

## CONVENIENT SYNTHESIS OF FRAGMENT B AND LINEAR MAIN SKELETON [FRAGMENT A-B-C'] DERIVATIVES OF AN ANTIBIOTIC, GE 2270 A

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**Abstract** - Convenient synthesis of the protected linear precursor [Fragment A-B-C'] of a macrocyclic antibiotic, GE 2270 A, was achieved by coupling of a 2,3,6-trithiazolyl-substituted pyridine skeleton [Fragment A-C'] with a thiazoloyl-thiazole segment [Fragment B]. The Fragment B was synthesized from an appropriate thioamide and  $\beta$ -bromo- $\alpha$ -oxoalkanoate, the latter of which was first derived by consecutive  $\beta$ -bromination and hydrolytic removal of the  $\alpha$ -(*N*-Boc)amino group of an  $\alpha$ -dehydroamino acid ester.

An antibiotic, GE 2270 A (**1**),<sup>1</sup> isolated from the culture of *Planobispora rosea*, has an unusual macrocyclic structure, as shown in Figure 1. The antibiotic (**1**) features a very unique main structure constructed of a 2,3,6-trithiazolylsubstituted pyridine skeleton (**4-5**) called Fragment A-C and a substituted thiazoloylthiazole segment (**6**) called Fragment B. Although the absolute configurations of

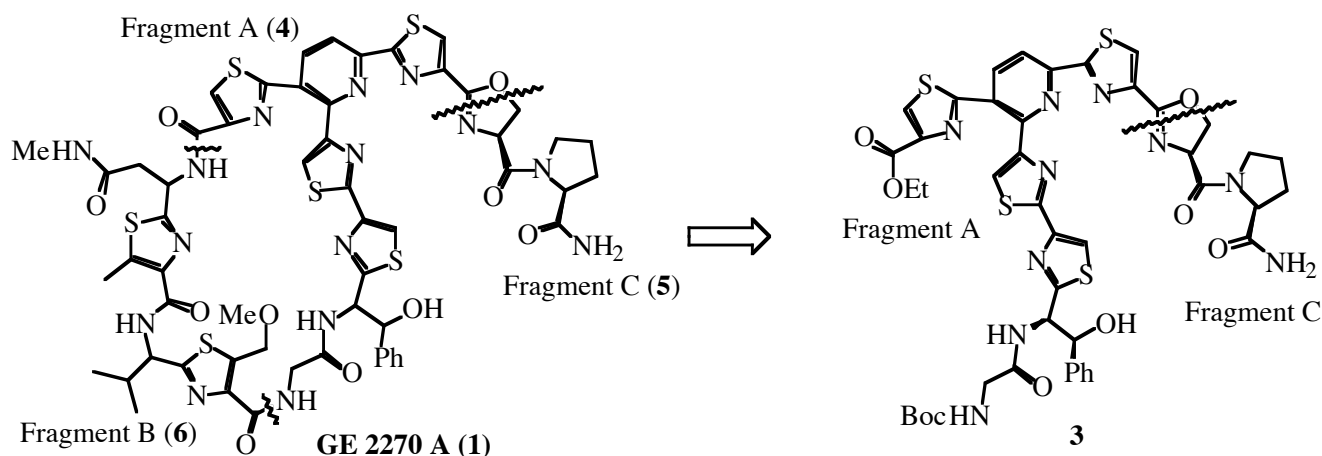
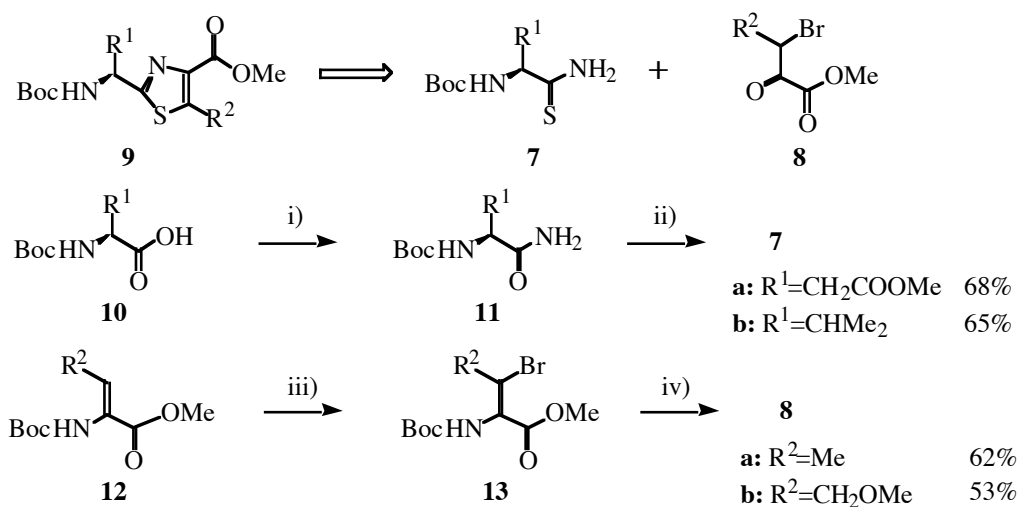


Figure 1. Retrosynthesis of **1**

the six chiral centers in **1** have not yet been identified, they are deduced to originate from natural L- $\alpha$ -amino acids. The interesting structure and bioactivity of **1** attracted our attention and prompted us to investigate its total synthesis and structure-bioactivity relationship. In the previous papers,<sup>2,3</sup> we have already reported the efficient syntheses of the protected Fragment A-C (**3**), besides the total syntheses of micrococcin P and P<sub>1</sub><sup>4,5</sup> structurally similar to **1**. Here, we wish to report a novel synthetic method for  $\beta$ -bromo- $\alpha$ -oxocarboxylates, which are a most promising building block for the thiazole ring formation. Furthermore, useful syntheses of the protected Fragment B derivative (**6**) and the protected linear full skeleton [Fragment A-B-C'] derivative (**2**) (Fragment C'=L-Ser(MOM)-L-Pro-NH<sub>2</sub>; MOM=methoxymethyl) segment are also described.

First of all, to synthesize methyl 2,5-disubstituted thiazole-4-carboxylates (**9**), which are comprised of many similar macrocyclic antibiotics,<sup>6</sup> a general synthetic method was further developed. By taking advantage of the Hantzsch method,<sup>7</sup> it was found that the compound (**9**) could be derived by reaction of an appropriate thioamide (**7**) with novel  $\beta$ -bromo- $\alpha$ -oxocarboxylate (**8**). First, for the synthesis of **7**, amidation of the respective Boc-L-Asp(OMe)-OH (**10a**) and Boc-L-Val-OH (**10b**) by the mixed anhydride method using ClCOOEt and 28% aqueous NH<sub>3</sub>, followed by thioamidation with Lawesson's reagent gave the corresponding thioamide derivatives (**7a**) (R<sup>1</sup>=CH<sub>2</sub>COOMe; pale yellow syrup) and (**7b**) (R<sup>1</sup>=CH(CH<sub>3</sub>)<sub>2</sub>; colorless crystals, mp 108-110 °C) respectively. On the other hand, to synthesize **8** from an appropriate  $\alpha$ -dehydroamino acid methyl ester, according to the method reported earlier,<sup>8,9</sup> Boc- $\Delta$ Abu-OMe ( $\Delta$ Abu=2-amino-2-butenic acid) (**12a**) was treated with *N*-bromosuccinimide (NBS) to give methyl 2-(*N*-Boc)amino-3-bromo-2-butenate (**13a**) (colorless syrup, 86%), the Boc and amino groups of which were successively deprotected and hydrolyzed with trifluoroacetic acid (TFA) and then

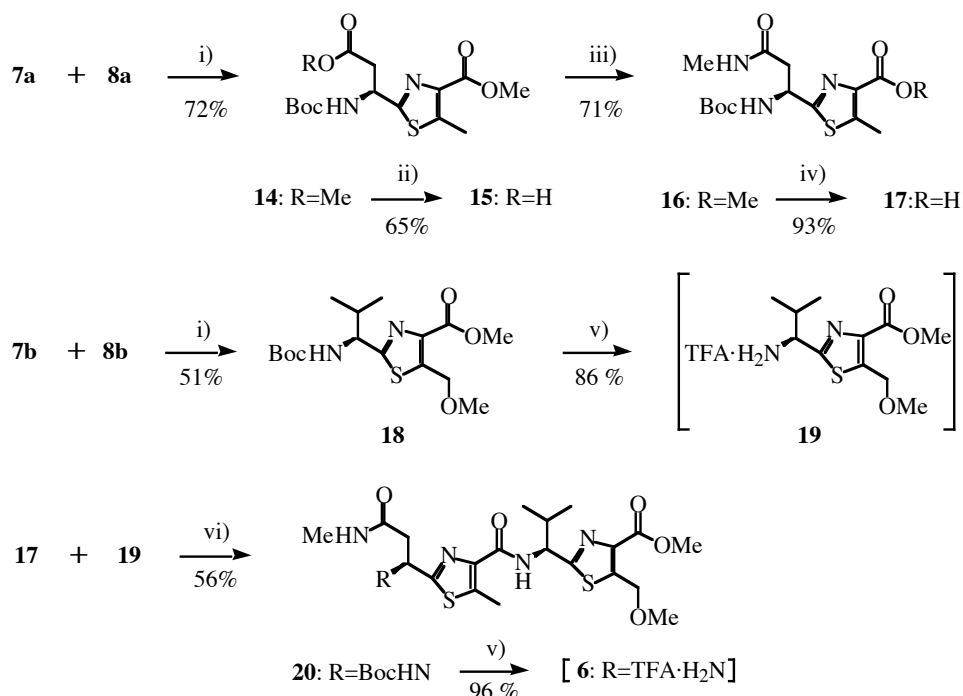


Reagents and conditions: i) a) ClCOOEt, Et<sub>3</sub>N, THF, 0 °C, 15 min, b) 28% aq. NH<sub>3</sub>, THF, 0 °C, 15 min, ii) Lawesson's reagent, DME, rt, overnight, iii) a) NBS, CHCl<sub>3</sub>, rt, 30 min, b) Et<sub>3</sub>N, CHCl<sub>3</sub>, rt, 30 min, iv) TFA, CHCl<sub>3</sub>, H<sub>2</sub>O, rt, 30 min.

**Scheme 1.**

with H<sub>2</sub>O to give methyl 3-bromo-2-oxobutanoate (**8a**; colorless syrup). Similarly, methyl 2-(*N*-Boc)amino-4-methoxy-2-butenate (**12b**) (colorless syrup, 65%), derived by the Wittig-Horner reaction of Boc-[PO(OEt)<sub>2</sub>]Gly-OMe with MeOCH<sub>2</sub>CHO, was worked up to give methyl 3-bromo-3-methoxy-2-oxobutanoate (**8b**; colorless syrup) *via* methyl 2-(*N*-Boc)amino-3-bromo-4-methoxy-2-butenate (**3b**; colorless syrup, 72%), as shown in Scheme 1. As a result, the synthetic method for **8** was found to be very useful and general.

Subsequently, thiazole ring formation between **7a** and **8a** by using consecutive KHCO<sub>3</sub> in 1,2-dimethoxyethane (DME), trifluoroacetic anhydride (TFAA) in the presence of pyridine, and then 28% aqueous NH<sub>3</sub> was tried successfully to give methyl 2-[1-(*N*-Boc)amino-3-methoxycarbonyl]ethyl-5-methylthiazole-4-carboxylate (**14**).<sup>10</sup> After selective hydrolysis of the side chain of the 2-methyl ester of **14** with 1 M LiOH at 0 °C for 4 h, the formed 2-carboxyl group of the hydrolyzate (**15**) was methylamidated with MeNH<sub>2</sub> by using BOP<sup>11</sup> as the condensing agent and (*i*-Pr)<sub>2</sub>NEt to give the corresponding 2-(methylamide)ethyl derivative (**16**).<sup>12</sup> Then, hydrolysis of the 4-methyl ester of **16** with 1 M LiOH at room temperature overnight proceeded to give the corresponding thiazole-4-carboxylic acid derivative (**17**) (colorless crystals, mp 195-196 °C) as a carboxy component. On the other hand, similarly to the case of **14**, thiazolation of **7b** with **8b** gave methyl 2-[1-(*N*-Boc)amino-2-methyl]propyl-5-methoxymethylthiazole-4-carboxylate (**18**; colorless syrup), the Boc group of which was



Reagents and conditions: i) a) KHCO<sub>3</sub>, DME, 0 °C, 30 min, rt, overnight, b) TFAA, pyridine, 0 °C, 2 h, c) 28% aq. NH<sub>3</sub>, EtOAc, 0 °C, 15 min, ii) 1M LiOH, THF, 0 °C, 4 h, iii) BOP, HCl·H<sub>2</sub>NMe, (*i*-Pr)<sub>2</sub>NEt, DMF, 0 °C, 30 min, rt, overnight, iv) 1M LiOH, MeOH, 0 °C, 30 min, rt, overnight, v) TFA, CHCl<sub>3</sub>, rt, 2 h, vi) BOP, (*i*-Pr)<sub>2</sub>NEt, DMF, 0 °C, 30 min, rt, overnight.

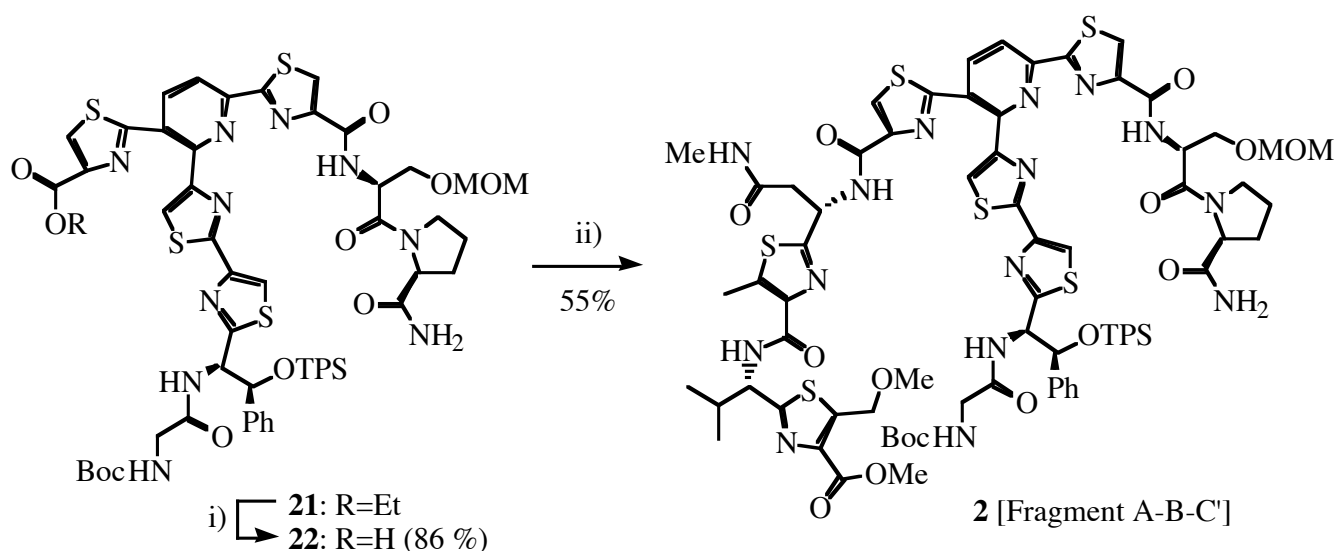
**Scheme 2.**

deprotected with TFA to give methyl 2-(1-amino-2-methyl)propyl-5-methoxymethylthiazole-4-carboxylate TFA salt (**19**) as an amine component. Without purification, immediate coupling of **19** with **17** by the BOP method was carried out to give the protected thiazoloylthiazole-4-carboxylate derivative (Fragment B segment) (**20**).<sup>13</sup> The Boc group was further deprotected with TFA to give the corresponding Fragment B (**6**) TFA salt derivative, as shown in Scheme 2.

From the <sup>1</sup>H NMR spectral data of **20**, it was found that no racemization at two 2-(1-amino)alkyl groups took place during the synthetic reactions of **17** and **19**.

Finally, in order to synthesize the Fragment A-B-C, attempts to hydrolyze the ethyl ester of the protected Fragment A-C (**3**)<sup>3</sup> obtained previously with 1 M LiOH resulted in the ring cleavage of the oxazoline. Therefore, after similar ester hydrolysis of the protected Fragment A-C' derivative (**21**) (colorless crystals, mp 128-129 °C), independently synthesized from Fragment A and Fragment C' by the method already reported,<sup>3</sup> fragment condensation of the hydrolyzate (**22**) (colorless crystals, mp 149-151 °C) with the protected Fragment B (**6**) by the BOP method was carried out to give the desired 2(1*R*,2*S*)-3(*S*,*S*)-6(*S*,*S*)-**2**<sup>14</sup> derivative as the protected linear main Fragment A-B-C' segment, as shown in Scheme 3.

The structures of all of the new compounds thus obtained were confirmed by the spectral data (IR and <sup>1</sup>H NMR) and the satisfactory elemental analyses. The structure of **2** was also definitely determined by the <sup>1</sup>H and <sup>13</sup>C NMR spectral data. Disappearance of the proton at δ 13.10 (br s) of the carboxyl group of **22** and appearance of the two amide protons at δ 7.13-8.68 and 9.51 and their vicinal methine protons at δ 5.00-5.05, 5.65-5.68 indicate apparently the formation of **2**. Unfortunately, however, although the macrocyclization of **2** by successive hydrolysis of the methyl ester with 1 M LiOH, deprotection of the Boc group with TFA and intramolecular condensation by the BOP method under high dilution conditions proceeded smoothly to give the corresponding macrocyclic compound [colorless crystals, 21% in 4 steps from **2**. MALDI-TOFMS Found: *m/z* 1309.0. Calcd for C<sub>56</sub>H<sub>57</sub>N<sub>15</sub>O<sub>11</sub>S<sub>6</sub>: 1308.3 (M + H)<sup>+</sup>], the final



Reagents and conditions: i) 1M LiOH, MeOH, 0 °C, 30 min, rt, overnight, ii) **6**, BOP, (*i*-Pr)<sub>2</sub>NEt, DMF, 0 °C, 1 h, rt, overnight.

**Scheme 3.**

exocyclic oxazolation so far has not succeeded.

In conclusion, useful synthetic methods for novel  $\beta$ -bromo- $\alpha$ -oxocarboxylate and the protected Fragment A-B-C' skeleton of GE 2270 A have been sufficiently developed. Further investigations on the total synthesis of **1** are currently under way in our laboratory.

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10. **14**: Yellow syrup. IR 3347, 2978, 2952, 1737, 1715, 1687, 1520  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ =1.47 (s, 9H, Boc's  $\text{CH}_3$  x 3), 2.73 (s, 3H, thiazole ring- $\text{CH}_3$ ), 2.94-3.40 (m, 2H,  $\text{CH}_2$ ), 3.67 and 3.91 (s x 2, 3H x 2,  $\text{COOCH}_3$  x 2), 5.25-5.33 (m, 1H,  $\text{NHCH}$ ), 5.93-5.96 (m, 1H, NH).
11. BOP=(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate; B. Castro, J. R. Dormoy, B. Dourtoglou, G. Evin, C. Selve, and J. C. Ziegler, *Synthesis*, 1976, 751.
12. **16**: Colorless crystals (hexane-ethyl acetate), mp 134.5-135.5  $^\circ\text{C}$ .  $[\alpha]_{\text{D}}^{26}$  -27.6 $^\circ$  (c 0.21, MeOH).

- IR 3337, 2951, 1704, 1675, 1649, 1520  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR (60  $^\circ\text{C}$ ,  $\text{DMSO}-d_6$ )  $\delta$ =1.41 (s, 9H, Boc's  $\text{CH}_3$  x 3), 2.66 (s, 3H,  $\text{NHCH}_3$ ), 2.67 (s, 3H, thiazole ring- $\text{CH}_3$ ), 2.73-3.10 (m, 2H,  $\text{CH}_2$ ), 3.85 (s, 3H,  $\text{COOCH}_3$ ), 5.16 (br s, 1H,  $\text{NHCH}$ ), 6.06 (br s, 1H,  $\text{NHCH}_3$ ), 6.62 (br d, 1H, NH,  $J$ =8.0 Hz). *Anal.* Calcd for  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_5\text{S}$ : C, 50.41; H, 6.49; N, 11.76. Found: C, 50.35; H, 6.37; N, 11.67.
13. **20**: Colorless crystals (hexane-ethyl acetate), mp 73.5-75.0  $^\circ\text{C}$ .  $[\alpha]_D^{26}$   $-24.6^\circ$  ( $c$  0.99, MeOH). IR 3369, 2967, 1715, 1657  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ =0.90 and 0.95 (each d, 3H x 2,  $\text{CH}(\text{CH}_3)_2$ ,  $J$ =6.7 Hz), 1.39 (s, 9H, Boc's  $\text{CH}_3$  x 3), 2.39-2.45 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 2.50-2.92 (m, 2H,  $\text{CHCH}_2$ ), 2.56 (d, 3H,  $\text{NHCH}_3$ ,  $J$ =4.6 Hz), 2.85 (s, 3H, thiazole ring- $\text{CH}_3$ ), 3.38 (s, 3H,  $\text{CH}_2\text{OCH}_3$ ), 3.81 (s, 3H,  $\text{COOCH}_3$ ), 4.89 (s, 2H,  $\text{CH}_2\text{OCH}_3$ ), 4.98-5.03 (m, 1H,  $\text{NHCHCH}$ ), 7.70 (br d, 1H, NH,  $J$ =8.0 Hz), 7.87 (br d, 1H,  $\text{NHCH}_3$ ,  $J$ =4.6 Hz), 8.34 (br s, 1H, NH,  $J$ =9.0 Hz). *Anal.* Calcd for  $\text{C}_{25}\text{H}_{37}\text{N}_5\text{O}_7\text{S}_2$ : C, 51.44; H, 6.39; N, 12.00. Found: C, 50.96; H, 6.51; N, 11.53.
14. **2**: Colorless crystals (hexane-ethyl acetate), mp 150.5-152.0  $^\circ\text{C}$ .  $[\alpha]_D^{26}$   $+49.1^\circ$  ( $c$  0.97, MeOH). IR 3396, 2959, 1664, 1536  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ =0.81 and 0.82 (s x 2, 9H, TPS's  $\text{CH}_3$  x 3), 0.90 and 0.95 (d x 2, 3H x 2,  $\text{CH}_3$  x 2,  $J$ =7.0 Hz), 1.31 (s, 9H, Boc's  $\text{CH}_3$  x 3), 1.83-2.07 (m, 4H, Pro's  $\text{CH}_2$  x 2), 2.40-2.52 (m, 1H, Ip's CH), 2.55 (d, 3H,  $\text{NHCH}_3$ ,  $J$ =4.5 Hz), 2.62 (s, 3H,  $\text{CH}_3$ ), 2.87-3.09 (m, 2H,  $\text{NHCHCH}_2$ ), 3.18-3.42 (m, 2H, Gly's  $\text{CH}_2$ ), 3.28 (s, 3H, MOM's  $\text{CH}_3$ ), 3.37 (s, 3H,  $\text{CH}_2\text{OCH}_3$ ), 3.70-3.93 (m, 4H, Ser's  $\beta$ -H and Pro's  $\text{CH}_2$ ), 3.81 (s, 3H,  $\text{COOCH}_3$ ), 4.26-4.29 (m, 1H, Pro's CH), 4.62 (dd, 2H, MOM's  $\text{CH}_2$ ,  $J$ =6.7 Hz,  $J$ =8.3 Hz), 4.88 (s, 2H,  $\text{CH}_2\text{OCH}_3$ ), 5.00-5.05 (m, 2H, Ser's  $\alpha$ -H and  $\text{NHCHCH}(\text{CH}_3)_2$ ), 5.22-5.25 (m, 1H,  $\text{PhCH}$ ), 5.44-5.46 (m, 1H,  $\text{NHCHCHPh}$ ), 5.65-5.68 (m, 1H,  $\text{NHCHCH}_2\text{CO}$ ), 6.85 (br t, 1H, Gly's NH,  $J$ =5.5 Hz), 6.96 (br s, 1H, NH), 7.13-8.68 (m, 20H, Ph x 3, Ser's NH,  $\text{NHCHCH}(\text{CH}_3)_2$ , NH and pyridine ring-H x 2), 7.74, 8.33, 8.43, and 8.54 (each s, 4H, thiazole ring-H x 4), 8.02 (br s, 1H,  $\text{NHCH}_3$ ,  $J$ =4.5 Hz), 8.19 (br d, 1H,  $\text{NHCHCHPh}$ ,  $J$ =8.5 Hz), 9.51 (br d, 1H,  $\text{NHCHCH}_2\text{CO}$ ,  $J$ =8.0 Hz).  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$ =12.2, 14.0, 18.3, 18.7, 19.3, 19.4, 20.7, 21.9, 24.4, 25.5, 26.5, 28.1, 29.1, 29.6, 31.8, 32.0, 35.2, 36.4, 36.4, 38.2, 38.3, 42.8, 46.9, 48.2, 51.0, 51.9, 54.7, 54.8, 55.8, 56.2, 56.7, 58.7, 58.5, 59.7, 59.8, 66.6, 67.6, 76.5, 78.0, 95.7, 95.9, 117.6, 119.0, 122.9, 127.1, 127.3, 127.5, 127.7, 127.8, 129.1, 129.6, 132.3, 132.4, 135.3, 135.4, 138.6, 139.6, 140.0, 141.0, 141.2, 147.6, 148.0, 148.9, 150.0, 150.2, 150.6, 150.9, 152.5, 155.5, 159.9, 160.0, 161.6, 161.9, 163.0, 167.1, 167.7, 168.9, 169.5, 169.9, 170.7, 173.2. *Anal.* Calcd for  $\text{C}_{80}\text{H}_{91}\text{N}_{15}\text{O}_{15}\text{S}_6\text{Si}3\text{H}_2\text{O}$ : C, 54.07; H, 5.50; N, 11.82. Found: C, 53.78; H, 5.32; N, 11.66.