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CONVENIENT SYNTHESES 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-tristhiazolyl-substituted pyridine skeleton [Fragment A-C'] with a thiazoloyl-thiazole segment [Fragment B]. The Fragment B was synthesized from an appropriate thioamide and β-bromo-α-oxoalkanoate, the latter of which was first derived by consecutive β-bromination and hydrolytic removal of the α-(*N*-Boc)amino group of an α-dehydroamino acid ester.

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**) features a very unique main structure constructed of a 2,3,6-tristhiazolylsubstituted pyridine skeleton (**4**-**5**) called Fragment A-C and a substituted thiazoloylthiazole segment (**6**) called Fragment B. Although the absolute configurations of

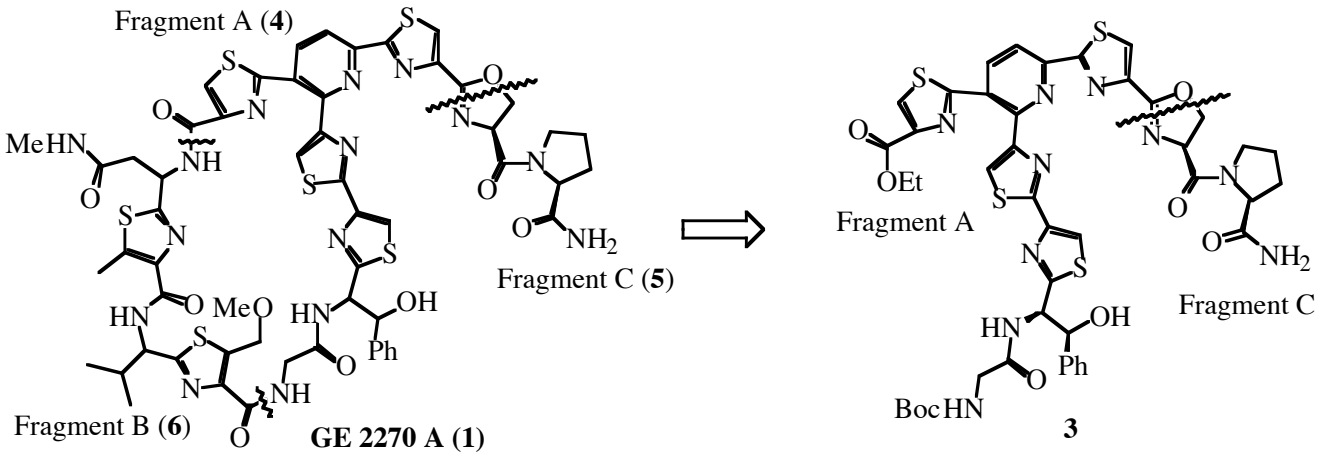
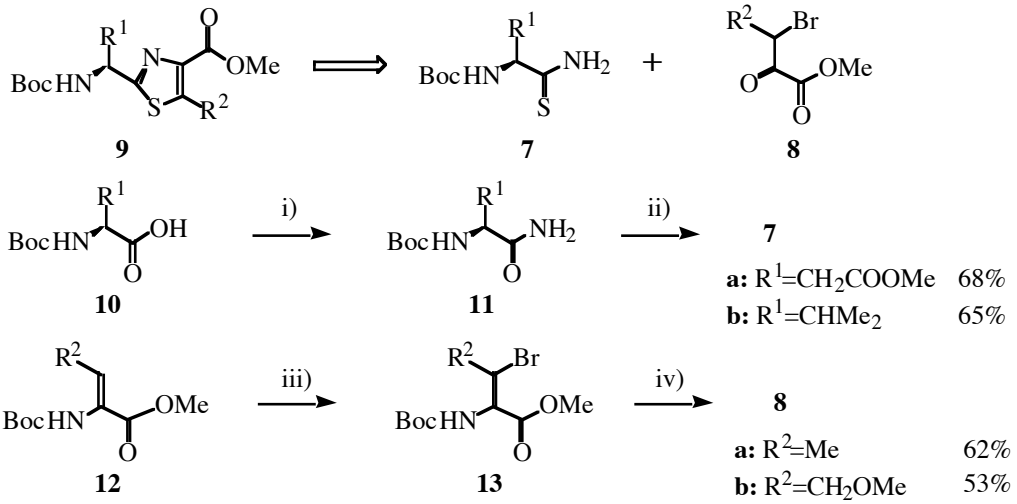


Figure 1. Retrosynthesis of **1**

the six chiral centers in **1** have not yet been identified, they are deduced to originate from natura 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. In the previous papers,[2,3] we have already reported the efficient syntheses of the protected Fragment A-C (**3**), besides the total syntheses of micrococcin P and P_1[4,5] structurally similar to **1**. Here, we wish to report a novel synthetic method for β-bromo-α-oxocarboxylates, which are a most promising building block for the thioazole 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_2; 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,[6] a general synthetic method was further developed. By taking advantage of the Hanztsch method,[7] it was found that the compound (**9**) could be derived by reaction of an appropriate thioamide (**7**) with novel β-bromo-α-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% aqeous NH_3, followed by thioamidation with Lawesson's reagent gave the corresponding thioamide derivatives (**7a**) (R^1=CH_2COOMe; pale yellow syrup) and (**7b**) (R^1=$CH(CH_3)_2$; colorless crystals, mp 108-110 °C) respectively. On the other hand, to synthesize **8** from an appropriate α-dehydroamino acid methyl ester, according to the method reported earlier,[8,9] Boc-ΔAbu-OMe (ΔAbu=2-amino-2-butenoic acid) (**12a**) was treated with *N*-bromosuccinimide (NBS) to give methyl 2-(*N*-Boc)amino-3-bromo-2-butenoate (**13a**) (colorless syrup, 86%), the Boc and amino groups of which were successively deprotected and hydrolyzed with trifluoroacetic acid (TFA) and then

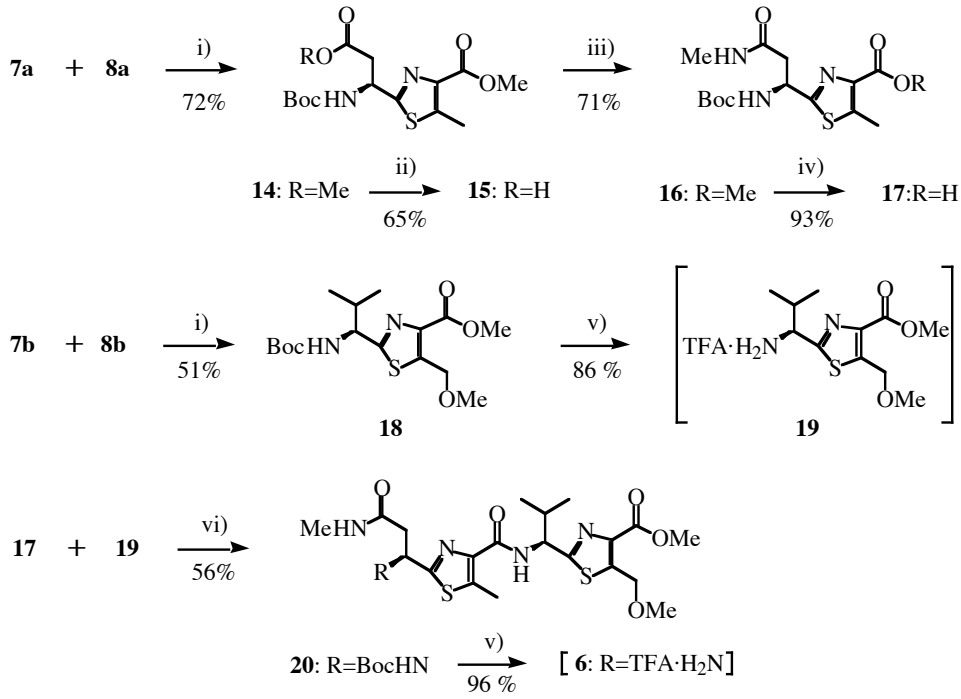


Reagents and conditions: i) a) ClCOOEt, Et_3N, THF, 0 °C, 15 min, b) 28% aq. NH_3, THF, 0 °C, 15 min, ii) Lawesson's reagent, DME, rt, overnight, iii) a) NBS, $CHCl_3$, rt, 30 min, b) Et_3N, $CHCl_3$, rt, 30 min, iv) TFA, $CHCl_3$, H_2O, rt, 30 min.

Scheme 1.

with H_2O to give methyl 3-bromo-2-oxobutanoate (**8a**; colorless syrup). Similarly, methyl 2-(*N*-Boc)amino-4-methoxy-2-butenoate (**12b**) (colorless syrup, 65%), derived by the Wittig-Horner reaction of Boc-[$PO(OEt)_2$]Gly-OMe with $MeOCH_2CHO$, 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-butenoate (**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 $KHCO_3$ in 1,2-dimethoxyethane (DME), trifluoroacetic anhydride (TFAA) in the presence of pyridine, and then 28% aqueous NH_3 was tried successfully to give methyl 2-[1-(*N*-Boc)amino-3-methoxycarbonyl]ethyl-5-methylthiazole-4-carboxylate (**14**).[10] 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 $MeNH_2$ by using BOP[11] as the condensing agent and $(i\text{-Pr})_2NEt$ to give the corresponding 2- (methylamide)ethyl derivative (**16**).[12] 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) $KHCO_3$, DME, 0 °C, 30 min, rt, overnight, b) TFAA, pyridine, 0 °C, 2 h, c) 28% aq. NH_3, EtOAc, 0 °C, 15 min, ii) 1M LiOH, THF, 0 °C, 4 h, iii) BOP, $HCl{\cdot}H_2NMe$, $(i\text{-Pr})_2NEt$, DMF, 0 °C, 30 min, rt, overnight, iv) 1M LiOH, MeOH, 0 °C, 30 min, rt, overnight, v) TFA, $CHCl_3$, rt, 2 h, vi) BOP, $(i\text{-Pr})_2NEt$, DMF, 0 °C, 30 min, rt, overnight.

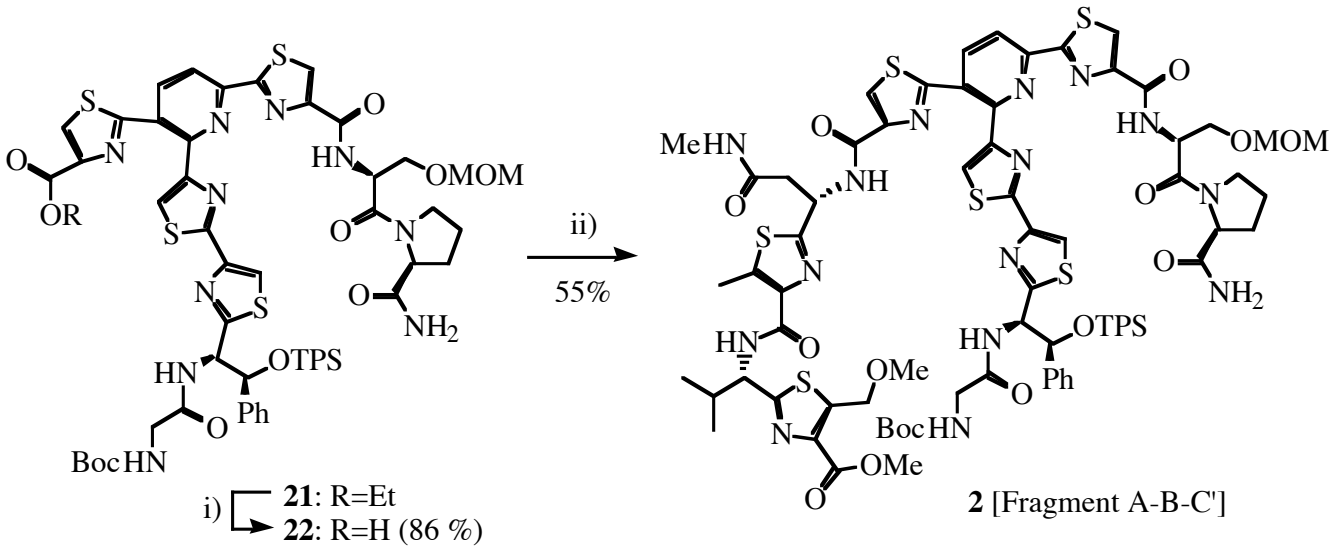
Scheme 2.

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**).[13] 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 ^{1}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**)[3] obtained previously with 1 M LiOH resulted in the ring cleavage of the oxazoline. Therefore, after similr 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,[3] 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**[14] 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 ^{1}H NMR) and the satisfactory elemental analyses. The structure of **2** was also definitely determined by the ^{1}H and ^{13}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 713-8.68 and 9.51 and their vicinal methine protons at δ 5.00-505, 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 $C_{56}H_{57}N_{15}O_{11}S_6$: 1308.3 $(M + H)^+$], the final



Reagents and conditions: i) 1M LiOH, MeOH, 0 °C, 30 min, rt, overnight, ii) **6**, BOP, $(i\text{-Pr})_2$NEt, DMF, 0 °C, 1 h, rt, overnight.

Scheme 3.

exocyclic oxazolination so far has not succeeded.

In conclusion, useful synthetic methods for novel β-bromo-α-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 cm^{-1}. ^1H NMR ($CDCl_3$) δ=1.47 (s, 9H, Boc's CH_3 x 3), 2.73 (s, 3H, thiazole ring-CH_3), 2.94-3.40 (m, 2H, CH_2), 3.67 and 3.91 (s x 2, 3H x 2, $COOCH_3$ x 2), 5.25-5.33 (m, 1H, NHC*H*), 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 °C. $[\alpha]_D^{26}$ -27.6° (c 0.21, MeOH).

IR 3337, 2951, 1704, 1675, 1649, 1520 cm^{-1}. ^1H NMR (60 °C, DMSO-d_6) δ=1.41 (s, 9H, Boc's CH_3 x 3), 2.66 (s, 3H, NHCH_3), 2.67 (s, 3H, thiazole ring-CH_3), 2.73-3.10 (m, 2H, CH_2), 3.85 (s, 3H, $COOCH_3$), 5.16 (br s, 1H, NHC*H*), 6.06 (br s, 1H, N*H*CH_3), 6.62 (br d, 1H, NH, *J*=8.0 Hz). *Anal.* Calcd for $C_{15}H_{23}N_3O_5S$: 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 °C. $[\alpha]_D^{26}$ –24.6° (*c* 0.99, MeOH). IR 3369, 2967, 1715,1657 cm^{-1}. ^1H NMR (DMSO-d_6) δ=0.90 and 0.95 (each d, 3H x 2, CH(CH_3)$_2$, *J*=6.7 Hz), 1.39 (s, 9H, Boc's CH_3 x 3), 2.39-2.45 (m, 1H, C*H*$(CH_3)_2$), 2.50-2.92 (m, 2H, CHCH_2), 2.56 (d, 3H, NHCH_3, *J*=4.6 Hz), 2.85 (s, 3H, thiazole ring-CH_3), 3.38 (s, 3H, CH_2OCH_3), 3.81 (s, 3H, $COOCH_3$), 4.89 (s, 2H, CH_2OCH_3), 4.98-5.03 (m, 1H, NHC*H*CH), 7.70 (br d, 1H, NH, *J*=8.0 Hz), 7.87 (br d, 1H, N*H*CH_3, *J*=4.6 Hz), 8.34 (br s, 1H, NH, *J*=9.0 Hz). *Anal.* Calcd for $C_{25}H_{37}N_5O_7S_2$: 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 °C. $[\alpha]_D^{26}$ +49.1° (*c* 0.97, MeOH). IR 3396, 2959, 1664, 1536 cm^{-1}. ^1H NMR (DMSO-d_6) δ=0.81 and 0.82 (s x 2, 9H, TPS's CH_3 x 3), 0.90 and 0.95 (d x 2, 3H x 2, CH_3 x 2, *J*=7.0 Hz), 1.31 (s, 9H, Boc's CH_3 x 3), 1.83-2.07 (m, 4H, Pro's CH_2 x 2), 2.40-2.52 (m, 1H, Ip's CH), 2.55 (d, 3H, NHCH_3, *J*=4.5 Hz), 2.62 (s, 3H, CH_3), 2.87-3.09 (m, 2H, NHCHCH_2), 3.18-3.42 (m, 2H, Gly's CH_2), 3.28 (s, 3H, MOM's CH_3), 3.37 (s, 3H, CH_2OCH_3), 3.70-3.93 (m, 4H, Ser's β-H and Pro's CH_2), 3.81 (s, 3H, $COOCH_3$), 4.26-4.29 (m, 1H, Pro's CH), 4.62 (dd, 2H, MOM's CH_2, *J*=6.7 Hz, *J*=8.3 Hz), 4.88 (s, 2H, CH_2OCH_3), 5.00-5.05 (m, 2H, Ser's α-H and NHC*H*CH$(CH_3)_2$), 5.22-5.25 (m, 1H, PhC*H*), 5.44-5.46 (m, 1H, NHC*H*CHPh), 5.65-5.68 (m, 1H, NHC*H*CH_2CO), 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, N*H*CHCH$(CH_3)_2$, 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, N*H*CH_3, *J*=4.5 Hz), 8.19 (br d, 1H, N*H*CHCHPh, *J*=8.5 Hz), 9.51 (br d, 1H, N*H*$CHCH_2CO$, *J*=8.0 Hz). ^{13}C NMR (DMSOd_6) δ=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, 1 61.9, 163.0, 167.1, 167.7, 168.9, 169.5, 169.9, 170.7, 173.2. *Anal.* Calcd for $C_{80}H_{91}N_{15}O_{15}$-$S_6Si{\cdot}3H_2O$: C, 54.07; H, 5.50; N, 11.82. Found: C, 53.78; H, 5.32; N, 11.66.