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CONVENIENT SYNTHESIS OF A 2,3,6–TRISTHIAZOLYL-SUBSTITUTED PYRIDINE SKELETON [FRAGMENT A-C] OF A MACROCYCLIC ANTIBIOTIC, GE 2270 A

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Abstract - Convenient synthesis of the 2,3,6-tristhiazolylsubstituted pyridine skeleton [Fragment A-C] of a macrocyclic antibiotic, GE 2270 A, was first achieved from a chiral 2-(2-{2-[(1*R*,2*S*)-(1-amino-2-hydroxy-2-phenyl)ethyl]-thiazol-4-yl}thiazol-4-yl)pyridine derivative [Fragment A] and H-L-Ser-L-Pro-NH_2 as the precursor of Fragment C.

An antibiotic, GE 2270 A (**1**),[1] isolated from the culture of *Planobispola rosea*, has an unusual macrocyclic structure, as shown in Figure 1. The antibiotic (**1**) includes a characteristic main structure, a 2,3,6-tristhiazolylsubstituted pyridine skeleton [Fragment A-C] constructed of a polythiazolated pyridine segment [Fragment A] and an oxazolinoyl-Pro-NH_2 moiety [Fragment C]. So far, although the absolute configurations of the six chiral centers of **1** have not yet been identified, they are deduced to originate from natural L-α-amino acids. The interesting structure and bioactivity of **1** attracted our attention and prompted us to investigate its total synthesis and structure-bioactivity relationship.

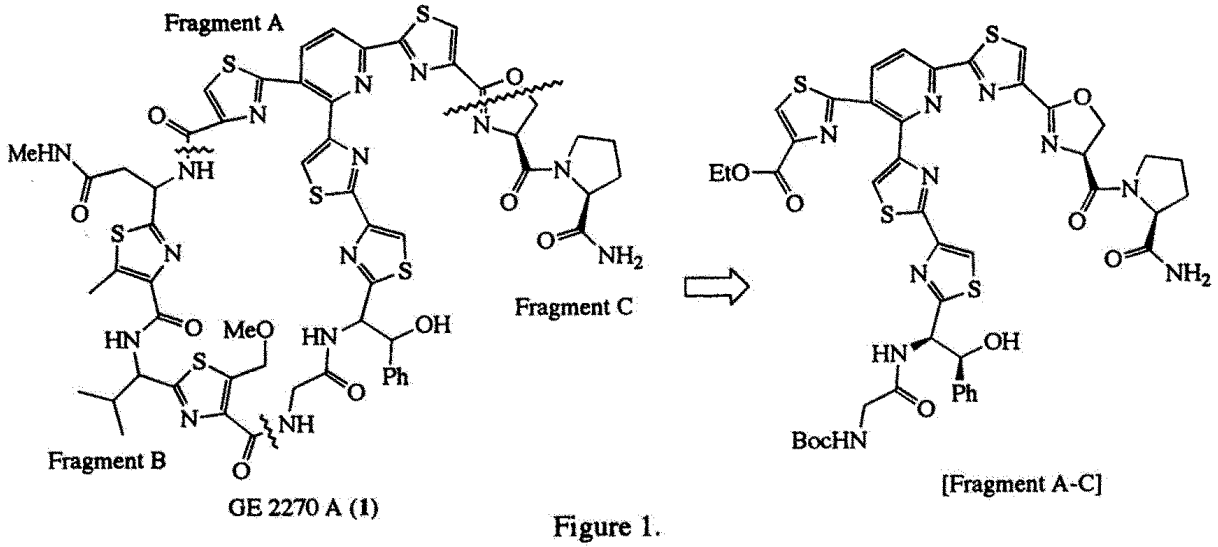
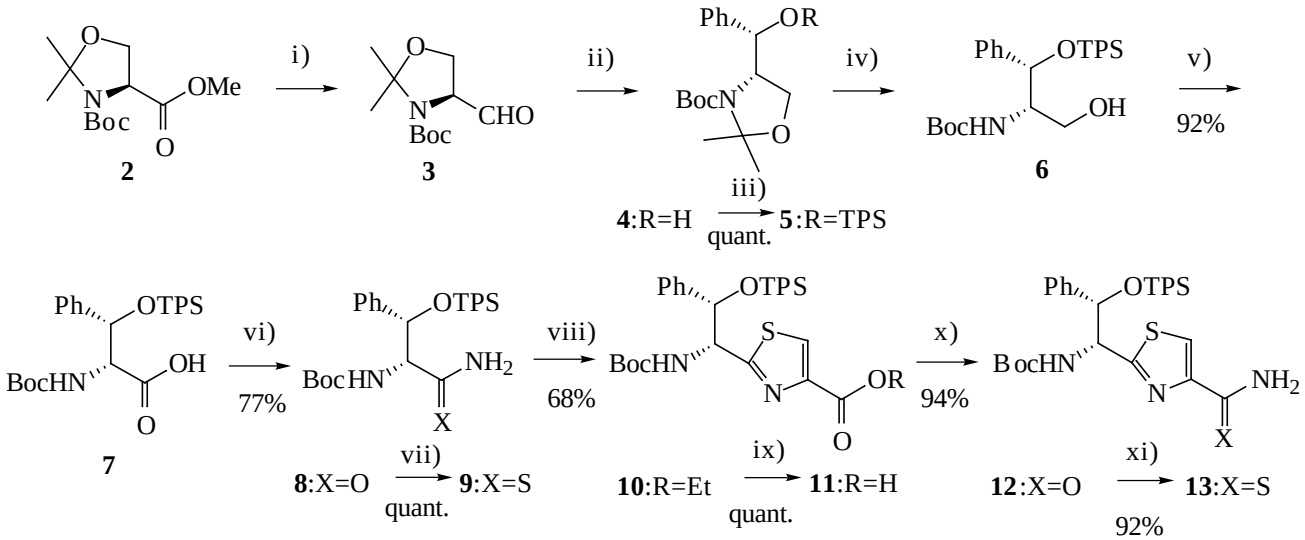


Figure 1.

Recently,[2,3] the first total syntheses of similar macrocyclic antibiotics such as micrococcins P and P_1 have been accomplished. Furthermore,[4] by taking advantage of the synthetic method for the central main skeleton of the micrococcins, the achiral Fragment A derivative of **1** has been synthesized by coupling of ethyl 2-(6-dimethoxymethyl-2-bromoacetyl-3-pyridyl)thiazole-4-carboxylate (**14**)[2-5] with 2-(*trans*-3-*tert*-butoxycarbonyl-2,2-dimethyl-5-phenyl-4-oxazolidinoyl)thiazole-4-carbothioamide. Unfortunately, however, it was found that the desired chiral Fragment A could not been synthesized by the above-mentioned method. Here, we report the first efficient synthesis of the chiral Fragment A-C derivatives, by a different synthetic method.

First of all, to obtain 2-[(1*R*,2*S*)-(1-amino-2-hydroxy-2-phenyl)ethyl]thiazole-4-carbothioamide (**13**) as an essential coupling component with **14**, *N*,*O*-diprotected L-Ser-OMe (**2**) was reduced with DIBAL-H to give the corresponding formyl derivative (**3**). Subsequently, Grignard reaction of **3** with PhMgBr gave a mixture of 5-[(1*S*,2*S*)-(2-hydroxy)benzyl]-2,2-dimethyloxazolidine (**4**) and its (1*S*,2*R*)-diastereomer almost quantitatively in 3:2 ratio by the method of Koskinen *et al.*[6] The separated (1*S*,2*S*)-isomer was then protected with *tert*-butyldiphenylsilyl chloride (TPSCl) to give the desired *O*-TPS protected oxazolidine derivative (**5**). Deprotection of the isopropylidene group with trifluoroacetic acid (TFA) gave the corresponding amino alcohol derivative (**6**), which was oxidized with Jones reagent to give the expected amino acid derivative (**7**).[7] Amidation of **7** by the mixed anhydride method using ClCOOEt and 28% aq NH_3 gave the expected amide derivative (**8**). Subsequent thioamidation of **8** with Lawesson's reagent, followed by thiazolation of the obtained thioamide derivative (**9**)[8] with $BrCH_2COCOOEt$ and then with trifluoroacetic anhydride (TFAA) gave ethyl 2-{(1*R*,2*S*)-[1-(*N*-

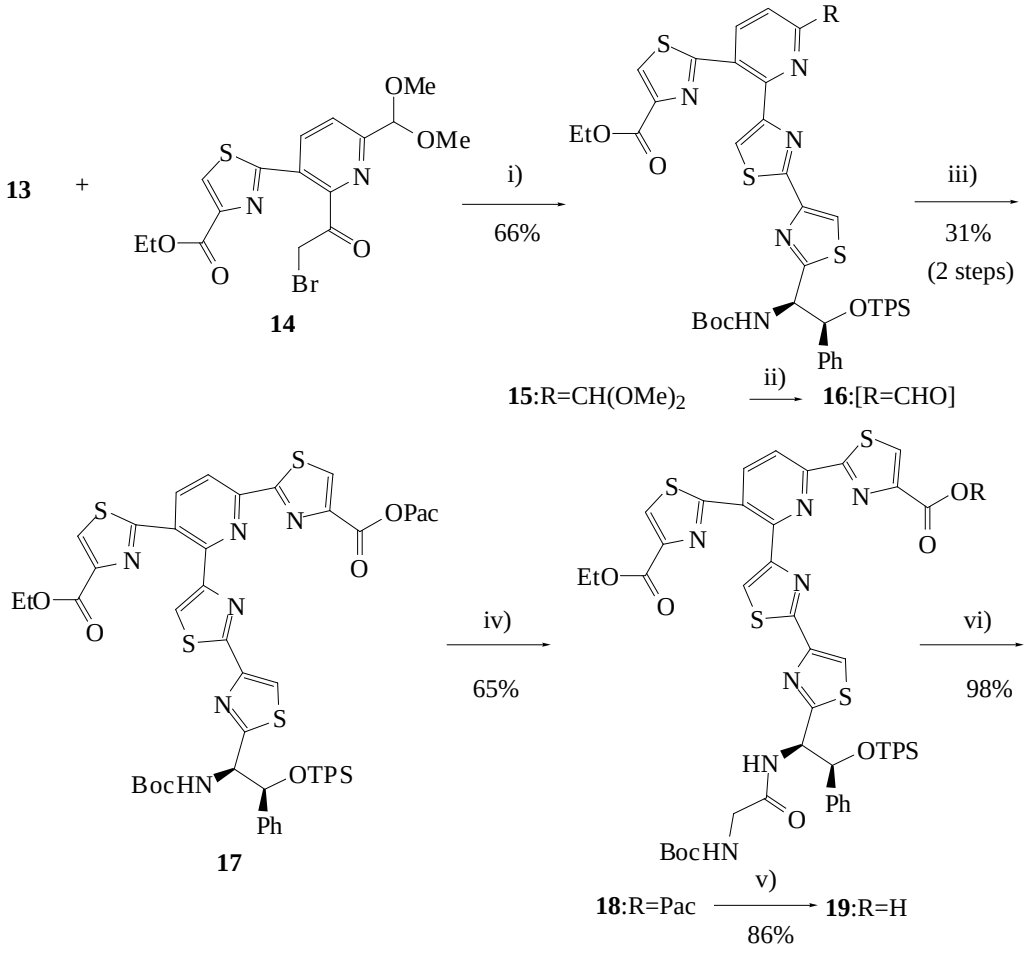


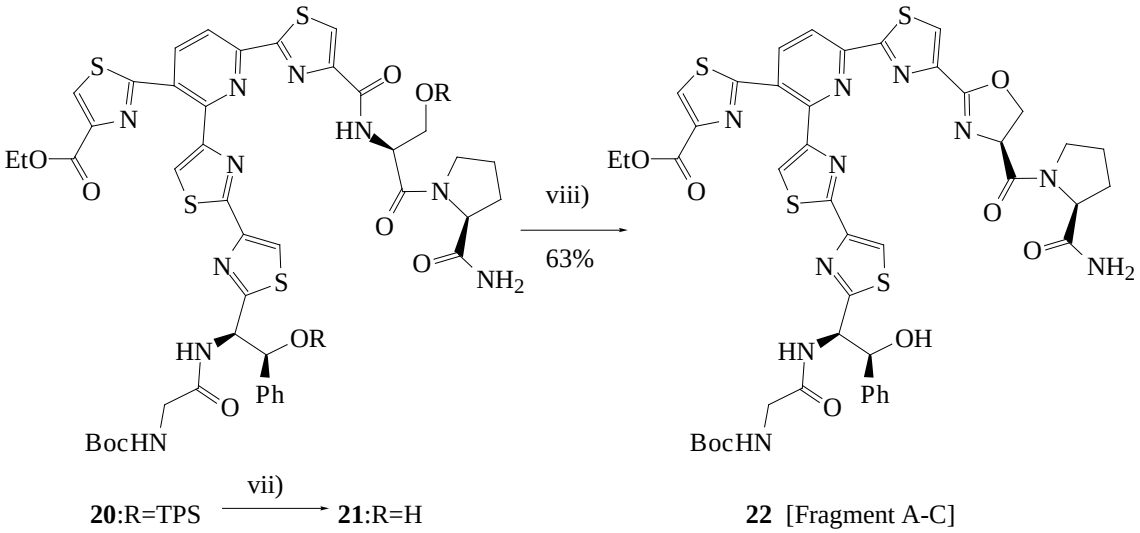
Reagents and conditions : i) DIBAL-H, toluene, -78 °C, 45 min, ii) PhMgBr, Et_2O, 0 °C, 1 h, iii) TPSCl, imidazole, $CHCl_3$, 0 °C, 30 min, rt, overnight, iv) TFA:$CHCl_3$=4:96, rt, 1 h, v) Jones reagent, acetone, 0 °C, 2 h, vi) a) ClCOOEt, Et_3N, THF, 0 °C, 15 min, b) 28% aq NH_3, THF, 0 °C, 15 min, vii) Lawesson's reagent, DME, rt, overnight, viii) a) $BrCH_2COCOOEt$, $KHCO_3$, DME, 0 °C, 1 h, b) TFAA, pyridine, DME, 0 °C, 2 h, c) 28% aq NH_3, EtOAc, 0 °C, 15 min, ix) 1 M LiOH, MeOH, 0 °C, 1 h, rt, overnight, x) a) ClCOOEt, Et_3N, THF, 0 °C, 15 min, b) 28% aq NH_3, THF, 0 °C, 15 min, xi) Lawesson's reagent, dioxane, 70 °C, 3 h.

Scheme 1.

Boc)amino-2-(*O*-TPS)hydroxy-2-phenyl]ethyl}thiazole-4-carboxylate (**10**).[9,10] After ester hydrolysis of **10** with 1 M LiOH (1 M=mol dm^{-3}), similarly to the case of **7**, the amidation of the hydrolysate (**11**) and then thioamidation of the obtained amide derivative (**12**)[11] gave the expected thioamide derivative (**13**),[12] as shown in Scheme 1. Subsequently, thiazole ring formation between **13** and **14** by the method reported[4] gave the desired 6-acetal-2-(bithiazol-4-yl)pyridine derivative (**15**).[10,13] After deprotection of the acetal group with 2 M HCl, the obtained formyl derivative (**16**) was further thiazolated with H-L-Cys-OPac[5] (Pac=phenacyl) in the presence of Et_3N and then with MnO_2 to give the corresponding 6-(thiazol-2-yl)pyridine derivative (**17**)[14] by the Shioiri method.[10,15] Furthermore, deprotection of the Boc group of **17** with TFA, followed by coupling with Boc-Gly-OH using BOP[16] and $(i\text{-Pr})_2$NEt gave the expected (1*S*,2*R*)-**19**[17] as the protected Fragment A derivative *via* hydrolysis of the Pac ester **18** with 1 M LiOH.

To accomplish the synthesis of the Fragment A-C, firstly, similarly to the case of **18**, coupling of **19** with H-L-Ser(TPS)-L-Pro-NH_2 was carried out to give the corresponding *O*-protected dipeptide precursor (**20**) of the Fragment A-C. Secondly, deprotection of TPS group of **20** with tetrabutylammonium fluoride (TBAF) gave the corresponding deprotected serylproline derivative (**21**).[18] Finally, oxazolination of **21** with methanesulfonyl chloride (MsCl) in the presence of Et_3N in CH_2Cl_2 at 0 ˚C for 30 min gave the desired (1*S*,2*R*)-(*S*,*S*)-**22**[10,19] as the protected Fragment A-C segment. Although the obtained **22** was found to be slightly unstable, the structure was definitely determined by the ^{1}H NMR spectral data. The amide proton of the Ser residue at δ 6.94 (br d, 1H, *J*=8.2 Hz) of **21** disappeared





Reagents and conditions : i) a) $KHCO_3$, DME, 0 °C, 30 min, rt, overnight, b) TFAA, pyridine, DME, 0 °C, 2 h, c) 28% aq NH_3, 0 °C, 15 min, ii) 2M HCl, THF, rt, overnight, iii) a) H-Cys-OPac, Et_3N, toluene, rt, 10 min, b) MnO_2, toluene, rt, overnight, iv) a) TFA:$CHCl_3$=1:1, rt, 3 h, b) Boc-Gly-OH, BOP, $(i\text{-}Pr)_2NEt$, 0 °C, 1 h, rt, overnight, v) 1M LiOH, THF, 0 °C, 3 h, vi) H-L-Ser(TPS)-L-Pro-NH_2, BOP, $(i\text{-}Pr)_2NEt$, 0 °C, 1 h, rt, overnight, vii) TBAF, THF, 0 °C, 3 h, viii) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 30 min, b) Et_3N, CH_2Cl_2, 0 °C, 30 min.

Scheme 2.

and the ring protons of the formed oxazoline moiety at δ 4.54-4.83 (m, 2H) and 5.19-5.23 (m, 1H) appeared clearly, besides all the ring protons of four thiazoles and a pyridine moiety. The structures of all of the new compounds thus obtained were confirmed by the spectral data (^{1}H NMR and IR) and the satisfactory elemental analyses.

In conclusion, a convenient synthetic method for the protected Fragment A-C skeleton of GE 2270 A has been sufficiently developed. Further investigations on the total synthesis of **1** are currently under way in our laboratory.

ACKNOWLEDGEMENT

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7. **7**: Colorless powder (hexane-ethyl acetate). mp 139-141 ˚C. $[\alpha]_D^{25}$ -86.9˚ (*c* 0.89, MeOH). IR (KBr): 3308, 3072, 2931, 2857, 2518, 1721, 1644 cm^{-1}. ^1H NMR (DMSO-d_6, 60 ˚C): δ 0.96 (s, 9H, TPS's CH_3 x 2), 1.26 (s, 9H, Boc's CH_3 x 3), 4.38 (br s, 1H, α-H), 5.06 (d, 1H, β-H, *J*=6.1 Hz), 5.97 (br s, 1H, NH), 7.15-7.56 (m, 15H, Ph x 3), 12.58 (s, 1H, COOH).
8. **9**: Colorless powder (hexane-ethyl acetate). mp 168-169 ˚C. $[\alpha]_D^{26}$ -77.1˚ (*c* 0.97, MeOH). IR (KBr): 3371, 3178, 2974, 2931, 2855, 2360, 1698, 1641 cm^{-1}. ^1H NMR (DMSO-d_6, 60 ˚C): δ 0.98 (s, 9H, TPS's CH_3 x 3), 1.24 (s, 9H, Boc's CH_3 x 3), 4.78-4.81 (m, 1H, NHC*H*), 5.19 (d, 1H, C*H*Ph, *J*=4.9 Hz), 5.85 (br s, 1H, NH), 7.07-7.56 (m, 15H, Ph x 3), 9.08 (br s, 1H, NH), 9.55 (br s, 1H, NH).
9. **10**: Colorless syrup. $[\alpha]_D^{26}$ -14.1˚ (*c* 0.64, MeOH). IR (KBr): 2930, 1716, 1494 cm^{-1}. ^1H NMR (DMSO-d_6, 60 ˚C): δ 0.98 (s, 9H, TPS's CH_3 x 3), 1.17 (s, 9H, Boc's CH_3 x 3), 1.31 (t, 3H, Et's CH_3, *J*=7.3 Hz),. 4.31 (q, 2H, Et's CH_2, *J*=7.3 Hz), 5.12-5.15 (m, 1H, NHC*H*), 5.20 (d, 1H, C*H*Ph, *J*=8.6 Hz), 7.10-7.38 (m, 16H, Ph x 3 and NH), 8.31 (s, 1H, thiazole ring H).
10. From the ^1H NMR spectral data of **10**, **15**, and **22**, it was found that no racemization has taken place during the formation of new thiazole and oxazoline rings.
11. **12**: Colorless powder (hexane-ethyl acetate). mp 154-156 ˚C. $[\alpha]_D^{26}$ -26.7˚ (*c* 0.98, MeOH). IR (KBr): 3352, 3246, 3069, 3013, 2967, 2856, 2359, 1692, 1665, 1604, 1587, 1521 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.79 (s, 9H, TPS's CH_3 x 3), 1.16 (s, 9H, Boc's CH_3 x 3), 5.10-5.15 (m, 2H, α-H and β-H), 7.15-7.54 (m, 18H, Ph x 3 and NH x 3), 8.10 (s, 1H, thiazole ring H).
12. **13:** Yellow syrup. $[\alpha]_D^{28}$ +4.0° (*c* 0.30, MeOH). ^1H NMR (DMSO-d_6): δ 0.81 (s, 9H, TPS's CH_3 x 3), 1.18 (s, 9H, Boc's CH_3 x 3), 5.10-5.15 (m, 2H, NHC*H* and C*H*Ph), 7.09-7.39 (m, 16H, Ph x 3 and NH), 8.30 (s, 1H, thiazole ring H), 9.26 (br s, 1H, NH), 9.94 (br s, 1H, N*H*CH).
13. **15**: Brown powder (hexane-ethyl acetate). mp 78-79.5 ˚C. $[\alpha]_D^{28}$ +13.5˚ (*c* 0.99, MeOH). IR (KBr): 3429, 2931, 2857, 2360, 2342, 1716, 1589, 1562 cm^{-1}. ^1H NMR (DMSO-d_6, 60 ˚C): δ 0.76 (s, 9H, TPS's CH_3 x 3), 1.16 (s, 9H, Boc's CH_3 x 3), 1.26 (t, 3H, Et's CH_3, *J*=7.5 Hz), 3.29-3.41 (m, 6H, OCH_3 x 2), 4.27 (q, 2H, Et's CH_2, *J*=7.5 Hz), 5.11-5.66 (m, 2H, NHC*H* and C*H*Ph), 5.44 (s, 1H, C*H*$(OCH_3)_2$), 6.95-7.36 (m, 16H, NH and Ph x 3), 7.70-7.72 (m, 2H, thiazole ring H and pyridine ring H), 8.17 and 8.53 (each s, 2H, thiazole ring H), 8.36 (d, 1H, pyridine ring H).
14. **17**: Pale yellow powder (hexane-ethyl acetate). mp 105-16.5 ˚C. $[\alpha]_D^{28}$ +9.7˚ (*c* 0.95, MeOH). IR (KBr): 3428, 3116, 2931, 2857, 2359, 2341, 1713, 1581 cm^{-1}. ^1H NMR

($CDCl_3$): δ 1.04 (s, 9H, TPS's CH_3 x 3), 1.39 (s, 9H, Boc's CH_3 x 3), 1.39 (t, 3H, Et's CH_3, *J*=7.0 Hz), 4.43 (q, 2H, Et's CH_2, *J*=7.0 Hz), 5.15-5.30 (m, 2H, NHC*H* and N*H*CH), 5.35 (d, 1H, C*H*Ph, *J*=4.3 Hz), 5.68 (s, 2H, Pac's CH_2), 7.09-8.03 (m, 22H, Ph x 4 and thiazole ring H x 2), 8.25, 8.48 (each s, 2H, thiazole ring H x 2), 8.36, 8.43 (each d, 2H, pyridine ring H, *J*=8.2 Hz).

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17. **19:** Brown powder (hexane-ethyl acetate). mp 256.0-257.0 °C. $[\alpha]_D^{28}$ -85.0° (*c* 0.68, EtOAc). IR (KBr): 3406, 3115, 2931, 2857, 2360, 1703, 1581 cm^{-1}. ^1H NMR (DMSO-d_6, 60 °C): δ 0.84 (s, 9H, TPS's CH_3 x 3), 1.27 (t, 3H, Et's CH_3, *J*=7.0 Hz), 1.31 (s, 9H, Boc's CH_3 x 3), 3.00-3.50 (m, 2H, Gly's CH_2), 4.28 (q, 2H, Et's CH_2, *J*=7.0 Hz), 5.29 (d, 1H, C*H*Ph, *J*=7.3 Hz), 5.47-5.50 (m, 1H, NHC*H*), 6.69 (br s, 1H, Gly's NH), 7.14-7.43 (m, 16H, Ph x 3 and COOH), 7.70, 8.18, 8.23, 8.55 (each s, 4H, thiazole ring H x 4), 7.90-8.05 (m, 1H, N*H*CH), 8.41-8.50 (m, 2H, pyridine ring H x 2).
18. **21**: Pale yellow powder (hexane-ethyl acetate). mp 169-170 °C. $[\alpha]_D^{28}$ +6.0° (*c* 1.00, MeOH). IR (KBr): 3396, 2976, 2361, 1674, 1583, 1535 cm^{-1}. ^1H NMR (DMSO-d_6): δ 0.92, 1.29 (each t, 3H, Et's CH_3, *J*=7.0 Hz), 1.22, 1.36 (each s, 9H, Boc's CH_3 x 3), 1.78-1.92 (m, 4H, Pro's CH_2 x 2), 3.13-4.14 (m, 9H, Pro's CH_2, CH_2O, CH_2N, Gly's CH_2, and Ser's α-H), 4.30 (q, 2H, Et's CH_2, *J*=7.0 Hz), 4.68-4.72 (m, 1H, Ser's β-H), 4.87-4.91 (m, 1H, Ser's α-H), 5.03-5.05 (m, 1H, PhC*H*OH), 5.26-5.36 (m, 1H, OH), 5.33-5.36 (m, 1H, NHC*H*), 6.94 (br t, 1H, NH, *J*=5.8 Hz), 7.06, 7.16 (each br s, 2H, NH_2), 7.21-7.31 (m, 5H, Ph), 7.78, 7.81, 8.27 (each s, 3H, thiazole ring H x 3), 8.37-8.60 (m, 5H, pyridine ring H x 2, thiazole ring H, and NH x 2).
19. **22:** Colorless syrup. $[\alpha]_D^{26}$ –22.3° (*c* 0.35, MeOH). ^1H NMR (DMSO-d_6, 60 °C): δ 1.29 and 1.30 (t x 2, 3H, Et's CH_3, *J*=7.0 Hz), 1.38, 1.41 (each s, 9H, Boc's CH_3 x 3), 1.90-2.20 (m, 4H, Pro's CH_2 x 2), 3.44- 4.03 (m, 4H, Gly's CH_2 and Pro's CH_2), 4.26-4.34 (m, 3H, Et's CH_2 and Pro's α-H), 4.54-4.83 (m, 2H, oxazoline's CH_2), 5.19-5.23 (m, 1H, oxazoline's CH), 5.32-5.40 (m, 2H, NHC*H* and OH), 5.79-5.83 (m, 1H, C*H*Ph), 6.78 (br s, 1H, NH), 6.85-7.30 (m, 1H, Gly's NH), 7.2.3-7.50 (m, 6H, Ph and NH), 7.88, 8.28, 8.47, (each s, 3H, thiazole ring H x 3), 8.22 (br d, 1H, NH, *J*=8.2 Hz), 8.31 (d, 1H, pyridine ring H, *J*=8.2 Hz), 8.53-8.58 (m, 2H, pyridine ring H and thiazole ring H). MALDI-TOFMS Found: *m*/*z* 1093.6. Calcd for $C_{44}H_{44}N_{10}O_9S_4Ag$: 1093.1 $(M + Ag)^+$.