 (each s, 2H, thiazole's H × 2). Found: C, 45.59; H, 4.41; N, 11.96%. Calcd for $C_{18}H_{22}N_4O_5S_3$: C, 45.94; H, 4.71; N, 11.91%.

Methyl (*S*,*R*)-2-{2-[2-(1-*t*-Butoxycarbonylamino-2-*t*-butyldiphenylsiloxyethyl)thiazol-4-yl]thiazol-4-yl}-4,5-dihydrothiazole-4-carboxylate (19). To a solution of **18** (100 mg, 0.21 mmol) in $CHCl_3$ (5 mL) were added, with stirring, TPS-Cl (6 µL, 0.25 mmol) and imidazole (29 mg, 0.42 mmol) at 0 °C. After stirring for 12 h, the reaction mixture was washed with brine (5 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **19** as a colorless syrup. Yield 97% (145 mg). $[\alpha]_D^{23}$ +10.0° (*c* 0.06, MeOH). IR 2926, 2855, 1717, 1489 cm^{-1}. ^1H NMR δ 0.97 (s, 9H, TPS's Bu^t), 1.49 (s, 9H, Boc), 3.69 (dd, 2H, thiazoline's CH_2, J = 5.8, 9.2 Hz), 3.86 (s, 3H, OCH_3), 3.97–4.18 (m, 2H, CH_2O), 5.10–5.20 (m, 1H, CHN), 5.33 (t, 1H, thiazoline's CH, J = 9.2 Hz), 6.58–6.68 (m, 1H, NH), 7.27–7.62 (m, 10H, TPS's Ph × 2), 8.04 and 8.05 (each s, 2H, thiazole's H × 2). Found: C, 57.81; H, 5.39: N, 8.01%. Calcd for $C_{34}H_{40}N_4O_5S_3Si$: C, 57.60; H, 5.67; N, 7.90%.

Methyl 6-Dimethoxymethyl-2-oxo-1,2-dihydropyridine-3-carboxylate (22). A solution of **20** (10.0 g, 51.5 mmol) and 6 M KOH (100 mL) in EtOH (100 mL) was refluxed for 8 h. Evaporation of EtOH gave an aqueous reaction mixture, which was washed with diethyl ether (30 mL × 3). The aqueous layer was acidified to pH 4 with citric acid hydrate and the resulting solution was extracted with EtOAc (100 mL × 5). The combined extracts were washed with brine (50 mL) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual substance **21**, which was dissolved in MeOH (200 mL). To the resulting solution was added *p*-toluenesulfonic acid hydrate (4.43 g) and, after refluxing overnight, the resultant solution was neutralized with Et_3N at room temperature. Concentration in vacuo gave crude crystals, which were purified on a silica gel column using a mixture of $CHCl_3$ and acetone (7:1 v/v) to give colorless crystals. Recrystallization from a hexane-EtOAc gave **22** as colorless needles. Yield 63% (7.73 g) from **20** in two steps. Mp 94–95 °C. IR 3046, 2944, 2830, 1740, 1641, 1599, 1566 cm^{-1}. ^1H NMR δ 3.42 (s, 6H, $CH(OCH_3)_2$), 3.92 (s, 3H, OCH_3), 5.31 (s, 1H, $CH(OCH_3)_2$), 6.60 (d, 1H, pyridone's H, J = 7.6 Hz), 8.25 (d, 1H, pyridone's H, J = 7.6 Hz), 10.69–10.92 (br s, 1H, NH). Found: C, 53.06; H, 5.75; N, 6.47%. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16%.

Methyl 6-Dimethoxymethyl-2-trifluoromethylsulfonyloxypyridine-3-carboxylate (23). To a solution of **22** (2.0 g, 8.80 mmol) in pyridine (50 mL) were added, with stirring, DMAP (1.51 g, 12.32 mmol) and Tf_2O (1.59 g, 9.68 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was concentrated in vacuo to give a residual substance, which was dissolved in EtOAc (70 mL). The resulting solution was washed with a saturated $NaHCO_3$ aqueous solution (10 mL × 3), and brine (10 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **23** as a colorless syrup. Yield 81% (2.56 g). IR 3478, 2932, 2836, 2248, 1725, 1608, 1557 cm^{-1}. ^1H NMR δ 3.44 (s, 6H, $CH(OCH_3)_2$), 4.00 (s, 3H, OMe), 5.29 (s, 1H, $CH(OCH_3)_2$), 7.75 (d, 1H, pyridine's H, J = 7.8 Hz), 8.50 (d, 1H, pyridine's H, J = 7.8 Hz). Found: C, 36.65; H, 3.39; N, 3.84%. Calcd for $C_{11}H_{12}NO_7SF_3$: C, 36.77; H, 3.37; N, 3.90%.

Methyl 6-Dimethoxymethyl-2-(1-ethoxyethenyl)pyridine-3-carboxylate (24). To a solution of **23** (2.64 g, 7.35 mmol) in toluene (50 mL) were added $Pd(OAc)_2$ (0.25 g, 1.11 mmol), dppp (0.45 g, 1.09 mmol), ethyl vinyl ether (8.49 mL, 88.30 mmol) and

Et_3N (3.08 mL, 22.10 mmol) at room temperature. The resulting suspension was refluxed for 6 h and then concentrated in vacuo to give a residual substance, which was dissolved in $CHCl_3$ (70 mL). The obtained solution was washed with brine (30 mL × 2) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **24** as a colorless syrup. Without purification, the compound **24** was used to the next reaction.

Methyl 2-Acetyl-6-dimethoxymethylpyridine-3-carboxylate (25). To a solution of **24** (1.43 g, 5.08 mmol) in THF (5 mL) was added, with stirring, 70% AcOH (50 mL) at room temperature. After stirring overnight, the reaction mixture was concentrated in vacuo to give a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **25** as a pale-yellow syrup. Yield 91% (1.28 g). IR 2926, 2838, 2620, 1704, 1584 cm^{-1}. ^1H NMR δ 2.69 (s, 3H, CH_3), 3.43 (s, 6H, $CH(OCH_3)_2$), 3.91 (s, 3H, OCH_3), 5.37 (s, 1H, $CH(OCH_3)_2$), 7.73 (d, 1H, pyridine's H, J = 8.1 Hz), 8.04 (d, 1H, pyridone's H, J = 8.1 Hz). Found: C, 56.56; H, 6.08; N, 5.31%. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53%.

(*RS*)-2-(1-Hydroxyethyl)-3-hydroxymethyl-6-dimethoxymethylpyridine (26). To a solution of **25** (2.58 g, 10.20 mmol) in EtOH (50 mL) were added, with stirring, $CaCl_2$ (6.80 g, 61.27 mmol) and $NaBH_4$ (2.32 g, 61.33 mmol) at 0 °C. After stirring for 30 min and for 3 h at room temperature, a saturated NH_4Cl aqueous solution (50 mL) was added to the reaction mixture. Evaporation in vacuo gave a residual aqueous layer. The layer was extracted with EtOAc (50 mL × 5) and the combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using EtOAc to give **26** as a colorless syrup. Yield 94% (2.17 g). IR 3384, 2935, 1579 cm^{-1}. ^1H NMR δ 1.41 (d, 3H, CH_3, J = 6.4 Hz), 3.38 and 3.40 (each s, 6H, $CH(OCH_3)_2$), 3.43–3.46 (m, 1H, OH), 4.68 (s, 2H, CH_2), 4.81-5.00 (m, 2H, $CHOH$, OH), 5.34 (s, 1H, $CH(OCH_3)_2$), 7.46 (d, 1H, pyridine's H, J = 7.8 Hz), 7.81 (d, 1H, pyridine's H, J = 7.8 Hz). Found: C, 57.94; H, 7.98; N, 6.24%. Calcd for $C_{11}H_{17}NO_4$: C, 58.14; H, 7.54; N, 6.16%.

(*RS*)-3-*t*-Butyldiphenylsiloxymethyl-6-dimethoxymethyl-2-(1-hydroxyethyl)pyridine (27). To a solution of **26** (0.31 g, 1.36 mmol) in CH_2Cl_2 (30 mL) were added, with stirring, Et_3N (0.23 mL, 1.64 mmol), DMAP (0.02 g, 0.16 mmol), and TPS-Cl (0.36 mL, 1.55 mmol) at 0 °C for 30 min. After stirring at room temperature for 2 h, diethyl ether (40 mL) was added to the reaction mixture. The resulting solution was washed successively with 10% citric acid (30 mL × 3), a saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **27** as a colorless syrup. Yield 86% (0.54 g). IR 3448, 2854, 2230, 1959, 1893, 1821, 1728, 1584 cm^{-1}. ^1H NMR δ 1.09 (s, 9H, TPS's Bu^t), 1.27 (d, 3H, CH_3, J = 6.1 Hz), 1.84 (s, 1H, OH), 3.40 and 3.43 (each s, 6H, $CH(OCH_3)_2$), 4.69–4.83 (m, 3H, $CHOH$, CH_2), 5.36 (s, 1H, $CH(OCH_3)_2$), 7.34–7.45 and 7.64–7.70 (each m, 10H, TPS's Ph × 2), 7.50 (d, 1H, pyridine's H, J = 8.1 Hz), 7.91 (d, 1H, pyridine's H, J = 8.1 Hz). Found: C, 69.35; H, 7.77; N, 3.18%. Calcd for $C_{27}H_{35}NO_4Si$: C, 69.64; H, 7.58; N, 3.18%.

(*RS*)-2-(1-Azidoethyl)-3-*t*-butyldiphenylsiloxymethyl-6-dimethoxymethylpyridine (28). To a solution of **27** (0.44 g, 0.94 mmol) in CH_2Cl_2 (40 mL) were added, with stirring, Et_3N (0.18 mL, 1.29 mmol) and Ms-Cl (0.10 mL, 1.23 mmol) at 0 °C. After stirring for 10 min, the reaction mixture was mixed with diethyl ether (60 mL) and the resulting solution was washed with brine (30 mL), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give a colorless syrup. The obtained syrup was again dissolved in DMF (40 mL) and the resulting solution was stirred with NaN_3 (0.31 g, 4.71 mmol) at room temperature for 30 min. The reaction mixture was extracted with EtOAc (30 mL × 3) and the combined extracts were washed with brine (30 mL) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (5:1 v/v) to give **28** as a colorless syrup. Yield 92% (0.42 g). IR 3304, 2902, 2074, 1902, 1821, 1737, 1587 cm^{-1}. ^1H NMR δ 1.08 (s, 9H, TPS's Bu^t), 1.58 (d, 3H, CH_3, J = 6.6 Hz), 3.42 and 3.47 (each s, 6H, $CH(OCH_3)_2$), 4.54 (d, 1H, CHN_3, J = 6.8 Hz), 4.77 (ABq, 2H, CH_2, J = 13.2 Hz), 5.34 (s, 1H, $CH(OCH_3)_2$), 7.34–7.46 and 7.62–7.69 (each m, 10H, TPS's Ph × 2), 7.54 (d, 1H, pyridine's H, J = 8.1 Hz), 7.77 (d, 1H, pyridine's H, J = 8.1 Hz). Found: C, 65.68; H, 6.91; N, 11.60%. Calcd for $C_{27}H_{34}N_4O_3Si$: C, 66.04; H, 6.98; N, 11.42%.

(*RS*)-2-(1-*t*-Butoxycarbonylaminoethyl)-3-*t*-butyldiphenylsiloxymethyl-6-dimethoxymethylpyridine (30). A suspension of **28** (1.0 g, 2.03 mmol) and 10% Pd–C (0.10 g) in EtOH (50 mL) was stirred under H_2 gas stream for 30 min at room temperature. After the Pd–C was filtered off, the filtrate was concentrated in vacuo and the residual substance **29**, which was in situ dissolved in $CHCl_3$ (50 mL). To the resulting solution were added, with stirring, Et_3N (0.28 mL, 2.03 mmol) and Boc_2O (0.53 g, 2.40 mmol) at 0 °C. After stirring for 30 min and at room temperature for 4 h, the reaction mixture was mixed with diethyl ether (70 mL), and then washed with 10% citric acid (30 mL × 2), saturated $NaHCO_3$ aqueous solution (30 mL × 2) and brine (30 mL × 2), and finally dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **30** as a colorless syrup. Yield 98% (1.14 g) from **28** in two steps. IR 3418, 2914, 1707, 1575 cm^{-1}. ^1H NMR δ 1.09 (s, 9H, TPS's Bu^t), 1.26 (d, 3H, CH_3, J = 6.6 Hz), 1.41 (s, 9H, Boc), 3.40 (s, 6H, $CH(OCH_3)_2$), 4.72–4.93 (m, 3H, $CHNH$ and CH_2), 5.36 (s, 1H, $CH(CH_3)_2$), 6.05 (br d, 1H, NH, J = 7.3 Hz), 7.33–7.47 and 7.63–7.69 (each m, 11H, TPS's Ph × 2 and pyridine's H), 7.85 (d, 1H, pyridine's H, J = 8.1 Hz). Found: C, 67.64; H, 8.05; N, 4.55%. Calcd for $C_{32}H_{44}N_2O_5Si$: C, 68.05; H, 7.85; N, 4.96%.

Methyl (*RS*)-2-[2-(1-*t*-Butoxycarbonylaminoethyl)-3-(*t*-butyldiphenylsiloxymethyl)pyridin-6-yl]thiazole-4-carboxylate (32). After a solution of **30** (3.0 g, 5.31 mmol) and 2 M HCl (40 mL) in THF (40 mL) was stirred at room temperature overnight, the reaction mixture was neutralized with saturated $NaHCO_3$ aqueous solution. After evaporating THF, the residue was extracted with EtOAc (50 mL × 3). The combined extracts were washed with saturated $NaHCO_3$ aqueous solution (50 mL × 3) and brine (50 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual substance **30**, which was dissolved in toluene (80 mL). The resultant solution was stirred with H-L-Cys-OMe·HCl (1.82 g, 10.62 mmol) in the presence of Et_3N (1.48 mL, 10.62 mmol) at 0 °C for 10 h. Concentration in vacuo gave a residual substance, which was dissolved again in EtOAc (100 mL) and then washed with 10% citric acid (40 mL × 3), a saturated $NaHCO_3$ aqueous solution (40 mL × 3), brine (40 mL × 3) and

then dried over anhydrous Na_2SO_4. After concentrating in vacuo, the obtained residue was dissolved in toluene (80 mL); to the resulting solution was added MnO_2 (9.23 g, 106.2 mmol), and the mixture was stirred at room temperature overnight. After removal of MnO_2, the reaction mixture was concentrated in vacuo to give a viscous syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **32** as a colorless amorphous material. Yield 57% (1.91 g). IR 3439, 2931, 1731, 1587 cm^{-1}. ^1H NMR δ 1.10 (s, 9H, TPS's Bu^t), 1.34 (d, 3H, CH_3, J = 6.6 Hz), 1.42 (s, 9H, Boc), 3.99 (s, 3H, OMe), 4.76–4.95 (m, 3H, C*H*NH, CH_2), 5.75 (br d, 1H, NH, J = 8.3 Hz), 7.33–7.45 and 7.64–7.69 (each m, 10H, TPS's Ph × 2), 7.86 (br d, 1H, pyridine's H, J = 8.6 Hz), 8.18 (d, 1H, pyridine's H, J = 7.8 Hz), 8.26 (s, 1H, thiazole's H). Found: C, 64.52; H, 6.86; N, 6.29%. Calcd for $C_{34}H_{41}N_3O_5SSi$: C, 64.63; H, 6.54; N, 6.65%.

(*RS*)-2-[2-(1-*t*-Butoxycarbonylaminoethyl)-3-(*t*-butyldiphenylsiloxymethyl)pyridin-6-yl]thiazole-4-carboxylic Acid (33). To a solution of **32** (6.20 g, 9.81 mmol) in H_2O–dioxane (60 mL, 1:1 v/v) was added, with stirring, 1 M LiOH (11.77 mL, 11.77 mmol) at 0 °C. After stirring for 10 min and for 5 h at room temperature, the resultant solution was acidified with citric acid hydrate to pH 4. The reaction mixture was extracted with EtOAc (50 mL × 3) and the combined extracts were washed with brine (30 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a colorless syrup **33**, which was intact used the next reaction.

Phenacyl (*RS*)-2-[2-(1-*t*-Butoxycarbonylaminoethyl)-3-(*t*-butyldiphenylsiloxymethyl)pyridin-6-yl]thiazole-4-carboxylate (34). To a solution of **33** (2.36 g, 3.82 mmol) in DMF (50 mL) were added, with stirring, Et_3N (0.80 mL, 5.73 mmol) and Pac-Br (1.14 g, 5.37 mmol) at 0 °C. After stirring for 30 min and at room temeperature for 6 h, the reaction mixture was added to water (50 mL). The resulting solution was extracted with EtOAc (30 mL × 3) and the combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **34** as a colorless amorphous material. Yield 83% (2.45 g). IR 3435, 3070, 2960, 2930, 2891, 2857, 2359, 1704, 1586 cm^{-1}. ^1H NMR δ 1.10 (s, 9H, TPS's Bu^t), 1.34 (d, 3H, CH_3, J = 6.6 Hz), 1.43 (s, 9H, Boc), 4.87 (s, 2H, CH_2), 4.75–4.97 (m, 1H, CHN), 5.66 (s, 2H, Pac's CH_2), 5.76 (br d, 1H, NH, J = 7.9 Hz), 7.35–7.72 (each m, 15H, TPS's and Pac's Ph × 3), 7.87 (d, 1H, pyridine's H, J = 7.9 Hz), 8.20 (d, 1H, pyridine's H, J = 7.9 Hz), 8.40 (s, 1H, thiazole's H). Found: C, 66.48; H, 6.01; N, 5.77%. Calcd for $C_{41}H_{45}N_3O_6SSi$: C, 66.91; H, 6.16; N, 5.71%.

Phenacyl (*RS*)-2-[2-(1-*t*-Butoxycarbonylaminoethyl)-3-(hydroxymethyl)pyridin-6-yl]thiazole-4-carboxylate (35). To a solution of **34** (1.0 g, 1.36 mmol) in THF (30 mL) was added, with stirring, TBAF (2.04 mL of 1 M THF, 2.04 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was concentrated in vacuo to give a residual substance. The residue was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give colorless crystals, which were recrystallized from a hexane–EtOAc to give **35** as colorless crystals. Yield 77% (0.52 g). Mp 173–174 °C. IR 3450, 3377, 3133, 2974, 2930, 2888, 1734, 1699, 1663, 1599, 1583 ,1518 cm^{-1}. ^1H NMR δ 1.41 (s, 9H, Boc), 1.51 (d, 3H, CH_3, J = 6.6 Hz), 3.95–4.80 (m, 1H, OH), 4.54–4.68 and 4.90–5.10 (each m, 2H, CH_2), 5.57 (br d, 1H, NH, J = 8.9 Hz), 5.65 (s, 2H, Pac's CH_2), 7.48–7.68 and 7.92–8.01 (each m, 5H, Pac's Ph), 7.84 (d, 1H, pyridine's H, J = 8.2 Hz), 8.19 (d, 1H, pyridine's H, J = 8.2 Hz), 8.40 (s, 1H, thiazole's H). Found: C, 60.27; H, 5.41; N, 8.58%. Calcd for $C_{25}H_{27}N_3O_6S$: C, 60.35; H, 5.47; N, 8.45%.

Phenacyl (*RS*)-2-(1*H*-2-*t*-Butoxycarbonyl-1-oxo-2,3-dihydropyrrolo[3,4-*b*]pyridin-5-yl)thiazole-4-carboxylate (36). To a solution of **35** (1.07 g, 2.15 mmol) in acetone (75 mL) was added 2.67 M Jones reagent (1.21 mL, 3.23 mmol) at 0 °C. After stirring for 40 min, the reaction mixture was mixed with *i*-PrOH (40 mL) and the precipitated Cr salt was filtered off. The filtrate was made to pH 9 with a saturated $NaHCO_3$ aqueous solution. Evaporation of acetone gave a residual solution, which was extracted with EtOAc (40 mL × 3); the combined extracts were washed with brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave residual crystals, which were purified on a silica-gel column using a mixture of hexane and EtOAc (1:2 v/v) to give crude crystals. Recrystallization from a hexane–EtOAc gave **36** as a colorless amorphous material. Yield 83% (0.88 g). IR 3749, 3417, 2931, 2360, 1738, 1596 cm^{-1}. ^1H NMR δ 1.63 (s, 9H, Boc), 1.77 (d, 3H, CH_3, J = 6.6 Hz), 5.14 (q, 1H, CHN, J = 6.6 Hz), 5.67 (s, 2H, CH_2), 7.50–7.68 and 7.97–8.00 (each m, 5H, Pac's Ph), 8.27 (d, 1H, pyridine's H, J = 7.9 Hz), 8.48 (d, 1H, pyridine's H, J = 7.9 Hz), 8.50 (s, 1H, thiazole's H). Found: C, 61.17; H, 4.52; N, 8.38%. Calcd for $C_{25}H_{23}N_3O_6S$: C, 60.84; H, 4.70; N, 8.51%.

(*RS*)-2-(1*H*-2-*t*-Butoxycarbonyl-1-oxo-2,3-dihydropyrrolo-[3,4-*b*]pyridin-5-yl)thiazole-4-carbonyl-L-Ser(TBS)-OBu^t (38). A solution of **36** (0.52 g, 1.05 mmol) and K_2CO_3 (0.44 g, 3.15 mmol) in water–THF (40 mL, 1:2 v/v) was stirred at 0 °C for 30 min and then at room temperature for 8 h. Evaporation of THF gave an aqueous solution, which was acidified to pH 4 with citric acid hydrate. The reaction mixture was extracted with EtOAc (20 mL × 2) and the combined extracts were washed with brine (10 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a free acid **37** as a residual substance, which was in situ dissolved in DMF (30 mL). To the resulting solution were added, with stirring, H-L-Ser(TBS)-OBu^t (0.32 g, 1.16 mmol), Et_3N (0.23 mL, 1.68 mmol), and DPPA (0.30 mL, 1.37 mmol) at 0 °C. After stirring for 30 min and at room temperature overnight, water (30 mL) was added to the reaction mixture, and the resulting solution was extracted with EtOAc (20 mL × 3). The combined extracts were washed with 10% citric acid (20 mL × 2), saturated $NaHCO_3$ aqueous solution (20 mL × 2), and brine (20 mL × 2) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of $CHCl_3$ and acetone (1:1 v/v) to give **38** as a colorless amorphous material. Yield 70% (0.47 g). IR 3418, 2932, 2857, 1783, 1748, 1682, 1594, 1537, 1506 cm^{-1}. ^1H NMR δ each 0.05 (each s, 6H, TBS's CH_3 × 2), 0.91 (s, 9H, TBS's Bu^t), 1.50 (s, 9H, Boc), 1.62 (s, 9H, OBu^t), diastereomer 1.74 and 1.75 (each d, 3H, CH_3, J = each 6.6 Hz), 3.94 and 4.17 (dABq, 2H, Ser's β-H, J = 2.3, 10.1 Hz), 4.68–4.78 (m, 1H, Ser's α-H), diastereomer each 5.12 (each q, 1H, C*H*CH_3, J = 6.6 Hz), 8.16 (br d, 1H, NH, J = 8.6 Hz), 8.25 (d, 1H, pyridine's H, J = 8.3 Hz), 8.29 (s, 1H, thiazole's H), 8.33 (d, 1H, pyridine's H, J = 8.3 Hz). Found: C, 56.75; H, 7.15; N, 8.45%. Calcd for $C_{30}H_{44}N_4O_7SSi$: C, 56.94; H, 7.01; N, 8.85%.

2-{3-Benzyloxycarbonyl-2-[(1*SR*)-1-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazole-4-carbonyl-L-Ser(TBS)-OBu^t (40). A solution of **38** (2.59 g, 4.09 mmol) and 1 M LiOH (12.27 mL, 12.27 mmol) in THF–water (100 mL, 2:1 v/v) was stirred at 0 °C for 30 min and at room temperature for 1 h. Evaporation of THF

gave a residual aqueous solution, which was extracted with EtOAc (50 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give a residue **39**, which was in situ dissolved in DMF (50 mL). To the resulting solution were added, with stirring, Et_3N (1.31 mL, 9.41 mmol) and Bn-Br (0.97 mL, 8.18 mmol) at 0 °C. After stirring for 30 min and at room temperature for 12 h, water (50 mL) was added to the reaction mixture and the resulting solution was extracted with EtOAc (30 mL × 3). The combined extracts were washed with 10% citric acid (30 mL × 3), saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **40** as a colorless amorphous material. Yield 67% (2.03 g) in two steps from **38**. IR 3419, 2977, 2931, 2885, 2857, 1720, 1677, 1584, 1536 cm^{-1}. ^1H NMR δ 0.04 and 0.05 (each s, 6H, TBS's CH_3 × 2), 0.90 (s, 9H, TBS's Bu^t), 1.37–1.50 (m, 12H, CH_3, Boc), 1.50 (s, 9H, O-*t*-Bu), 4.33 and 4.56 (dABq, 2H, Ser's β-H, J = 2.3, 10.1 Hz), 4.70–4.79 (m, 1H, Ser's α-H), 5.40 (s, 2H, Bn's CH_2), 5.68–5.88 (m, 2H, N*H*Boc, CH_3C*H*), 7.35–7.52 (m, 5H, Bn's Ph), diastereomer 8.08 and 8.09 (each d, 1H, pyridine's H, J = each 8.3 Hz), 8.14 (d, 1H, NH, J = 8.9 Hz), 8.26 (s, 1H, thiazole's H), 8.33 (d, 1H, pyridine's H, J = 8.3 Hz). Found: C, 59.88; H, 7.13; N, 7.17%. Calcd for $C_{37}H_{52}N_4O_8SSi$: C, 59.97; H, 7.07; N, 7.56%.

2-{3-Benzyloxycarbonyl-2-[(1*RS*)-1-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazole-4-thiocarbonyl-L-Ser(TBS)-OBu^t (41). A solution of **40** (1.31 g, 1.77 mmol) and Lawesson's reagent (0.72 g, 1.77 mmol) in DME (50 mL) was stirred at 50 °C for 12 h. The reaction mixture was concentrated in vacuo to give a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **41** as a yellow amorphous material. Yield 68% (0.91 g). IR 3439, 3352, 3115, 3091, 3066, 3033, 2928, 1956, 1722, 1583, 1501 cm^{-1}. ^1H NMR δ 0.01 and 0.04 (each s, 6H, TBS's CH_3 × 2), 0.88 (s, 9H, TBS's Bu^t), 1.43 (s, 9H, Boc), 1.46 (d, 3H, CH_3, J = 6.3 Hz), 1.52 (s, 9H, OBu^t), 4.17–4.19 (m, 2H, Ser's β-H), 5.27–5.32 (m, 1H, Ser's α-H), 5.41 (s, 2H, Bn's CH_2), 5.66–5.90 (m, 2H, N*H*Boc, CH_3C*H*), 7.34–7.50 (m, 5H, Bn's Ph), diastereomer 8.08 and 8.09 (each d, 1H, pyridine's H, J = each 8.3 Hz), diastereomer 8.33 and 8.34 (each d, 1H, pyridine's H, J = 8.3 Hz), 8.56 (s, 1H, thiazole's H), 9.96 (d, 1H, NH, J = 10.0 Hz). Found: C, 59.01; H, 6.88; N, 7.10%. Calcd for $C_{37}H_{52}N_4O_7S_2Si$: C, 58.69; H, 6.92; N, 7.40%.

2-{3-Benzyloxycarbonyl-2-[(1*R*)- and (1*S*)-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazole-4-thiocarbonyl-L-Ser-OBu^t (42 and 43). To a solution of **41** (0.22 g, 0.29 mmol) in THF (30 mL) was added, with stirring, 2 M HCl (30 mL) at room temperature for a few minutes. Evaporation of THF gave a aqueous solution, which was extracted with EtOAc (20 mL × 3). The combined extracts were washed with saturated $NaHCO_3$ aqueous solution (20 mL × 2), and brine (10 mL × 2), and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give a mixture of diastereomeric isomers as a crystalline material. The obtained crystals were again chromatographed on a silica-gel column using a mixture of $CHCl_3$ and acetone (50:1 v/v) to give **42** from first eluate and **43** from last eluate as yellow crystals. **42**: Yield 41% (76 mg). Mp 174.5–176.5 °C. $[\alpha]_D^{25}$ −33.6° (*c* 1.00, $CHCl_3$). IR 3392, 3302, 2981, 2934, 1725, 1692, 1584, 1522 cm^{-1}. ^1H NMR δ 1.43 (s, 9H, Boc), 1.45 (d, 3H, CH_3, J = 6.6 Hz), 1.55 (s, 9H, OBu^t), 2.20 (t, 1H, OH, J = 6.3 Hz), 4.12–4.20 and 4.28–4.46 (each m, 2H, Ser's β-H), 5.29–5.34 (m, 1H, Ser's α-H), 5.40 (s, 2H, Bn's CH_2), 5.63–5.91 (m, 2H, BocN*H*, CH_3C*H*), 7.34–7.49 (m, 5H, Bn's Ph), 8.14 (d, 1H, pyridine's H, J = 8.3 Hz), 8.34 (d, 1H, pyridine's H, J = 8.3 Hz), 8.55 (s, 1H, thiazole's H), 9.98 (br d, 1H, NH, J = 7.3 Hz). **43**: Yield 41% (76 mg). Mp 141–145 °C. $[\alpha]_D^{24}$ +95.7° (*c* 0.92, $CHCl_3$). IR 3551, 3428, 3331, 2978, 2932, 1710, 1581, 1509 cm^{-1}. ^1H NMR δ 1.43 (s, 9H, Boc), 1.45 (d, 3H, CH_3, J = 6.6 Hz), 1.55 (s, 9H, OBu^t), 2.15–2.17 (m, 1H, OH), 4.12–4.20 and 4.28–4.36 (each m, 2H, Ser's β-H), 5.28–5.33 (m, 1H, Ser's α-H), 5.40 (s, 2H, Bn's CH_2), 5.63–5.91 (m, 2H, BocN*H*, CH_3C*H*), 7.36–7.49 (m, 5H, Bn's Ph), 8.14 (d, 1H, pyridine's H, J = 8.3 Hz), 8.30 (d, 1H, pyridine's H, J = 8.3 Hz), 8.55 (s, 1H, thiazole's H), 9.98 (br d, 1H, NH, J = 7.3 Hz). Found: C,57.92; H, 6.01; N, 8.63%. Calcd for $C_{31}H_{38}N_4O_7S_2$: C, 57.93; H, 5.96; N, 8.72%.

***t*-Butyl (4*S*)-2-(2-{3-Benzyloxycarbonyl-2-[(1*R*)-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazol-4-yl)-4,5-dihydrothiazole-4-carboxylate (44).** To a solution of **42** (460 mg, 0.72 mmol) in THF (10 mL) were added, with stirring, Ph_3P (0.28 g, 1.08 mmol) and DEAD (0.28 mL, 1.08 mmol) (40% in toluene) at 0 °C. After stirring for 30 min, THF in the reaction mixture was evaporated and the residual substance was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **44** as a colorless syrup. **44**: Yield 69% (340 mg). $[\alpha]_D^{26}$ −50.9° (*c* 0.70, $CHCl_3$). IR 3435, 3113, 2977, 2931, 2360, 1719, 1606, 1583 cm^{-1}. ^1H NMR δ 1.43 (s, 9H, Boc), 1.46 (d, 3H, CH_3, J = 6.3 Hz), 1.53 (s, 9H, OBu^t), 3.63 (d, 2H, thiazoline's CH_2, J = 9.2 Hz), 5.22 (t, 1H, thiazoline's H, J = 9.2 Hz), 5.39 (s, 2H, Bn's CH_2), 5.62–5.89 (m, 2H, BocN*H*, C*H*NH), 7.34–7.49 (m, 5H, Bn's Ph), 8.17 (d, 1H, pyridine's H, J = 8.3 Hz), 8.20 (s, 1H, thiazole's H), 8.34 (d, 1H, pyridine's H, J = 8.3 Hz). Found: C, 59.50; H, 5.85; N, 8.90%. Calcd for $C_{31}H_{36}N_4O_6S_2$: C, 59.61; H, 5.77; N, 8.97%.

***t*-Butyl (4*S*)-2-(2-{3-Benzyloxycarbonyl-2-[(1*R*)-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazol-4-yl)thiazole-4-carboxylate (45).** A suspension of **44** (31 mg, 0.05 mmol) and MnO_2 (65 mg, 0.75 mmol) in toluene (1 mL) was stirred at room temperature for 20 h. The MnO_2 was filtered off and the filtrate was concentrated in vacuo to give a residual substance, which was purified on a silica-gel column using a mixture of hexane and EtOAc (3:1 v/v) to give **45** as a colorless syrup. Yield 77% (24 mg). $[\alpha]_D^{25}$ −44.7° (*c* 0.43, $CHCl_3$). IR 3434, 3108, 2975, 2931, 2361, 2342, 1718, 1583 cm^{-1}. ^1H NMR δ 1.44 (s, 9H, Boc), 1.47 (d, 3H, CH_3, J = 6.3 Hz), 1.64 (s, 9H, OBu^t), 5.40 (s, 2H, Bn's CH_2), 5.64–5.92 (m, 2H, BocN*H*, C*H*NH), 7.34–7.50 (m, 5H, Bn's Ph), 8.09 (s, 1H, thiazole's H), 8.18 (d, 1H, pyridine's H, J = 8.3 Hz), 8.32 (s, 1H, thiazole's H), 8.37 (d, 1H, pyridine's H, J = 8.3 Hz). Found: C, 59.69; H, 5.74; N, 8.66%. Calcd for $C_{31}H_{34}N_4O_6S_2$: C, 59.79; H, 5.50; N, 9.00%.

(4*S*)-2-(2-{3-Benzyloxycarbonyl-2-[(1*S*)-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazol-4-yl)-4,5-dihydrothiazole-4-carboxylate (46) and 2-(2-{3-Benzyloxycarbonyl-2-[(1*S*)-*t*-butoxycarbonylaminoethyl]pyridin-6-yl}thiazol-4-yl)thiazole-4-carboxylate (47). Similarly to the case of **42**, a treatment of **43** (460 mg) with Ph_3P (0.28 g) and DEAD (0.28 mL, 40% in toluene) was worked up to give a mixture of two chemical species, which were easily separated on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **46** from last eluate and **47** from first eluate as a colorless syrup. **46**: Yield 19% (84 mg). $[\alpha]_D^{26}$ +47.1° (*c* 0.31, $CHCl_3$). IR 3435, 3113, 2976, 2930, 2360, 1716, 1582 cm^{-1}. ^1H NMR δ 1.43 (s, 9H, Boc), 1.46 (d, 3H, CH_3,

J = 6.3 Hz), 1.53 (s, 9H, OBu^t), 3.63 (d, 2H, thiazoline's CH_2, J = 9.2 Hz), 5.23 (t, 1H, thiazoline's CH, J = 9.2 Hz), 5.39 (s, 2H, Bn's CH_2), 5.62–5.89 (m, 2H, BocN*H*, C*H*NH), 7.34–7.48 (m, 5H, Bn's Ph), 8.17 (d, 1H, pyridine's H, J = 8.3 Hz), 8.20 (s, 1H, thiazole's H), 8.34 (d, 1H, pyridine's H, J = 8.3 Hz). **47**: Yield 48% (211 mg). $[\alpha]_D^{26}$ +54.0° (c 0.50, $CHCl_3$). Found: C, 59.72; H, 5.63; N, 8.59%. Calcd for $C_{31}H_{36}N_4O_6S_2$: C, 59.60; H, 5.77; N, 8.97%. The IR and ^{1}H NMR spectra of **47** were completely identical with those of **45**.

(*S*)-2-(1-Hydroxyethyl)pyridine [(*S*)-49]. According to the method reported,[14] the treatment of 2-acetylpyridine (2.50 g, 26.64 mmol) with dry Yeast (56 g) and D-glucose (64 g) in water (500 mL) at room temperature for 24 h gave **(*S*)-49** as a colorless oil. Yield 48% (1.22 g). $[\alpha]_D^{26}$ −55.5° (c 1.61, EtOH). {lit.[14] $[\alpha]_D$ −55.5° (c 1.50, EtOH)}.

(*R*)-2-(1-Hydroxyethyl)pyridine [(*R*)-49]. A solution of **(*S*)-49** (1.56 mg, 1.27 mmol) and Ms-Cl (0.15 mL, 2.54 mmol) in the presence of Et_3N (0.53 mL, 3.81 mmol) in $CHCl_3$ (20 mL) was stirred at 0 °C for 30 min. The reaction mixture was washed with brine (10 mL × 3), dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give a residue. The residue was dissolved in DMF (20 ml), to which was added AcONa (313 mg, 3.81 mmol) and 15-crown-5-ether (18 µL, 0.13 mmol) at room temperature. After stirring for 24 h, to the reaction mixture was added water (20 mL) and then the resulting solution was extracted with EtOAc (20 mL × 2). The combined extracts were washed with brine (20 mL × 3), dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give a residue. The obtained residue was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give a residual oil. The oil was again dissolved in a MeOH–water (20 mL, 2:1 v/v), to which was added, with stirring, K_2CO_3 (263 mg, 1.91 mmol) at 0 °C for 30 min. After stirring for 3 h at room temperature, MeOH was evaporated and the residual aqueous layer was extracted with EtOAc (20 mL × 5). The combined extracts were washed once with brine (20 mL), dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give a residual oil. The obtained oil was purified on a silica gel column using EtOAc to give **(*R*)-49** as a colorless oil. Yield 46% (72 mg). $[\alpha]_D^{24}$ +56.2° (c 1.53, EtOH).

(*R*)-2-(1-Azidoethyl)pyridine [(*R*)-50]. A solution of **(*S*)-49** (185 mg, 1.50 mmol) and Ms-Cl (0.23 mL, 3.00 mmol) in the presence of Et_3N (0.62 mL, 4.50 mmol) in $CHCl_3$ (20 mL) was stirred at 0 °C for 30 min. The reaction mixture was washed with brine (10 mL × 3), dried over anhydrous Na_2SO_4 and then concentrated in vacuo to give a residual substance. The residue was dissolved in DMF (20 mL) and treated with NaN_3 (293 mg, 450 mmol) at room temperature. After stirring overnight, the reaction mixture was diluted with water (20 mL) and the resulting solution was extracted with EtOAc (20 mL × 2). The combined extracts were washed with brine (20 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual oil, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **(*R*)-50** as a colorless oil. Yield 75% (166 mg). $[\alpha]_D^{25}$ +61.1° (c 1.09, MeOH). IR 2981, 2933, 2110, 1592, 1473, 1436 cm^{-1}. ^{1}H NMR δ 1.61 (d, 3H, CH_3, J = 6.8 Hz), 4.68 (q, 1H, CH, J = 6.8 Hz), 7.18–7.30 (m, 1H, pyridine's H), 7.35 (d, 1H, pyridine's H, J = 7.8 Hz), 7.72 (dt, 1H, pyridine's H, J = 1.7, 7.8 Hz), 8.59 (d, 1H, pyridine's H, J = 4.9 Hz).

(*S*)-2-(1-Azidoethyl)pyridine [(*S*)-50]. Similarly to the above case, **(*R*)-50** was obtained from **(*R*)-49**. Yield 72% (160 mg). $[\alpha]_D^{24}$ −50.4° (c 1.10, MeOH).

(*R*)-2-(1-*t*-Butoxycarbonylaminoethyl)pyridine [(*R*)-51]. A suspension of **(*R*)-50** (166 mg, 1.12 mmol) and 10% Pd–C (10 mg) in EtOH (20 mL) under H_2 gas stream was stirred at room temperature for 30 min. The Pd–C was filtered off, the filtrate was concentrated in vacuo to give a residue, which was dissolved in $CHCl_3$ (20 mL). To the resulting solution was added, with stirring, Boc_2O (367 mg, 1.68 mmol) and Et_3N (0.91 mL, 1.34 mmol) at 0 °C. After stirring for 3 h, the reaction mixture was washed with brine (10 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **(*R*)-51** as a colorless syrup. Yield 81% (202 mg). $[\alpha]_D^{25}$ +49.7° (c 1.01, MeOH). IR 3336, 2976, 2931, 1712, 1592, 1572, 1496, 1444 cm^{-1}. ^{1}H NMR δ 1.44 (s, 9H, Boc), 1.37–1.52 (m, 3H, CH_3), 4.74–4.94 (m, 1H, CH), 5.64–5.78 (m, 1H, NH), 7.12–7.28 (m, 2H, pyridine's H × 2), 7.64 (dt, 1H, pyridine's H, J = 1.7, 7.8 Hz), 8.54 (d, 1H, pyridine's H, J = 4.9 Hz). Found: C, 64.37; H, 7.97; N, 12.23%. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60%.

(*S*)-2-(1-*t*-Butoxycarbonylaminoethyl)pyridine [(*S*)-51]. Similarly to the above case, **(*S*)-51** was obtained from **(*S*)-50**. Yield 78% (194 mg). $[\alpha]_D^{25}$ −54.1° (c 0.98, MeOH). Found: C, 64.88; H, 8.05; N, 12.62%. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-OMe (53). A solution of **52** (3.0 g, 12.92 mmol), DCC (2.9 g, 14.21 mmol), HOSu (1.6 g, 14.21 mmol), and HCl·H-Gly-OMe (1.15 g, 12.92 mmol) in CH_2Cl_2 (70 mL) was stirred at 0 °C for 30 min and at room temperature for 6 h. The precipitated DCC urea salt was filtered off, the filtrate was added to diethyl ether (80 mL). The resulting solution was washed with 10% citric acid (50 mL × 3), saturated $NaHCO_3$ aqueous solution (50 mL × 3), and brine (50 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give colorless crystals. Recrystallization from a hexane–EtOAc gave **53** as colorless needles. Yield 70% (2.64 g). Mp 135–137 °C. $[\alpha]_D^{23}$ −4.40° (c 1.80, MeOH). IR 3328, 2980, 1755, 1710, 1671, 1566 cm^{-1}. ^{1}H NMR δ 1.38 (d, 3H, Thr's CH_3, J = 5.7 Hz), 1.44 (s, 9H, Boc), 1.61 and 1.63 (each s, 6H, Isop's CH_3 × 2), 3.77 (s, 3H, OMe), 3.75–3.78 (m, 1H, Thr's β-H), 4.08 (d, 2H, Gly's CH_2, J = 5.1 Hz), 4.05–4.11 (m, 1H, Thr's α-H), 6.38–6.70 (br d, 1H, Gly's NH). Found: C, 44.07; H, 9.54; N, 9.98%. Calcd for $C_{17}H_{26}N_2O_6$: C, 44.43; H, 9.69; N, 10.36%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-OH (54). To a solution of **53** (205 mg, 0.60 mmol) in water–dioxane (30 mL, 1:1 v/v) was added 1 M LiOH (0.90 mL, 0.90 mmol) at 0 °C. After stirring for 30 min, the reaction mixture was washed with diethyl ether (10 mL × 3), and the resulting aqueous solution was acidified to pH 4 with citric acid hydrate and then extracted with EtOAc (10 mL × 3). The combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo gave colorless crystals, which were recrystallized from a hexane–EtOAc to give **54** as colorless needles. Yield 98% (194 mg). Mp 175–176 °C. $[\alpha]_D^{24}$ +180.8° (c 0.1, MeOH). IR 3289, 2980, 2932, 1749, 1668, 1578 cm^{-1}. ^{1}H NMR δ 1.40 (d, 3H, Thr's CH_3, J = 6.1 Hz), 1.44 (s, 9H, Boc), 1.59 and 1.62 (each s, 6H, Isop's CH_3 × 2), 3.89 (d, 1H, Thr's β-H, J = 7.6 Hz), 4.08–4.11 (m, 2H, Gly's CH_2), 4.23–4.18 (m, 1H, Thr's α-H), 6.68–6.95 (br s, 1H, Gly's NH), 8.46–8.70 (br s, 1H, COOH). Found: C, 53.05; H, 7.55; N, 8.53%. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N,

8.86%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-L-Thr(TBS)-OMe (55). To a solution of **54** (4.84 g, 14.22 mmol) in DMF (50 mL) were added, with stirring, HOBt (2.88 g, 21.33 mmol) at 0 °C for 10 min and then DCC (3.95 g, 19.13 mmol). After stirring for 30 min at 0 °C, H-L-Thr(TBS)-OMe (3.52 g, 14.22 mmol) was added, and the resulting solution was further stirred at room temperature for 6 h. The precipitated DCC urea salt was filtered off and the filtrate was added to water (50 mL). The solution was extracted with EtOAc (40 mL × 3) and the combined extracts were washed with 10% citric acid (30 mL × 2), a saturated $NaHCO_3$ aqueous solution (30 mL × 2), and brine (30 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and EtOAc (2:1 v/v) to give **55** as a colorless syrup. Yield 96% (7.45 g). $[\alpha]_D^{28}$ −51.4° (*c* 0.86, MeOH). IR 3376, 3334, 2920, 2890, 2854, 1662, 1503 cm^{-1}. ^1H NMR (DMSO-d_6) δ 0.01 and 0.05 (each s, 6H, TBS's CH_3 × 2), 0.86 (s, 9H, TBS's Bu^t), 1.11 (d, 3H, Thr's CH_3, J = 6.3 Hz), 1.31 (d, 3H, Thr's CH_3, J = 5.9 Hz), 1.36 (s, 9H, Boc), 1.51 and 1.52 (each s, 6H, Isop's CH_3 × 2), 3.65 (s, 3H, OCH_3), 3.65–3.85 (m, 2H, Gly's CH_2), 3.98–4.19 (m, 2H, Thr's α-H, Thr's β-H), 4.31–4.36 (m, 1H, Thr's β-H), 4.43–4.47 (m, 1H, Thr's α-H), 7.44 (d, 1H, Thr's NH, J = 8.9 Hz), 8.19–8.23 (br s, 1H, Gly's NH). Found: C, 55.02; H, 8.97; N, 7.56%. Calcd for $C_{25}H_{47}N_3O_8Si$: C, 55.02; H, 8.68; N, 7.70%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-L-Thr-OMe (56). A solution of **55** (3.48 g, 6.38 mmol) in THF (80 mL) in the presence of TBAF (9.57 mL in 1 M THF, 9.57 mmol) was stirred at 0 °C for 5 min and then at room temperature for 30 min. The reaction mixture was concentrated in vacuo to give a residue, which was purified on a silica-gel column using EtOAc to give **56** as a colorless syrup. Yield 83% (2.28 g). $[\alpha]_D^{23}$ −44.3° (*c* 0.94, MeOH). IR 3338, 3079, 2981, 2937, 1748, 1666, 1534 cm^{-1}. ^1H NMR δ 1.22 (d, 3H, Thr's CH_3, J = 6.3 Hz), 1.40 (d, 3H, Thr's CH_3, J = 5.9 Hz), 1.45 (s, 9H, Boc), 1.61 (s, 6H, Isop's CH_3 × 2), 3.59–3.76 (br s, 1H, OH), 3.76 (s, 3H, OCH_3), 3.80–3.83 (m, 1H, Thr's α-H), 4.16–4.24 (m, 1H, Thr's β-H), 4.34–4.41 (m, 1H, Thr's β-H), 4.61 (dd, 1H, Thr's β-H, J = each 9.2 Hz), 7.00–7.24 (br s, 2H, NH × 2). Found: C, 52.07; H, 7.75; N, 9.14%. Calcd for $C_{19}H_{33}N_3O_8 \cdot 0.5H_2O$: C, 51.81; H, 7.78; N, 9.54%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-(*Z*)-ΔAbu-OMe (57). A solution of **56** (1.16 g, 2.69 mmol) and Ms-Cl (0.25 mL, 3.23 mmol) in $CHCl_3$ (50 mL) in the presence of Et_3N (0.75 mL, 5.38 mmol) was stirred at 0 °C for 30 min. To the resulting solution was further added DBU (4.02 mL, 26.90 mmol). After stirring at 0 °C for 10 min and at room temperature for 6 h, the reaction mixture was washed with 10% citric acid (20 mL × 2), saturated $NaHCO_3$ aqueous solution (20 mL × 3), and brine (20 mL × 2) and the dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using EtOAc to give a crystalline residue. Recrystallization from a hexane–EtOAc gave **57** as colorless fibrous. Yield 89% (0.99 g). Mp 141–142 °C. $[\alpha]_D^{28}$ −15.6° (*c* 0.87, MeOH). IR 3286, 2968, 1701, 1641, 1521 cm^{-1}. ^1H NMR δ 1.35 (d, 3H, Thr's CH_3, J = 5.9 Hz), 1.37 (s, 9H, Boc), 1.58 (s, 6H, Isop's CH_3 × 2), 1.74 (d, 3H, ΔAbu's CH_3, J = 7.1 Hz), 3.71 (s, 3H, OMe), 3.76–4.40 (m, 4H, Thr's α-H, Thr's β-H, Gly's CH_2), 6.84 (q, 1H, ΔAbu's H, J = 7.1 Hz), 6.92–7.20 (br s, 1H, Gly's NH), 8.29–8.64 (br s, 1H, ΔAbu's NH). Found: C, 55.32; H, 7.80; N, 9.68%. Calcd for $C_{19}H_{31}N_3O_7$: C, 55.19; H, 7.56; N, 10.16%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-(*Z*)-ΔAbu-OH (58). To a solution of **57** (1.50 g, 3.63 mmol) in water–dioxane (100 mL, 1:1 v/v) was added, with stirring, 1 M LiOH (5.45 mL, 5.45 mmol) at 0 °C. After stirring for 30 min and at room temperature for 6 h, the reaction mixture was washed with diethyl ether (30 mL × 2) and acidified to pH 4 with citric acid hydrate. The resulting solution was extracted with EtOAc (30 mL × 3) and the combined extracts were washed with brine (20 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a crystalline residue, which was recrystallized from a hexane–EtOAc to give **58** as colorless needles. Yield 98% (1.43 g). Mp 174–175 °C. $[\alpha]_D^{26}$ −17.4° (*c* 1.01, MeOH). IR 3281, 3058, 2981, 2936, 2360, 2342, 1707, 1669, 1528 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.31 (d, 3H, Thr's CH_3, J = 5.9 Hz), 1.36 (s, 9H, Boc), each 1.52 (each s, 6H, Isop's CH_3 × 2), 1.67 (d, 3H, ΔAbu's CH_3, J = 7.3 Hz), 3.75–4.10 (m, 4H, Thr's α-H, Thr's β-H, Gly's CH_2), 6.58 (q, 1H, ΔAbu's H, J = 7.3 Hz), 8.15–8.23 (br s, 1H, Gly's NH), 8.70–8.59 (br s, 1H, ΔAbu's NH), 12.07–12.21 (br s, 1H, COOH). Found: C, 54.28; H, 7.46; N, 10.20%. Calcd for $C_{18}H_{29}N_3O_7$: C, 54.13; H, 7.32; N, 10.52%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-(*Z*)-ΔAbu-L-Pro-OMe (59). To a solution of **58** (1.38 g, 3.45 mmol) in DMF (50 mL) were added, with stirring, HOBt (0.70 g, 5.18 mmol) at 0 °C for 10 min and DCC (0.89 g, 4.31 mmol). After stirring for 30 min, H-Pro-OMe (0.53 g, 4.14 mmol) was added to the resulting solution, which was then further stirred at 0 °C for 30 min and at room temperature for 6 h. The precipitated DCC urea salt was filtered off, the filtrate was added to water (60 mL), and the solution was extracted with EtOAc (30 mL × 3). The combined extracts were washed with 10% citric acid (30 mL × 2), saturated $NaHCO_3$ aqueous solution (30 mL × 3), and brine (30 mL × 3) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was purified on a silica-gel column using a mixture of hexane and acetone (1:1 v/v) to give **59** as a colorless amorphous. Yield 71% (1.25 g). $[\alpha]_D^{24}$ −41.4° (*c* 0.4, MeOH). IR 3310, 2980, 1877, 1746, 1671, 1617 cm^{-1}. ^1H NMR (DMSO-d_6) δ 1.29 (d, 3H, Thr's CH_3, J = 5.5 Hz), 1.35 (s, 9H, Boc), 1.50 and 1.51 (each s, 6H, Isop's CH_3 × 2), 1.65 (d, 3H, ΔAbu's CH_3, J = 6.7 Hz), 1.75–1.92 (m, 3H, Pro's H and H_2), 2.08–2.15 (m, 1H, Pro's H), 3.38–3.43 (br s, 1H, Pro's H), 3.56–3.62 (m, 1H, Pro's H), 3.62 (s, 3H, OCH_3), 3.72–4.09 (m, 4H, Thr's α-H, Thr's β-H, and Gly's CH_2), 4.29–4.45 (br s, 1H, Pro's H), 5.45–5.69 (br s, 1H, ΔAbu's H), 8.10–8.20 (br s, 1H, Gly's NH), 8.94–9.12 (br s, 1H, ΔAbu's NH). Found: C, 56.98; H, 7.11; N, 10.83%. Calcd for $C_{24}H_{38}N_4O_8$: C, 56.75; H, 7.54; N, 11.03%.

(*S*)-3-*t*-Butoxycarbonyl-2,2,5-trimethyloxazolidine-4-carbonyl-Gly-(*Z*)-ΔAbu-L-Pro-OH [(P)-6]. A solution of **59** (1.25 g, 2.45 mmol) and 1 M LiOH (3.68 mL) in a mixture of H_2O–dioxane (30 mL, 1:1 v/v) was stirred at 0 °C for 10 min and then at room temperature for 1 h. The reaction mixture was washed with diethyl ether (30 mL × 3). The aqueous layer was acidified with citric acid hydrate to pH 4 and then extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (30 mL × 3) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a colorless syrup **(P)-6**, quantitatively, which was used to the reaction with **(P)-3**.

The Protected Fragment A-B [(P)-3]. To a solution of **44** (78 mg, 0.13 mmol) in $CHCl_3$ (2 mL) was added TFA (3 mL) at room temperature. After stirring for 5 h, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in

$CHCl_3$ (5 mL). The resulting solution was stirred with Et_3N (30 µL, 0.20 mmol) and Boc_2O (42 mg, 0.20 mmol) at 0 °C for 30 min and at room temperature for 5 h. The reaction mixture was mixed with 10% citric acid (5 mL). The organic layer was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a colorless syrup **60**, which was dissolved in DMF (10 mL). To the resultant solution was added **(P)-4**, derived by deprotection of the Boc group of **19** (92 mg, 0.13 mmol) with TFA–$CHCl_3$ (10 mL, 2:3 v/v) at room temperature for 30 min, and then *N*,*N*-diisopropylethylamine (40 µL, 0.23 mmol) and BOP (75 mg, 0.17 mmol) at 0 °C. After stirring for 30 min and at room temperature for 4 h, the reaction mixture was mixed with water (10 mL) and extracted with EtOAc (10 mL × 3). The combined extracts were washed with 10% citric acid (10 mL × 2), saturated $NaHCO_3$ aqueous solution (10 mL × 2), brine (10 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silica-gel column using a mixture of hexane and EtOAc (1:1 v/v) to give **(P)-3** as a colorless syrup. Yield 58% (87 mg) from **44** in three steps. $[\alpha]_D^{22}$ +11.1° (*c* 0.27, $CHCl_3$). IR 3389, 2929, 2333, 1715, 1684, 1582, 1489, 1438 cm^{-1}. ^1H NMR δ diastereomer 0.93 and 0.95 (each s, 9H, TPS's Bu^t), 1.29–1.65 (m, 12H, Boc, C*H*$_3$CH), 3.62–3.85 (m, 4H, thiazoline's CH_2 × 2), diastereomer 3.86 (each s, 3H, OCH_3), 3.94–4.14 (m, 2H, CH_2O), 4.37 (d, 1H, C*H*CH_2O, J = 10.5 Hz), 5.28–5.39 (m, 2H, thiazoline's H × 2), 5.40 (s, 2H, Bn's CH_2), 5.46–5.54 (m, 1H, CONH), 5.63–5.85 (m, 2H, BocNH, CH_3CH), 7.20–7.60 (m, 15H, TPS's Ph × 2, Bn's Ph), 7.98–8.10 (m, 3H, thiazole's H × 3), 8.15 and 8.34 (each d, 2H, pyridine's H, J = 7.5 Hz). Found: C, 58.00; H, 4.99; N, 9.88%. Calcd for $C_{56}H_{58}N_8O_8S_5Si$: C, 58.01; H, 5.04; N, 9.66%.

The Protected Fragment A-B-C [(P)-2]. A solution of **(P)-3** (51 mg, 0.04 mmol) and TFA (1 mL) in $CHCl_3$ (1.5 mL) was stirred at room temperature for 30 min. The reaction mixture was concentrated in vacuo to give a residual syrup, which was dissolved in DMF (5 mL). To the resulting solution were added, with stirring, **(P)-6** (44 mg, 0.08 mmol), *N*,*N*-diisopropylethylamine (14 µL, 0.07 mmol), and BOP (25 mg, 0.05 mmol) at 0 °C. After stirring for 30 min and at room temperature for 12 h, the reaction mixture was mixed with water (5 mL) and the resulting solution was extracted with EtOAc (10 mL × 2). The combined extracts were washed with 10% citric acid (5 mL × 2), saturated $NaHCO_3$ aqueous solution (5 mL × 2), and brine (5 mL × 2), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a syrup, which was purified on a silica-gel column using a mixture of $CHCl_3$ and MeOH (20:1 v/v) to give **(P)-2** as a pale-yellow syrup. Yield 76% (47 mg). $[\alpha]_D^{22}$ −38.8° (*c* 0.50, MeOH). IR 3310, 2973, 2931, 1677, 1507, 1437 cm^{-1}. ^1H NMR (DMSO-d_6, 80 °C) δ 0.90–0.98 (m, 9H, TPS's Bu^t), 1.28–1.55 (m, 15H, Thr's CH_3, ΔAbu's CH_3, pyridine-CHC*H*$_3$, Isop's CH_3 × 2), 1.37 (s, 9H, Boc), 1.67–1.80 (m, 2H, Pro's H_2), 1.83–1.93 (m, 1H, Pro's H), 1.97–2.07 (m, 1H, Pro's H), 3.32–3.44 (m, 1H, Pro's H), diastereomer 3.77 and 3.79 (each s, 3H, OCH_3), 3.56–4.27 (m, 11H, Pro's H_2, thiazoline's CH_2 × 2, Thr's β-H, Gly's CH_2, CHC*H*$_2$O), 5.45 (s, 2H, Bn's CH_2), 5.36–5.53 (m, 4H, Pro's H, C*H*CH_2O, thiazoline's CH × 2), 5.71–5.84 (m, 2H, ΔAbu's olefin-H, pyridine-C*H*CH_3), 7.32–7.62 (m, 15H, TPS's Ph × 2, Bn's Ph), 8.03–8.42 (m, 7H, pyridine-CHN*H*, pyridine's H × 2, thiazole's H × 3, Gly's NH), 9.05 (br s, 1H, ΔAbu's NH). Found: C, 57.95; H, 5.67: N, 10.49%. Calcd for $C_{74}H_{84}N_{12}O_{13}S_5Si$: C, 57.79; H, 5.51; N, 10.93%.

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