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-[(1R,2S)-(1-amino-2-hydroxy-2-phenyl)ethyl]-thiazol-4-yl]thiazol-4-yl)pyridine derivative [Fragment A] and H-L-Ser-L-Pro-NH₂ as the precursor of Fragment C.

An antibiotic, GE 2270 A (1),¹ isolated from the culture of Planobispora 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-NH₂ 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, the first total syntheses of similar macrocyclic antibiotics such as micrococcins P and P₁ have been accomplished. Furthermore, 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) 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-[(1R,2S)-(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-[(1S,2S)-(2-hydroxy)benzyl]-2,2-dimethyloxazolidine (4) and its (1S,2R)-diastereomer almost quantitatively in 3:2 ratio by the method of Koskinen et al. The separated (1S,2S)-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). Amidation of 7 by the mixed anhydride method using CICOOEt and 28% aq NH₃ gave the expected amide derivative (8). Subsequent thioamidation of 8 with Lawesson’s reagent, followed by thiazolation of the obtained thioamide derivative (9) with BrCH₂COCOOEt and then with trifluoroacetic anhydride (TFAA) gave ethyl 2-[(1R,2S)-1-(N-
Bocamino-2-(O-TPS)hydroxy-2-phenyl]ethyl]thiazole-4-carboxylate (10).\textsuperscript{9,10} After ester hydrolysis of 10 with 1 M LiOH (1 M=mol dm\textsuperscript{-3}), similarly to the case of 7, the amidation of the hydrolysate (11) and then thioamidation of the obtained amide derivative (12)\textsuperscript{11} gave the expected thioamide derivative (13),\textsuperscript{12} as shown in Scheme 1. Subsequently, thiazole ring formation between 13 and 14 by the method reported\textsuperscript{4} gave the desired 6-acetal-2-(bithiazol-4-yl)pyridine derivative (15).\textsuperscript{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\textsuperscript{5} (Pac=phenacyl) in the presence of Et\textsubscript{3}N and then with MnO\textsubscript{2} to give the corresponding 6-(thiazol-2-yl)pyridine derivative (17)\textsuperscript{14} by the Shioiri method.\textsuperscript{10,15} Furthermore, deprotection of the Boc group of 17 with TFA, followed by coupling with Boc-Gly-OH using BOP\textsuperscript{16} and (\textit{i}-Pr)\textsubscript{2}NEt gave the expected (1\textit{S},2\textit{R})-19\textsuperscript{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\textsubscript{2} was carried out to give the corresponding \textit{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).\textsuperscript{18} Finally, oxazolination of 21 with methanesulfonyl chloride (MsCl) in the presence of Et\textsubscript{3}N in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C for 30 min gave the desired (1\textit{S},2\textit{R})-(\textit{S},\textit{S})-22\textsuperscript{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 \textit{1}H NMR spectral data. The amide proton of the Ser residue at \(\delta\) 6.94 (br d, 1H, \(J=8.2\) Hz) of 21 disappeared...
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 (1H 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.

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REFERENCES


7. Colorless powder (hexane-ethyl acetate). mp 139-141 °C. \([\alpha]_{D}^{25} -86.9^\circ (c 0.89, \text{MeOH})\). IR (KBr): 3308, 3072, 2931, 2857, 2518, 1721, 1644 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 60 °C): \(\delta\) 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, \(\alpha\)-H), 5.06 (d, 1H, \(\beta\)-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. Colorless powder (hexane-ethyl acetate). mp 168-169 °C. \([\alpha]_{D}^{26} -77.1^\circ (c 0.97, \text{MeOH})\). IR (KBr): 3371, 3178, 2974, 2931, 2855, 2360, 1698, 1641 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 60 °C): \(\delta\) 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, NHCH\(_2\)), 5.19 (d, 1H, CH-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. Colorless syrup. \([\alpha]_{D}^{26} -14.1^\circ (c 0.64, \text{MeOH})\). IR (KBr): 2930, 1716, 1494 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 60 °C): \(\delta\) 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, NHCH\(_2\)), 7.10-7.38 (m, 16H, Ph x 3 and NH x 3), 8.31 (s, 1H, thiazole ring H).

10. From the \(^1\)H 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. Colorless powder (hexane-ethyl acetate). mp 154-156 °C. \([\alpha]_{D}^{26} -26.7^\circ (c 0.98, \text{MeOH})\). IR (KBr): 3352, 3246, 3069, 3013, 2967, 2856, 2359, 1692, 1665, 1587, 1521 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 60 °C): \(\delta\) 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, \(\alpha\)-H and \(\beta\)-H), 7.15-7.54 (m, 18H, Ph x 3 and NH x 3), 8.10 (s, 1H, thiazole ring H).

12. Yellow syrup. \([\alpha]_{D}^{28} +4.0° (c 0.30, \text{MeOH})\). \(^1\)H NMR (DMSO-\(d_6\)): \(\delta\) 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, NHCH\(_2\)), 5.20 (d, 1H, CH-Ph, \(J=8.6\) Hz), 7.10-7.38 (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, NHCH).

13. Brown powder (hexane-ethyl acetate). mp 78-79.5 °C. \([\alpha]_{D}^{28} +13.5^\circ (c 0.99, \text{MeOH})\). IR (KBr): 3428, 3116, 2931, 2857, 2359, 2341, 1713, 1581 cm\(^{-1}\). \(^1\)H NMR (DMSO-\(d_6\), 60 °C): \(\delta\) 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, NHCH and CH-Ph), 5.44 (s, 1H, CH(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. Pale yellow powder (hexane-ethyl acetate). mp 105-165 °C. \([\alpha]_{D}^{28} +9.7° (c 0.95, \text{MeOH})\). IR (KBr): 3428, 3116, 2931, 2857, 2359, 2341, 1713, 1581 cm\(^{-1}\). \(^1\)H NMR
(CDCl<sub>3</sub>): δ 1.04 (s, 9H, TPS's CH<sub>3</sub> x 3), 1.39 (s, 9H, Boc’s CH<sub>3</sub> x 3), 1.39 (t, 3H, Et’s CH<sub>3</sub>, J=7.0 Hz), 4.43 (q, 2H, Et’s CH<sub>2</sub>, J=7.0 Hz), 5.15-5.30 (m, 2H, NHCH and NHCH), 5.35 (d, 1H, CHPh, J=4.3 Hz), 5.68 (s, 2H, Pac’s CH<sub>2</sub>), 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).


17. 19: Brown powder (hexane-ethyl acetate). mp 256.0-257.0 °C. [α]<sub>D</sub><sup>28</sup> -85.0˚ (c 0.68, EtOAc).

18. 21: Pale yellow powder (hexane-ethyl acetate). mp 169-170 °C. [α]<sub>D</sub><sup>28</sup> +6.0˚ (c 1.00, MeOH).

19. 22: Colorless syrup. [α]<sub>D</sub><sup>26</sup> -22.3˚ (c 0.35, MeOH). 1H NMR (DMSO-d<sub>6</sub>, 60 °C): δ 1.29 and 1.30 (t x 2, 3H, Et’s CH<sub>3</sub>, J=7.0 Hz), 1.38, 1.41 (each s, 9H, Boc’s CH<sub>3</sub> x 3), 1.90-2.20 (m, 4H, Pro’s CH<sub>2</sub> x 2), 3.44-4.03 (m, 4H, Gly’s CH<sub>2</sub> and Pro’s CH<sub>2</sub>, 3.57-4.44 (m, 2H, oxazoline’s CH<sub>2</sub>), 5.19-5.23 (m, 1H, oxazoline’s CH), 5.32-5.40 (m, 2H, NHCH and OH), 6.85-7.30 (m, 1H, Gly’s NH), 7.23-7.50 (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<sub>44</sub>H<sub>44</sub>N<sub>10</sub>O<sub>9</sub>S<sub>4</sub>Ag: 1093.1 (M + Ag).