Convenient Synthesis of the Central 3,6-Di(2-thiazolyl)-2-(4-thiazolyl)-pyridine Skeleton of a Macrocyclic Antibiotic, GE 2270 A

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It was shown that 6-dimethoxymethyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**5**) is easily convertible into the titled ring system by a stepwise method. Both the 3-cyano and 6-dimethoxymethyl groups of **5** were converted into 2-thiazolyl groups via the thioamide and carbaldehyde groups by Hantzsch and Shioiri methods, respectively. The 2-pyridone function was changed to a bromoacetyl group via the coupling reaction between the corresponding triflate and ethyl vinyl ether, and then converted into the 4-thiazolyl group. Thus, the useful 3,6-di(2-thiazolyl)-2-(4-thiazolyl)pyridine derivative for the total synthesis of GE 2270 A was obtained. In fact, the method was recently applied to the total synthesis of an antibiotic, micrococcin P, which has a similar central skeleton.

Antibiotics, GE 2270 A (**1**)[1] and micrococcin P (**2**),[2] isolated from the cultures of *Planobispora rosea* and *Bacillus pumilus*, respectively, have very unusual macrocyclic structures. These two antibiotics both include a unique central heterocyclic skeleton, 3,6-di(2-thiazolyl)-2-(4-thiazolyl)pyridine; however, the thiazolylthiazole function at the 6-position in the latter (**2**) is 4-(2-thiazolyl)thiazol (**4**), but it is 2-(4-thiazolyl)thiazol (**3**) at the 2-position in the former (**1**), as shown in Fig. 1. Although the absolute configurations of the six chiral centers in **1** have not yet been identified, they are deduced to originate from natural amino acids. The interesting structures and bioactivities of **1** and **2** attracted and prompted us to investigate their total syntheses and structure-bioactivity relationships.

In connection with the synthesis of **2**, the micrococcinic acid (**4**, R = propanoyl), obtained by the acidic hydrolysis of **2**, has already been synthesized by the cross-coupling method of heterocycles into the 2,3,6-positions of the pyridine nucleus,[3] and recently, synthesis of a similar derivative by the ring closure of 1,5-diketone provided with thiazoles by ammonia was also reported.[4] Independently, we have investigated the synthesis of a useful derivative of **4**[5] by the stepwise construction of thiazole substituents into 6-dimethoxymethyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (**5**)[6] and, very recently, the first total synthesis of **2** was reported.[7] Moreover, a similar central heterocyclic skeleton of 3-pyridinol (Fragment A)[8] of an antibiotic, nosiheptide,[9] was also synthesized by a similar method, starting from 5-hydroxypyridine-3-carbonitrile.

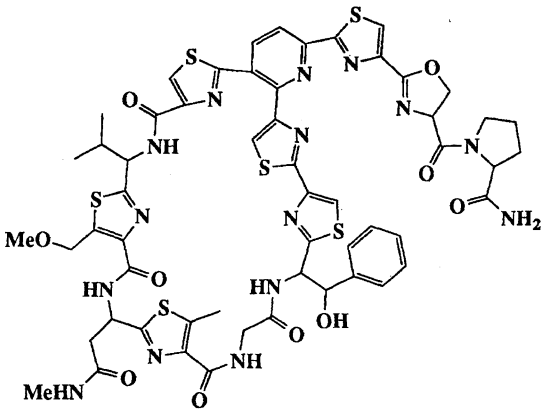
In this paper, we would like to report in detail the convenient synthesis of **27** [**3**: R = 3-*t*-butoxycarbonyl (Boc)-2,2-dimethyl-5-phenyl-4-oxazolidinyl] by extending the method used for the synthesis of **4**.

Results and Discussion

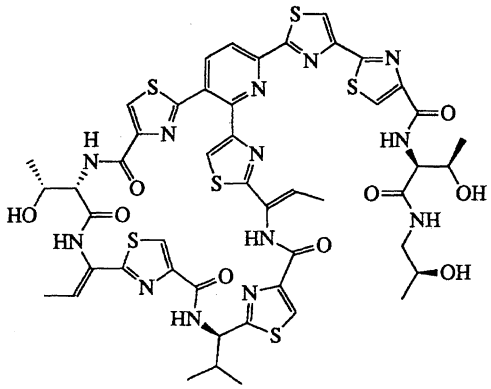
First of all, to synthesize the key compound ethyl 2-[6-dimethoxymethyl-2-(1-ethoxyvinyl)-3-pyridyl]thiazole-4-carboxylate (**9**), of which the 2-(1-ethoxyvinyl) and 6-dimethoxymethyl (acetal) groups, respectively, are convertible into the bromoacetyl and formyl groups and further to the desired thiazole moieties by the Hantzsch[10] and Shioiri methods,[11] compound **5** was chosen as the starting material.

The 3-cyano group of **5** was readily thioamidated with H_2S gas in the presence of 4-dimethylaminopyridine (DMAP) and Et_3N to give 6-dimethoxymethyl-1,2-dihydro-2-oxopyridine-3-carbothioamide (**6**) in 90% yield. Subsequently, by the Hantzsch method, thiazolination of the 3-thioamido group with ethyl 3-bromo-2-oxopropanoate in the presence of $KHCO_3$ and then dehydration with trifluoroacetic anhydride (TFAA) in the presence of pyridine afforded the corresponding 2-(3-pyridyl)thiazole-4-carboxylate derivative **7**. Then, triflation of **7** with trifluoromethanesulfonic (triflic) anhydride (Tf_2O) in the presence of DMAP proceeded smoothly to give ethyl 2-(6-dimethoxymethyl-2-trifluoromethylsulfonyloxy-3-pyridyl)thiazole-4-carboxylate (**8**) in 93% yield. The thus-obtained **8** had the 2-TfO group replaced with an ethoxyvinyl group. Reaction of **8** with ethyl vinyl ether in the presence of Et_3N using 1,3-bis(diphenylphosphino)propane (dppp) and $Pd(OAc)_2$ as catalysts gave the expected corresponding 2-(1-ethoxyvinyl)pyridine derivative **9** in 73% yield.

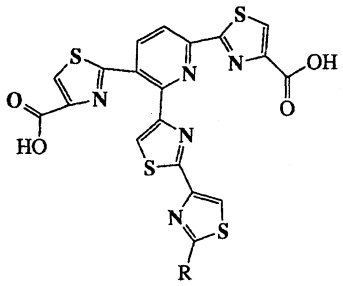
The next steps are the conversion of the 2-(1-ethoxyvinyl) and 6-dimethoxymethyl groups of **9** into 2-(4-thiazolyl) and 6-(2-thiazolyl) groups, respectively; the former was examined after changing the acid-labile acetal group into a stable carboxylic group. Thus, the 6-acetal group of **8**



GE 2270 A (1)



Micrococcin P (2)



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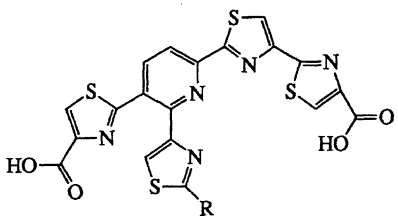

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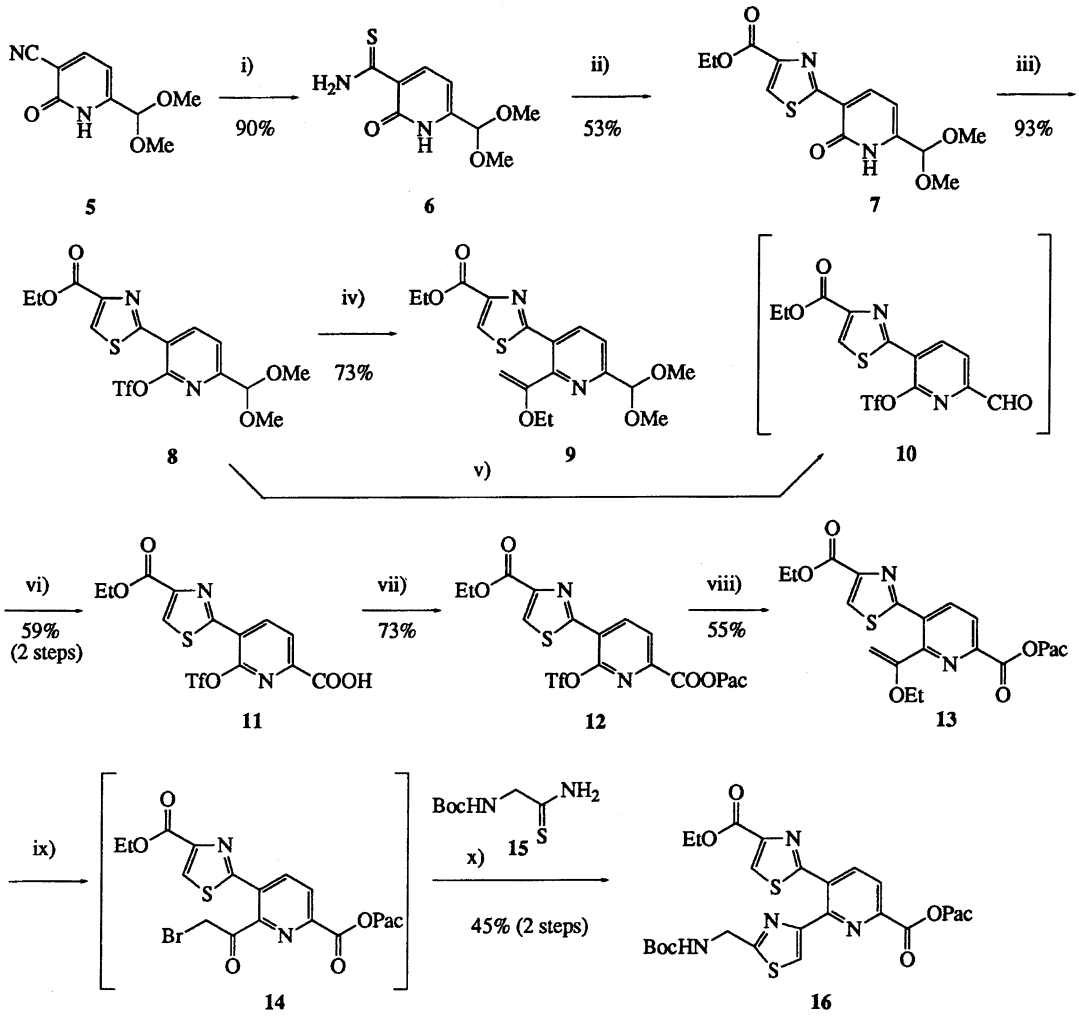
Fig. 1.

was transformed successively to 6-formyl-**10**, 6-carboxy-**11**, and 6-phenacyloxycarbonyl-**12** groups. A substitution reaction of **12** with ethyl vinyl ether gave the corresponding 2-(1-ethoxyvinyl)-6-phenacyloxycarbonyl derivative **13**. The subsequent bromination of **13** with NBS in H_2O–THF occurred eventually to give the corresponding 2-bromoacetyl derivative **14** as an unstable intermediate. Without isolation, one-pot thiazolation of the bromoacetyl group of **14** in situ with 2-(*N*-*t*-butoxycarbonyl)aminoethanethioamide (**15**) in the presence of $KHCO_3$ and then with TFAA in the presence of pyridine gave the expected phenacyl 6-[2-(*t*-butoxycarbonylaminomethyl)-4-thiazolyl]-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine-2-carboxylate (**16**) in 45% yield in two steps, as shown in Scheme 1. Thus, the bromination of the 1-ethoxyvinyl group of **13** was found to proceed readily.

From the ^{1}H NMR spectrum of **16**, the disappearance of the signals due to vinyl protons of the ethoxyvinyl group at the 2-position of **13**, the appearance of two thiazole ring protons at $\delta = 7.82$ and 8.24 as two singlets, and the presence of 4,5-vicinal protons of the pyridine ring at $\delta = 8.30$ and 8.48 (d, $J = 7.9$ Hz) indicate unambiguously the formation of the expected 5,6-dithiazolylpyridine derivative.

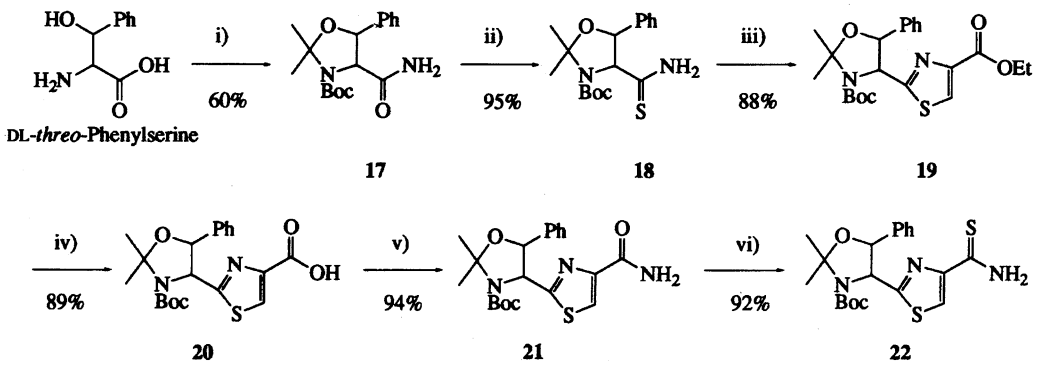
As the necessary building block for the construction of the 2-(4-thiazolyl)thiazol-4-yl group, 2-[3-(*t*-butoxycarbonyl)-2,2-dimethyl-5-phenyl-4-oxazolidinyl]thiazole-4-carbothioamide (**22**) was synthesized as follows. At first, *N*-protection of DL-*threo*-3-phenylserine (3-PhSer–OH) with di-*t*-butyl dicarbonate (Boc_2O) in the presence of Et_3N formed the corresponding *N*-Boc–3-PhSer–OH derivative. Both the Boc–amino and hydroxy groups were further protected with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTS) and then the ester group was amidated with 28% aqueous NH_3 to give *trans*-3-(*t*-butoxycarbonyl)-2,2-dimethyl-5-phenyloxazolidine-4-carboxamide (**17**) in 60% yield in three steps. Subsequent thioamidation of **17** with Lawesson's reagent gave the corresponding carbothioamide derivative (**18**), the thioamide group of which was thiazolated by treatment with ethyl 3-bromo-2-oxopropanoate and then with TFAA to give ethyl 2-(3-*t*-butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidin-4-yl)thiazole-4-carboxylate (**19**) in 88% yield. After the ester hydrolysis of **19** with excess NaOH, the obtained free acid **20** was transformed into the corresponding amide **21**, the amide group of which was thioamidated to give the expected **22** in an almost quantitative yield, as shown in Scheme 2.

Subsequently, the thus-obtained **22** was submitted to the formation of the thiazolylthiazole function. Similarly to the case of **16**, the compound **9** was converted to the corresponding bromoacetyl derivative **23** by treatment with NBS, which was soon treated with the thioamide **22** to give the corresponding 2-[2-(4-thiazolyl)thiazol-4-yl]pyridine derivative **24**. For the conversion of the 6-acetal group of **24** into the 2-thiazolyl group, it was hydrolyzed with 3 M (1 M = 1 mol dm^{-3}) HCl in THF to form the corresponding 6-formylpyridine derivative (**25**), and then condensed with phenacyl L-cysteinate (**26**),[12] which was readily derived from L-cysteine via 3-*t*-butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxylic acid via its phenacyl ester, by the method reported by



i) H_2S, DMAP, Et_3N, pyridine, r.t., 3 days, ii) a) $KHCO_3$, $BrCH_2COCOOEt$, THF, 0 °C, 1 h, then r.t., overnight, b) TFAA, pyridine, THF, 0 °C, 1 h, then r.t., overnight, iii) Tf_2O, DMAP, pyridine, 0 °C, 1 h, then r.t., overnight, iv) ethyl vinyl ether, Et_3N, dppp, $Pd(OAc)_2$, toluene, reflux, overnight, v) 3 M HCl, THF, r.t., 2 d, vi) Jones reagent, acetone, 0 °C, 15 min, vii) PacBr, Et_3N, DMF, 0 °C, 1 h, then, r.t., overnight, viii) ethyl vinyl ether, Et_3N, dppp, $Pd(OAc)_2$, toluene, reflux, 6 h, ix) NBS, THF–H_2O, r.t., 5 min, x) a) $KHCO_3$, **15**, DME, 0 °C, 1 h, then r.t., overnight, b) TFAA, pyridine, 0 °C, 2 h.

Scheme 1.

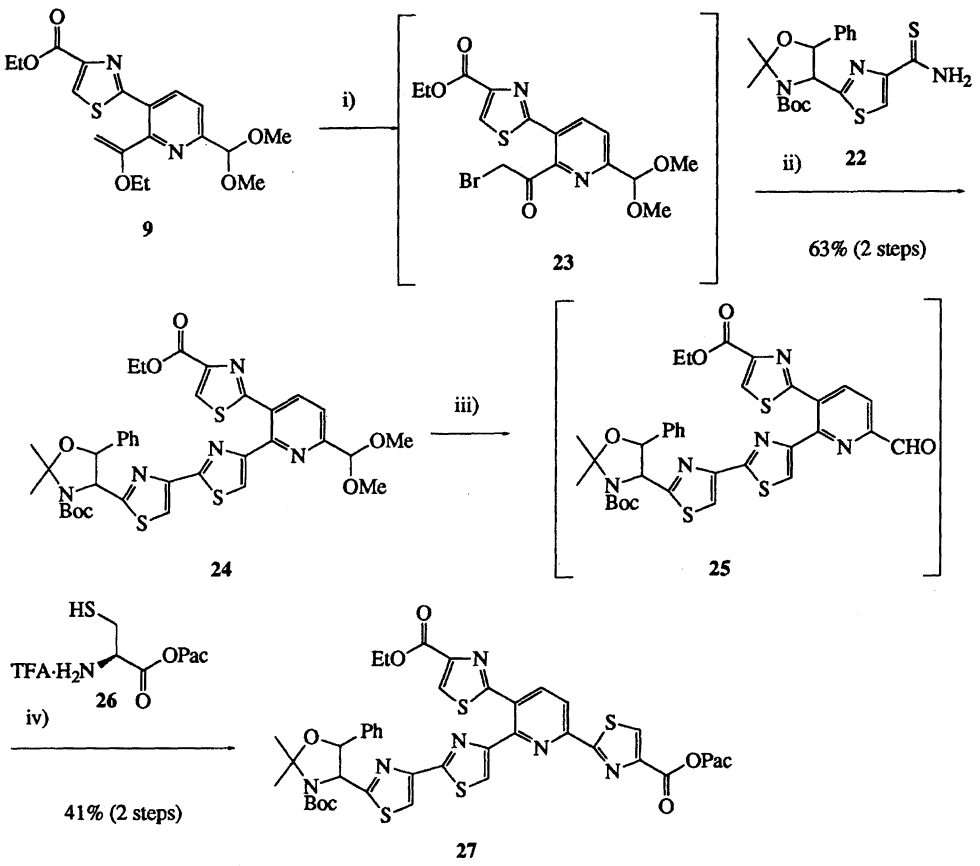


i) a) Boc_2O, dioxane, H_2O, 0 °C, 30 min, then r.t., 6 h, b) DMP, PTS, CH_2Cl_2, r.t., 24 h, c) ClCOOEt, Et_3N, THF, 0 °C, 20 min, d) 28% NH_3, THF, 0 °C, 30 min, ii) Lawesson's reagent, dioxane, reflux, 3 h, iii) a) $KHCO_3$, $BrCH_2COCOOEt$, THF, 0 °C, 30 min, then r.t., 24 h, b) TFAA, pyridine, 0 °C, 2 h, iv) MeOH–H_2O, NaOH, 0 °C, 30 min, then r.t., 24 h, v) a) ClCOOEt, Et_3N, THF, 0 °C, 10 min, b) 28% NH_3, THF, 0 °C, 10 min, vi) Lawesson's reagent, DME, r.t., 24 h.

Scheme 2.

Shioiri and co-workers,[11] followed by treatment with MnO_2, to give the desired ethyl 2-(2-{2-[2-(3-*t*-butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidin-4-yl)thiazol-4-yl]thiazol-4-yl}-6-[4-(phenacyloxycarbonyl)thiazol-2-yl]pyridin-3-yl)-thiazole-4-carboxylate (**27**), as shown in Scheme 3.

The structures of all new products thus obtained were confirmed by the ^1H NMR spectral data and the satisfactory results of the elemental analyses. In particular, from the



i) NBS, THF–H_2O, r.t., 5 min, ii) a) $KHCO_3$, **22**, DME, 0 °C, 1 h, then r.t., overnight, b) TFAA, pyridine, 0 °C, 2 h, iii) THF–2 M HCl, r.t., 24 h, iv) a) **26**, Et_3N, toluene, r.t., 15 min, b) MnO_2, toluene, r.t., 12 h.

Scheme 3.

^{1}H NMR spectrum of **27**, the chemical shifts of 4,5-vicinal protons of the pyridine ring at $\delta = 8.36$ and 8.52 (d, $J = 8.2$ Hz) and the four thiazole ring protons at $\delta = 7.83$, 8.26, 8.55, and 8.97 as singlets were found to be very similar to those of **16** and of GE 2270 A [$\delta = 8.27$, 8.38 (pyridine), 7.35, 8.26, 8.50, and 8.56 (thiazole) respectively].[1b]

In conclusion, a convenient synthetic method for the 3, 6-di(2-thiazolyl)-6-(4-thiazolyl)pyridine skeleton has been sufficiently developed. Further investigations on the total synthesis of **1** are currently under way in our laboratory.

Experimental

The melting points were measured using a Yamato (Model Mp-21) micromelting point apparatus, and are uncorrected. The IR spectra were recorded using a Hitachi EPI-G2 spectrometer in KBr. The ^{1}H NMR spectra were measured with JEOL EX 90 and FX 200 spectrometers in $CDCl_3$ and DMSO-d_6 with tetramethylsilane as the internal standard. The optical rotations were measured with a DIP-4 polarimeter (Japan Spectroscopic Co., Ltd.).

Starting Materials. 2,2-Dimethoxypropane, DL-*threo*-phenylserine, and L-cysteine were purchased from Merck K GaA Co., Ltd., Sigma-Aldrich Japan K. K., and Nippon Rikagakuyakuhin Co., Ltd., respectively.

6-Dimethoxymethyl-1,2-dihydro-2-oxo-3-pyridinecarbonitrile (5). The compound **5** was prepared according to the method of Sanchez et al.[6]

6-Dimethoxymethyl-1,2-dihydro-2-oxopyridine-3-carbothioamide (6). A solution of **5** (5.0 g, 25.7 mmol) in pyridine (90 ml) in the presence of Et_3N (4.0 ml, 28.3 mmol) was saturated with H_2S gas at room temperature. After it was stirred for 72 h, the reaction mixture was concentrated in vacuo to give crude crystals, which were washed with MeOH and then recrystallized from MeOH to give **6** as yellowish crystals. Yield 5.2 g (90%). Mp 200—201 °C. IR 3082, 1635, 1587, 1554 cm^{-1}. ^{1}H NMR $\delta = 3.26$ (s, 6H, OMe×2), 5.30 (s, 1H, C*H*(OMe)$_2$), 6.60 (d, 1H, $J = 7.7$ Hz, 4-H), 8.95 (d, 1H, $J = 7.7$ Hz, 5-H), 10.02 (br s, 1H, NH), 11.27 and 12.56 (each br s, 2H, NH_2). Found: C, 47.64; H, 5.36; N, 12.45%. Calcd for $C_9H_{12}N_2O_3S$: C, 47.57; H, 4.88; N, 12.32%.

Ethyl 2-(6-Dimethoxymethyl-1,2-dihydro-2-oxopyridin-3-yl)-thiazole-4-carboxylate (7). To a suspension of **6** (5.6 g, 24.0 mmol) and $KHCO_3$ (7.4 g, 78.3 mmol) in THF (100 ml) was added, with stirring, ethyl 3-bromo-2-oxopropanoate (4.64 g, 36.9 mmol) under cooling. After stirring for 6 h, a solution of TFAA (10.2 ml, 73.9 mmol) and pyridine (16.68 ml, 208.8 mmol) in THF (20 ml) was added further to the resulting solution and the combined solution was stirred at room temperature overnight. Concentration in vacuo gave a residual syrup, which was dissolved in $CHCl_3$ (100 ml). The resulting solution was washed with brine (2×30 ml) 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 CH_2Cl_2 and EtOAc (8 : 1 v/v) to give yellow crystals. Recrystallization from EtOH gave **7** as yellow crystals. Yield 4.41 g (53%). Mp 195—196 °C. IR 3118, 2836, 2320, 1734, 1644, 1554 cm^{-1}. ^{1}H NMR $\delta = 1.43$ (t, 3H, $J = 7.0$ Hz, CH_3), 3.45 (s, 6H, OMe×2), 4.45 (q, 2H, $J = 7.0$ Hz, OCH_2), 5.43 (s, 1H, C*H*(OMe)$_2$),

7.91 (d, 1H, $J=7.5$ Hz, 4-H), 8.25 (s, 1H, Th-H), 8.82 (d, 1H, $J=7.0$ Hz, 5-H), 11.40 (br s, 1H, NH). Found: C, 51.54; H, 5.12; N, 8.17%. Calcd for $C_{14}H_{16}N_2O_3S$: C, 51.83; H, 4.97; N, 8.64%.

Ethyl 2-(6-Dimethoxymethyl-2-trifluoromethylsulfonyloxy-3-pyridyl)thiazole-4-carboxylate (8). A solution of **7** (4.96 g, 16.0 mmol) and Tf_2O (2.89 ml, 18.0 mmol) in the presence of DMAP (2.88 g, 24 mmol) in pyridine (100 ml) was stirred at 0 °C overnight. The reaction mixture was combined with $CHCl_3$ (100 ml) and the combined solution was washed with brine (2×30 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was purified on a silical gel column using a mixture of hexane and EtOAc (3 : 1 v/v) to give colorless crystals. Recrystallization from hexane–EtOAc gave **8** as colorless crystals. Yield 6.66 g (93%). Mp 70.0—70.5 °C. IR 3120, 2968, 2840, 1736, 1610, 1554 cm^{-1}. ^1H NMR $\delta=1.48$ (t, 3H, $J=7.0$ Hz, CH_3), 3.46 (s, 6H, OMe×2), 4.47 (q, 2H, $J=7.0$ Hz, OCH_2), 5.30 (s, 1H, C*H*$(OMe)_2$), 7.76 (d, 1H, $J=7.5$ Hz, H-4), 8.35 (s, 1H, Th-H), 8.08 (d, 1H, $J=7.5$ Hz, 5-H). Found: C, 39.47; H, 3.31; N, 6.14%. Calcd for $C_{15}H_{15}F_3N_2O_7S$: C, 39.47; H, 3.38; N, 6.10%.

Ethyl 2-[6-Dimethoxymethyl-2-(1-ethoxyvinyl)-3-pyridyl]thiazole-4-carboxylate (9). A suspension of **8** (5.00 g, 10.95 mmol), $Pd(OAc)_2$ (369.0 mg, 1.64 mmol), dppp (678.0 mg, 1.64 mmol), and ethyl vinyl ether (12.5 ml, 130.0 mmol) in the presence of Et_3N (4.56 ml, 32.86 mmol) in toluene (150 ml) was refluxed for 12 h. The reaction mixture was washed with brine (2×50 ml) 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 : 2 v/v) to give **9** as a reddish brown syrup. Yield 3.0 g (73%). IR 3112, 2974, 2830, 2434, 1716, 1614, 1587, 1557 cm^{-1}. ^1H NMR δ=1.08 (t, 3H, J=7.3 Hz, Ethoxyvinyl-CH_3), 1.43 (t, 3H, $J=7.3$ Hz, CH_3), 3.46 (s, 6H, OMe×2), 3.80 (q, 2H, $J=7.3$ Hz, Ethoxyvinyl-OCH_2), 4.43—4.51 (m, 3H, OCH_2 and Vinyl-H), 4.79 (d, 1H, $J=2.4$ Hz, Vinyl-H), 7.64 and 8.26 (each d, 2H, $J=8.1$ Hz, H-4,5), 8.26 (s, 1H, Th-H). Found: C, 56.98; H, 5.66; N, 7.24%. Calcd for $C_{18}H_{22}N_2O_5S$: C, 57.13; H, 5.86; N, 7.40%.

5-(4-Ethoxycarbonyl-2-thiazolyl)-6-(trifluoromethylsulfonyloxy)pyridine-2-carboxylic Acid (11). A solution of **8** (1.33 g, 2.6 mmol) in a mixture of THF (50 ml) and 3 M HCl (50 ml) was stirred at room temperature for 24 h. After removal of the organic solvent in vacuo, the aqueous layer was extracted with EtOAc (3×50 ml). The combined extracts were washed with brine (2×20 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a crude residual syrup, which was again dissolved in acetone (30 ml). To the resulting solution was added Jones reagent (2.79 ml, 4.68 mmol) under cooling. After this was stirred for 15 min, the substance deposited was filtered off and the filtrate was poured into water (100 ml). Evaporation of the organic solvent in vacuo gave an aqueous layer, which was extracted with EtOAc (3×30 ml). The combined extracts were washed with brine (2×30 ml) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from hexane–EtOAc to give **11** as colorless crystals. Yield 0.84 g (59%). Mp 194.0—195.5 °C. IR 2986, 2260, 1734, 1704, 1554 cm^{-1}. ^1H NMR (DMSO-d_6) $\delta=1.42$ (t, 3H, $J=7.1$ Hz, CH_3), 4.37 (q, 2H, $J=7.1$ Hz, OCH_2), 8.08 and 8.38 (each d, 2H, $J=7.8$ Hz, H-4,5), 8.91 (s, 1H, Th-H), 13.90 (br s, 1H, COOH). Found: C, 36.62; H, 2.13; N, 6.57%. Calcd for $C_{13}H_9F_3N_2O_5S$: C, 36.70; H, 2.17; N, 7.03%.

Phenacyl 5-(4-Ethoxycarbonyl-2-thiazolyl)-6-(trifluoromethylsulfonyloxy)pyridine-2-carboxylate (12). A solution of **11** (3.02 g, 7.1 mmol) and PacBr (1.56 g, 7.8 mmol) in DMF (100 ml) in the presence of Et_3N (1.09 ml, 7.8 mmol) was stirred under cooling overnight. The reaction mixture was combined with water (100 ml) and the resulting solution was extracted with EtOAc (3×50 ml). The combined extracts were washed with saturated $NaHCO_3$ aqueous solution (2×30 ml), with brine (2×30 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 (2 : 1 v/v) to give colorless crystals. Recrystallization from hexane–EtOAc gave **12** as colorless needles. Yield 2.92 g (73%). Mp 133—134 °C. IR 1986, 1740, 1692, 1599 cm^{-1}. ^1H NMR $\delta=1.45$ (t, 3H, $J=7.3$ Hz, CH_3), 4.48 (q, 2H, $J=7.3$ Hz, OCH_2), 5.56 (s, 2H, OCH_2CO), 7.50—7.99 (m, 5H, Ph-H), 8.35 and 9.10 (each d, 2H, $J=7.9$ Hz, H-4,5), 8.42 (s, 1H, Th-H). Found: C, 46.25; H, 2.89; N, 5.28%. Calcd for $C_{21}H_{15}F_3N_2O_6S$: C, 46.33; H, 2.78; N, 5.15%.

Phenacyl 5-(4-Ethoxycarbonyl-2-thiazolyl)-6-(1-ethoxyvinyl)pyridine-2-carboxylate (13). A suspension of **17** (0.51 g, 0.93 mmol), ethyl vinyl ether (1.07 ml, 11.16 mmol), and $Pd(OAc)_2$ (63.0 mg, 0.28 mmol) in toluene (50 ml) in the presence of dppp (123 mg, 0.281 mmol) and Et_3N (0.77 ml, 5.58 mmol) was refluxed for 6 h. The reaction mixture was washed with brine (2×15 ml) 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 : 2 v/v) to give crude crystals. Recrystallization from hexane–EtOAc gave **13** as pale brownish needles. Yield 0.24 g (55%). Mp 121—122 °C. IR 3124, 3084, 2984, 2932, 1740, 1702, 1622 cm^{-1}. ^1H NMR $\delta=1.10$ (t, 3H, $J=6.8$ Hz, CH_3), 1.43 (t, 3H, $J=7.1$ Hz, Ethoxyvinyl-CH_3), 3.82 (q, 2H, $J=6.8$ Hz, OCH_2), 4.46 (q, 2H, $J=7.1$ Hz, Ethoxyvinyl-OCH_2), 4.71 and 4.87 (ABq, 2H, $J=2.7$ Hz, Vinyl-H), 5.68 (s, 2H, OCH_2CO), 7.47—8.00 (m, 5H, Ph-H), 8.26 and 8.48 (each d, 2H, $J=8.0$ Hz, H-4,5), 8.31 (s, 1H, Th-H). Found: C, 61.77; H, 4.24; N, 5.96%. Calcd for $C_{24}H_{22}N_2O_6S$: C, 61.79; H, 4.36; N, 6.01%.

Phenacyl 6-[2-(*t*-Butoxycarbonylaminomethyl)-4-thiazolyl]-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine-2-carboxylate (16). A solution of **13** (0.20 g, 0.44 mmol) and NBS (0.11 g, 0.64 mmol) in THF (15 ml) and water (15 ml) was stirred at room temperature for 5 min. The reaction mixture was extracted with Et_2O (2×20 ml) and the combined extracts were washed with water (2×10 ml) and then dried over anhydrous Na_2SO_4. Concentration in vacuo under 10 °C gave 2-bromoacetyl intermediate **14** as a syrup, which was dissolved in DME (10 ml). To the resulting solution was added Boc–Gly–thioamide (**15**) (0.08 g, 0.44 mmol) and $KHCO_3$ (0.15 g, 1.4 mmol) at 0 °C, and then stirred for 35 min at 0 °C and overnight at room temperature. The resultant solution was added, with stirring, into a solution of TFAA (0.1 ml, 0.72 mmol) and pyridine (0.13 ml, 1.6 mmol) in DME (3 ml) under cooling. After this was stirred for 2 h, the reaction mixture was concentrated in vacuo to give a residue. The residue was dissolved in $CHCl_3$ (25 ml) and washed with brine (2×10 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 (1 : 2 v/v) to give crude crystals. Recrystallization from hexane–EtOAc gave **16** as pale yellowish crystals. Yield 48.0 mg (45%). Mp 126—127 °C. IR 3364, 1736, 1694, 1624 cm^{-1}. ^1H NMR $\delta=1.42$ (t, 3H, $J=7.1$ Hz, CH_3), 1.47 (s, 9H, *t*-Bu), 4.45 (q, 2H, $J=7.1$ Hz, OCH_2), 4.52 (d, 2H, $J=5.6$ Hz, NCH_2), 5.16 (br t, 1H, $J=5.6$ Hz, NH), 5.69 (s, 2H, OCH_2CO), 7.49—8.00 (m, 5H, Ph-H), 7.82 and 8.24 (each s, 2H, Th-H×2), 8.30 and 8.48 (each d, 2H, $J=7.9$ Hz, H-4, 5). Found: C, 57.58; H, 4.79; N, 9.14%. Calcd for $C_{29}H_{28}N_4O_7S_2$: C, 57.23; H, 4.64; N, 9.20%.

***trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidine-4-carboxamide (17).** To a solution of DL-*threo*-phenylserine (10.5

g, 55.2 mmol) in water (150 ml) was added a solution of Boc_2O (13.91 g, 63.7 mmol) and Et_3N (8.87 ml, 63.7 mmol) in dioxane (150 ml) under cooling. After this was stirred for 6 h, the resulting solution was washed with Et_2O (2×20 ml) and acidified to pH 3 with citric acid. The solution was extracted with EtOAc (3×100 ml) and the combined extracts were washed with brine (2×50 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, to which were added CH_2Cl_2 (300 ml) and 2,2-dimethoxypropane (150 ml) in the presence of PTS (1.2 g, 6.30 mmol), with stirring, at room temperature. After continuous stirring for 24 h, the reaction mixture was poured into saturated $NaHCO_3$ aqueous solution (300 ml) and then evaporated in vacuo. The aqueous layer was washed with $CHCl_3$ (3×50 ml) and acidified to pH 3 with citric acid. The resulting solution was extracted with EtOAc (3×50 ml) and the combined extracts were washed with brine (3×50 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was dissolved in THF (300 ml). To the resulting solution were added Et_3N (7.76 ml, 57.8 mmol) and ethyl chloroformate (5.31 ml, 57.8 mmol) under cooling and, after stirring for 20 min, 28% NH_3 aq (5.07 ml, 760.0 mmol) was further added. After this was stirred for 30 min, a saturated NH_4Cl aqueous solution (100 ml) was added to the reaction mixture. After this was stirred for 5 min, evaporation of THF in vacuo gave an aqueous layer, which was extracted with EtOAc (3×100 ml) and the combined extracts were washed with brine (20 ml) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from hexane–EtOAc to give **17** as colorless crystals. Yield 11.14 g, (60%). Mp 151—152 °C. IR 3424, 3334, 3292, 3226, 2980, 2932, 2254, 1683, 1629 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.38 (s, 9H, *t*-Bu), 1.61 and 1.62 (each s, 6H, CH_3×2), 4.00 (d, 1H, J = 7.9 Hz, β-H), 4.90 (d, 1H, J = 7.9 Hz, α-H), 6.94 and 7.24 (each br s, 2H, NH_2), 7.34—7.39 (m, 5H, Ph). Found: C, 63.41; H, 7.24; N, 8.84%. Calcd for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74%.

***trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidine-4-carbothioamide (18).** A suspension of **17** (11.14 g, 34.8 mmol) and Lawesson's reagent (7.74 g, 19.1 mmol) in dioxane (200 ml) was refluxed for 3 h. The precipitates deposited were filtered off and the filtrate was concentrated in vacuo to give a residual syrup. Purification on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) gave colorless crystals, which were recrystallized from hexane–EtOAc to give **18** as colorless prisms. Yield 11.16 g (95%). Mp 192.0—193.5 °C. IR 3718, 3340, 3178, 2980, 2932, 2638, 2212, 1896, 1686, 1641 cm^{-1}. ^1H NMR δ = 1.33 (s, 9H, *t*-Bu), 1.62 and 1.71 (each s, 6H, CH_3×2), 4.24 and 5.15 (each d, 2H, J = 7.0 Hz, β-H and α-H), 7.22—7.40 (m, 5H, Ph), 9.26—9.64 (each br s, 2H, NH_2). Found: C, 60.83; H, 6.96; N, 8.42%. Calcd for $C_{17}H_{24}N_2O_3S$: C, 60.69; H, 7.19; N, 8.33%.

Ethyl 2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyl-2-oxazolidinyl)thiazole-4-carboxylate (19). To a suspension of **18** (10.60 g, 31.5 mmol) in the presence of $KHCO_3$ (25.24 g, 252.0 mmol) in DME (200 ml) was added ethyl 3-bromo-2-oxopropanoate (11.86 g, 94.5 mmol) under cooling. After this was stirred for 24 h under cooling, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in $CHCl_3$ (150 ml) and the solution was washed with brine (50 ml) and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was again dissolved in DME (200 ml) and to the resulting solution was added more TFAA (17.48 ml, 127.0 mmol) and pyridine (18.85 ml, 274.0 mmol) under cooling. After this was stirred for 2 h, the reaction mixture was made weakly alkaline (pH 8) with Et_3N and then concentrated in vacuo to give a residual syrup. The residue was dissolved in $CHCl_3$ (3×50 ml) and the solution was washed with brine 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 (5 : 1 v/v) to give colorless crystals. Recrystallization from hexane–EtOAc gave **19** as colorless crystals. Yield 12.05 g (88%). Mp 127.5—128.5 °C. IR 3442, 3094, 2980, 2710, 2254, 1707 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.25 (s, 9H, *t*-Bu), 1.30 (t, 3H, J = 6.9 Hz, CH_3), 1.72 and 1.76 (each s, 6H, CH_3×2), 4.30 (q, 2H, J = 6.9 Hz, OCH_2), 5.02 (d, 1H, J = 7.9 Hz, β-H), 5.19 (d, 1H, J = 7.9 Hz, α-H), 7.37 (s, 5H, Ph), 8.46 (s, 1H, Th-H). Found: C, 61.00; H, 6.49; N, 6.31%. Calcd for $C_{22}H_{28}N_2O_5S$: C, 61.09; H, 6.52; N, 6.48%.

2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyl-4-oxazolidinyl)thiazole-4-carboxylic Acid (20). A solution of **19** (12.05 g, 27.9 mmol) in MeOH (100 ml) and water (50 ml) in the presence of excess solid NaOH (11.16 g, 279.0 mmol) was stirred for 24 h under cooling. The reaction mixture was concentrated in vacuo to give a residue, which was washed with Et_2O (2×20 ml) and acidified to pH 3 with citric acid. The solution was extracted with EtOAc (3×50 ml) and then washed with brine (2×40 ml) and finally dried over anhydrous Na_2SO_4. Concentration in vacuo gave crude crystals, which were recrystallized from hexane–EtOAc to give **20** as colorless crystals. Yield 10.05 g (89%). Mp 197.5—198.5 °C. IR 3916, 3880, 3610, 3448, 3112, 2980, 2722, 2260, 2146, 1881, 1842, 1707, 1686, 1611 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.24 (s, 9H, *t*-Bu), 1.72 and 1.75 (each s, 6H, CH_3×2), 5.00 (d, 1H, J = 7.6 Hz, β-H), 5.19 (d, 1H, J = 7.6 Hz, α-H), 7.35—7.37 (m, 5H, Ph), 8.39 (s, 1H, Th-H), 12.99 (br s, 1H, COOH). Found: C, 59.55; H, 6.04; N, 6.86%. Calcd for $C_{10}H_{24}N_2O_5S$: C, 59.39; H, 5.98; N, 6.93%.

2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyl-4-oxazolidinyl)thiazole-4-carboxamide (21). A solution of **20** (10.05 g, 24.8 mmol) and ethyl chloroformate (2.60 ml, 27.3 mmol) in THF (100 ml) in the presence of Et_3N (3.79 ml, 27.3 mmol) was stirred under cooling for 10 min. To the resulting solution was added 28% NH_3 aq (2.49 ml, 40.0 mmol) and, after stirring for 10 min, saturated NH_4Cl aqueous solution (150 ml). After this was concentrated in vacuo, the residue was extracted with EtOAc (3×50 ml), washed with brine (2×30 ml), and then dried over anhydrous Na_2SO_4. Concentration in vacuo gave colorless crystals, which were recrystallized from hexane–EtOAc to give **21** as colorless prisms. Yield 9.39 g (94%). Mp 168.5—170.0 °C. IR 3886, 3586, 3460, 3268, 3154, 2974, 2932, 2290, 1683, 1596 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.25 (s, 9H, *t*-Bu), 1.72 and 1.76 (each s, 6H, CH_3×2), 4.99 (d, 1H, J = 7.6 Hz, β-H), 5.27 (d, 1H, J = 7.6 Hz, α-H), 7.28 (br s, 1H, NH), 7.33—7.37 (m, 6H, Ph and NH), 8.22 (s, 1H, Th-H). Found: C, 59.82; H, 6.25; N, 10.76%. Calcd for $C_{20}H_{25}N_3O_4S$: C, 59.53; H, 6.26; N, 10.41%.

2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyl-4-oxazolidinyl)thiazole-4-carbothioamide (22). A suspension of **21** (9.39 g, 23.3 mmol) and Lawesson's reagent (5.18 g, 12.8 mmol) in DME (200 ml) was stirred at room temperature for 24 h. The precipitates deposited were filtered off and the filtrate was concentrated in vacuo to give a residual syrup. Purification on a silica gel column using a mixture of hexane and EtOAc (3 : 1 v/v) gave yellow crystals, which were recrystallized from hexane–EtOAc to give **22** as yellow prisms. Yield 9.00 g (92%). Mp 134.5—135.5 °C. IR 3790, 3376, 3256, 3154, 2968, 2584, 2254, 1707, 1614 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.26 (s, 9H, *t*-Bu), 1.71 and 1.76 (each s, 6H, CH_3×2), 4.99 (d, 1H, J = 7.6 Hz, β-H), 5.32 (d, 1H, J = 7.6 Hz, α-H), 7.34 (s, 5H, Ph), 8.43 (s, 1H, Th-H), 9.01 and 9.68 (each br s, 2H, NH_2). Found: C, 57.64; H, 6.11; N, 10.05%. Calcd for

$C_{20}H_{25}N_3O_3S_2$: C, 57.25; H, 6.01; N, 10.02%.

Ethyl 2-(2-{2-[2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidin-4-yl)thiazol-4-yl]thiazol-4-yl}-6-dimethoxymethylpyridin-3-yl)thiazole-4-carboxylate (24). A solution of **9** (1.43 g, 3.79 mmol) and NBS (741.0 mg, 4.17 mmol) in a mixture of THF (15 ml) and water (15 ml) was stirred at room temperature for 5 min. The reaction mixture was extracted with Et_2O (3×20 ml) and the combined extracts were dried over anhydrous Na_2SO_4. Concentration in vacuo gave 2-bromoacetylpyridine derivative **23** as a residual syrup, to which was added a chilled solution of **22** (1.58 g, 3.74 mmol) in DME (50 ml) in the presence of $KHCO_3$ (3.03 g, 30.3 mmol). The resulting solution was stirred under cooling for 30 min and at room temperature overnight. Concentration in vacuo gave a residual syrup, which was dissolved in $CHCl_3$ (100 ml) and the resultant solution was washed with brine (2×30 ml), and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residual syrup, which was again dissolved in DME (50 ml) under cooling. TFAA (2.1 ml, 15.1 mmol) and pyridine (2.27 ml, 32.9 mmol) were further added to the above prepared solution. After this was stirred for 2 h, the resulting solution was concentrated in vacuo to give a residue, which was dissolved again in $CHCl_3$ (50 ml), washed twice with brine (2×30 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 (1 : 1 v/v) to give **24** as a colorless syrup. Yield 1.79 g (63%). IR 3442, 2974, 2224, 1788, 1704, 1632, 1548, 1479 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.24 (s, 9H, *t*-Bu), 1.29 (t, 3H, J = 6.9 Hz, CH_3), 1.74 and 1.79 (s, 6H, CH_3×2), 3.43 (each s, 6H, OCH_3×2), 4.30 (q, 2H, J = 6.9 Hz, OCH_2), 5.03 (d, 1H, J = 7.6 Hz, β-H), 5.22 (d, 1H, J = 7.6 Hz, α-H), 5.42 (s, 1H, C*H*$(OMe)_2$), 7.38 (s, 5H, Ph), 7.69 and 8.32 (each d, 2H, J = 7.9 Hz, H-4,5), 7.79, 8.11, and 8.52 (each s, 3H, Th-H×3). Found: C, 57.79; H, 5.34; N, 9.04%. Calcd for $C_{36}H_{39}N_5O_7S_3$: C, 57.66; H, 5.24; N, 9.39%.

Phenacyl 3-*t*-Butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxylate. To a solution of 3-*t*-butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxylate (6.00 g, 22.96 mmol)[12] in DMF (200 ml) was added, with stirring, PacBr (4.80 g, 24.11 mmol) and Et_3N (4.15 ml, 29.85 mmol) under cooling. After this was stirred overnight, the reaction mixture was combined with water (100 ml) and then extracted with EtOAc (3×30 ml). The combined extracts were washed with saturated $NaHCO_3$ (2×20 ml), and with brine (2×20 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 (2 : 1 v/v) to give colorless crystals. Recrystallization from hexane–EtOAc gave phenacyl 3-*t*-butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxylate as colorless needles. Yield 7.19 g (83.7%). Mp 78.5—80.0 °C. $[\alpha]_D^{24}$ −103.3° (*c* 1.03, MeOH). IR 3970, 3778, 3532, 3262, 2974, 2458, 2254, 1881, 1758, 1695, 1599 cm^{-1}. ^1H NMR δ = 1.45—1.56 (m, 9H, Boc), 1.78 and 1.89 (each s, 6H, Me×2), 3.37—3.41 (m, 2H, β-H), 4.98—5.09 (m, 1H, α-H), 5.19—5.65 (m, 2H, OCH_2CO), 7.46—7.92 (m, 5H, Ph). Found: C, 60.59; H, 6.71; N, 3.37%. Calcd for $C_{19}H_{25}NO_5S$: C, 60.14; H, 6.64; N, 3.69%.

Phenacyl L-Cysteinate·TFA (26). A solution of phenacyl 3-*t*-butoxycarbonyl-2,2-dimethylthiazolidine-4-carboxylate (2.54 g, 6.70 mmmol) in CH_2Cl_2–TFA (100 ml, 3 : 1 v/v) was stirred for 1 h at room temperature and then concentrated in vacuo. The obtained syrupy residue was dissolved in water–EtOH (80 ml, 1 : 1 v/v) and stirred for 3 h at room temperature. Concentration in vacuo gave a residue, which was dissolved in toluene (30 ml) and the toluene was distilled azeotropically three times to give a residual syrup (**26**). Without isolation, **26** was used in the next final reaction.

Ethyl 2-(2-{2-[2-(*trans*-3-*t*-Butoxycarbonyl-2,2-dimethyl-5-phenyloxazolidin-4-yl)thiazol-4-yl]thiazol-4-yl}-6-[4-(phenacyloxycarbonyl)thiazol-2-yl]pyridin-3-yl)thiazole-4-carboxylate (27). A solution of **24** (2.51 g, 3.35 mmol) in 2 M HCl (40 ml) and THF (40 ml) was stirred at room temperature for 24 h. The reaction mixture was concentrated in vacuo to give a residue, which was extracted with EtOAc (3×30 ml). The combined extracts were washed with saturated $NaHCO_3$ aqueous solution (2×20 ml), with brine (2×20 ml), and dried over anhydrous Na_2SO_4. Concentration in vacuo gave 6-formylpyridine derivative **25** as an intermediate. To a solution of **25** in toluene (50 ml) was added, with stirring, a solution of **26** in toluene (50 ml) at room temperature for 10 min. After continuous stirring for **15** min, the resulting solution was washed with brine (2×30 ml) and dried over anhydrous Na_2SO_4. Concentration in vacuo gave a residue, which was again dissolved in toluene (150 ml), to which was added activated MnO_2 (7.64 g, 87.87 mmol). After this was stirred for 12 h, the MnO_2 deposited was filtered off and the filtrate was washed with a small amount of acetone. The combined filtrates were concentrated in vacuo to give residual crystals, which were purified on a silica gel column using a mixture of $CHCl_3$ and acetone (15 : 1 v/v) to give brownish crystals. Recrystallization from hexane–EtOAc gave **27** as pale brownish crystals. Yield 485.0 mg (41%). Mp 180.5—182.0 °C. IR 3814, 3718, 3446, 3208, 3106, 2974, 2932, 2254, 1818, 1710, 1584 cm^{-1}. ^1H NMR (DMSO-d_6) δ = 1.24 (s, 9H, *t*-Bu), 1.31 (t, 3H, J = 7.0 Hz, CH_3), 1.74 and 1.78 (each s, 6H, CH_3×2), 4.31 (q, 2H, J = 7.0 Hz, OCH_2), 5.04 (d, 1H, J = 7.6 Hz, β-H), 5.76 (d, 1H, J = 7.6 Hz, α-H), 5.76 (s, 2H, OCH_2CO), 7.39 and 7.59—8.03 (m, 5H, Ph), 7.83, 8.26, 8.55, and 8.79 (each s, 4H, Th-H×4), 8.36 and 8.52 (each d, 2H, J = 7.9 Hz, H-4,5). Found: C, 58.63; H, 4.08; N, 8.92%. Calcd for $C_{45}H_{40}N_6O_8S_4$: C, 58.68; H, 4.38; N, 9.12%.

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