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USEFUL SYNTHESIS OF THE MAIN CENTRAL 2,3,6-TRISUBSTITUTED PYRIDINE SKELETON OF VARIOUS THIOSTREPTON-TYPE MACROCYCLIC ANTIBIOTICS

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Abstract-A useful synthetic method for the main central 2-(2-oxazol-4-yl)-3-(4-thiazol-2-yl)-6-carboxypyridine skeleton [Fragment A] constructing various thiostrepton-type macrocyclic antibiotics is described, in which the precursor of Fragment A was derived from the authentic ethyl 2-(6-dimethoxymethyl-2-trifluoromethanesulfonyloxy-3-pyridyl)thiazole-4-carboxylate in 14 steps. Finally, the fragment condensation of Fragment A with the already prepared carboxy component dipeptide [Fragment B] proceeded first to give the precursor of Fragment A-B.

The thiostrepton-type antibiotics, isolated from various kinds of strains, are very interesting macrocyclic secondary metabolites. So far, many structurally similar antibiotics have been well-known and the main central skeletons can be classified into mainly two categories, one of which is comprised of a 2-(thiazol-4-yl)-3,6-di(thiazol-2-yl)pyridine segment, such as micrococcins,[1] GE 2270 A,[2] and thiocilline I[3] (A group). The other constitutes of a 2-(oxazol-4-yl)-3-(thiazol-2-yl)-6-carboxypyridine segment (B group) (Fragment A: **2**), such as berninamycins,[4] sulfomycins,[5] thioxamycin,[6] and A 10255.[4b,7] For example, the structure and the retrosynthtic analysis of only berninamycin (**1**) are shown in Figure 1. At present, no total synthesis of any similar antibiotics has yet been reported, except for the synthesis of micrococcins[8-10] and the synthetic study of GE 2270 A.[11] All of the antibiotics mentioned above feature a very unique structure and interesting bioactivities, which attracted our attention and prompted us to investigate their total synthesis and structure-bioactivity relationship.

In previous papers, we (C. S.) have reported in detail the synthesis of the 2,3,6-trithiazole-substituted pyridine skeleton[8,9] of the A group and briefly the synthesis of the precursor of **2**.[12] Although the synthesis of **2** has been already achieved, at present, it was found that the obtained skeleton can not be utilized for

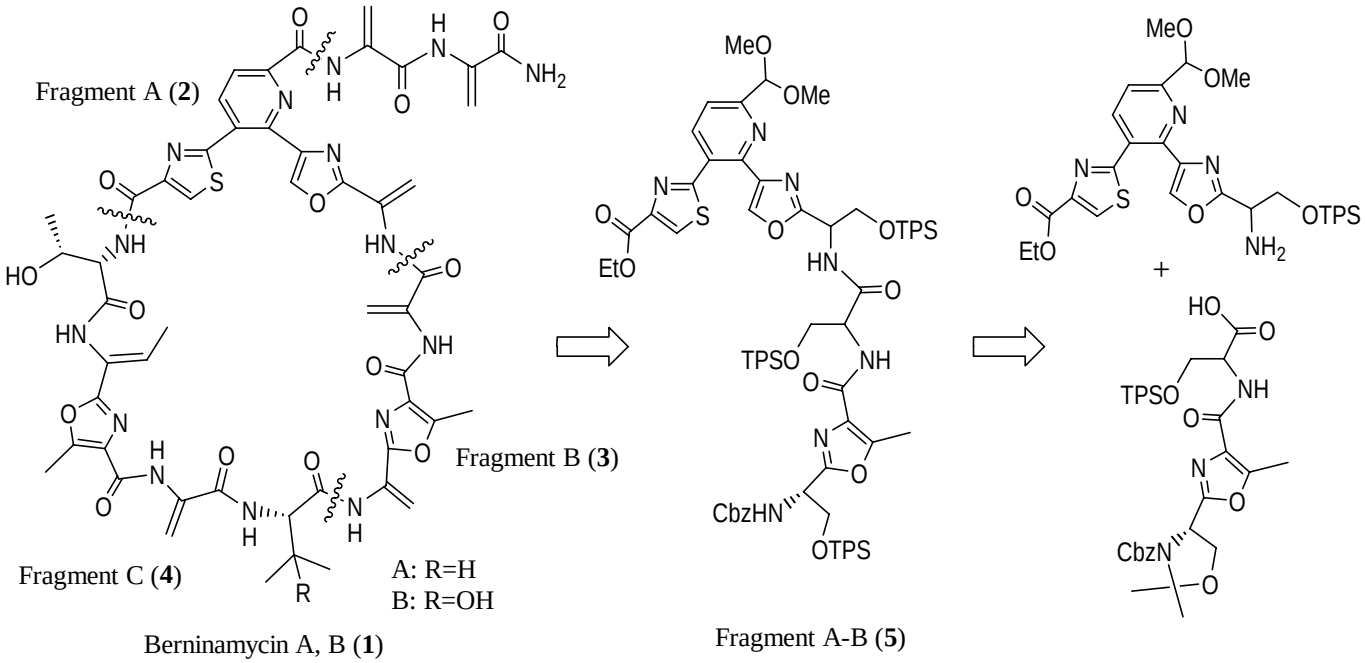


Figure 1. Retrosynthesis of **1**.

the synthesis of B group antibiotics, because the deprotection of Cbz resulted in the elimination of the amino group along with the Cbz group by any means, even by mild hydrogenolysis using 10% Pd-C under H_2 gas stream. Accordingly, the desired elongation by coupling with the appropriate peptide was found to be entirely impossible, as shown in Figure 2.

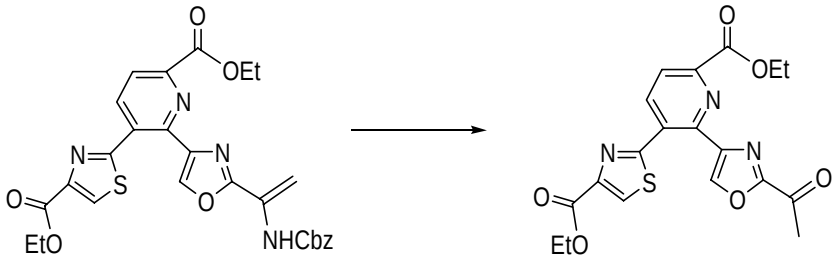
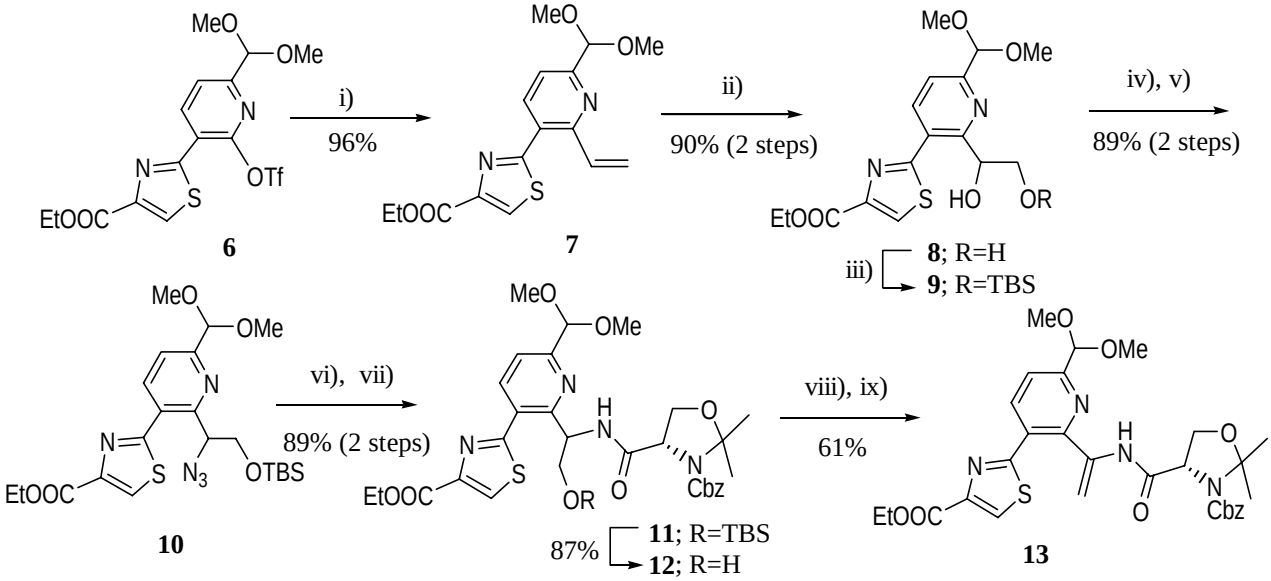


Figure 2. Deprotection of Cbz group.

In this paper, we wish to report briefly on a useful alternative synthetic method for **2** and the coupling with the precursor of the carboxy component dipeptide, which is the common structure constructing B group antibiotics.

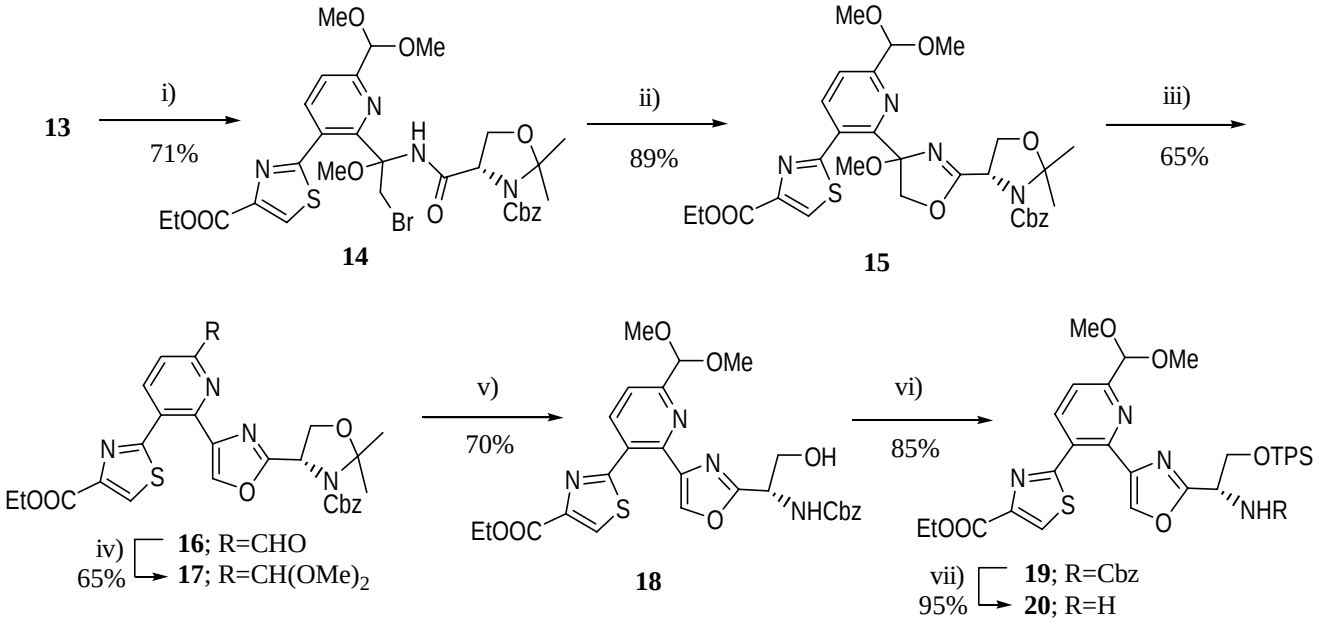
First of all, to synthesize the promising starting material, the vinylation of ethyl 2-[6-dimethoxymethyl-2-trifloxy (TfO)-3-pyridyl]thiazole-4-carboxylate (**6**)[9,10] with CH_2=$CHSnBu_3$ and LiCl in the presence of $Pd(PPh_3)_4$ was performed to give the expected 2-vinylpyridine derivative (**7**). Subsequent dihydroxylation of **7** with OsO_4 in the presence of *N*-methylmorpholine *N*-oxide (NMO) gave the corresponding 2-(1,2-dihydoxyethyl)pyridine derivative (**8**). Selective protection of the primary OH group of **8** with TBS-Cl (TBS=*t*-butyldimethylsilyl) gave the 2-[1-hydroxy-2-(*O*-TBS)hydroxy]-ethylpyridine derivative (**9**), the secondary OH group of which was then treated with methanesulfonyl chloride (Ms-Cl) in the presence of Et_3N and with NaN_3 to give the expected 1-azide derivative (**10**).

Subsequently, the one-pot reduction of the azido group of **10** with 10% Pd-C under H_2 gas stream and coupling of the 2-[1-amino-2-(*O*-TBS)hydroxyethyl]pyridine derivative formed as an unstable intermediate with *N*-Cbz-*N*,*O*-Ip-L-Ser-OH (Ip=isopropylidene) using diphenyl phosphorazidate (DPPA) as a condensing agent in the presence of Et_3N proceeded to give the protected 2-[(1-seryl)amino-2-(*O*-TBS)hydroxy]- ethylpyridine derivative (**11**). Deprotection of the TBS group using 1 M TBAF (tetrabutylammonium fluoride) gave the corresponding 2-(1-hydroxy)ethylpyridine derivative (**12**). Furthermore, in order to dehydrate the OH group, treatment of **12** with Ms-Cl in the presence of Et_3N and then DBU was carried out to give the desired 2-(1-ethenyl)pyridine derivative (**13**),[13] as shown in Scheme 1.



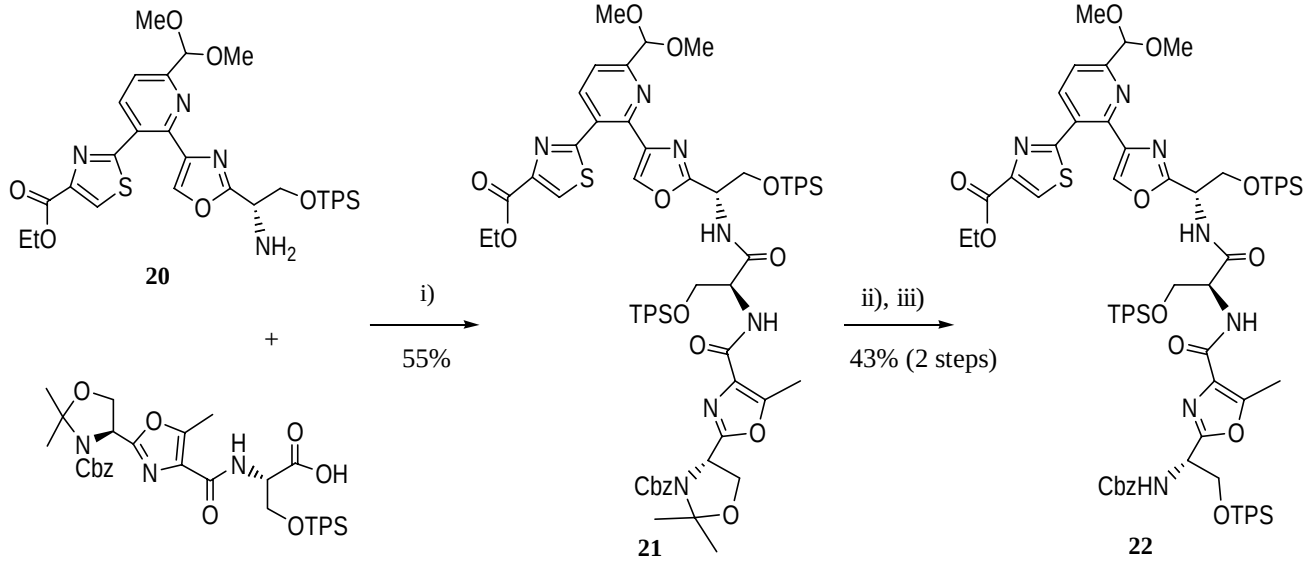
Scheme 1. Reagents and conditions: i) CH_2=$CHSnBu_3$, LiCl, $Pd(PPh_3)_4$ /THF, ii) OsO_4, NMO/$CHCl_3$, iii) TBSCl, Et_3N, iv) MsCl, Et_3N, v) NaN_3/DMF, vi) H_2, 10%Pd-C/MeOH, vii) *N*-Cbz-*N*,*O*-Ip-Ser-OH, DPPA, Et_3N, viii) TBAF/THF, ix) MsCl, Et_3N, DBU/$CHCl_3$.

Secondly, to construct the oxazole ring, treatment of **13** with NBS in MeOH and then with NaOMe gave the corresponding 2-(1-methoxyoxazolin-4-yl)pyridine derivative (**15**) *via* 2-(1-methoxy-1-bromoethyl)-pyridine derivative (**14**). Then, β-elimination of the methoxy group of **15** with camphorsulfonic acid (CSA) in toluene proceeded to give a 6-formylated 2-(oxazol-4-yl)pyridine derivative (**16**). For the conversion of the formyl group to an acetal group, treatment of **16** with MeOH in an aqueous solution of *p*-toluenesulfonic acid (TsOH) gave readily the corresponding acetal derivative (**17**). Then, deprotection of the Ip group with TFA, followed by protection of the hydroxy group of the formed hydroxyethyl derivative (**18**) with TPS-Cl (*t*-butyldiphenylsilyl chloride) gave 2-{2-[1-(*N*-Cbz)amino-2-(*O*-TPS)-hydroxyethyl]oxazol-4-yl}pyridine derivative (**19**),[14] the Cbz group of which was then deprotected with 10% Pd-C/H_2 to give first the expected amino group free derivative (**20**) as the promising skeleton for elongation of sequence, as shown in Scheme 3.



Scheme 2. Reagents and conditions: i) NBS, MeOH, ii) MeONa/THF, iii) CSA/toluene, iv)TsOH**,** MeOH**,** v) 70%AcOH, vi) TPSCl, imidazole/$CHCl_3$ vii) H_2, 10%Pd-C/MeOH

To elongate the peptide sequence, fragment condensation of **20** as the amine component with the already prepared 2-[(3-Cbz-2,2-dimethyl)oxazolidin-4-yl]-5-methyloxazole-4-carbonyl-L-Ser(TPS)-OH[15] by



Scheme 3. Reagents and conditions: i) BOP, (*i*-Pr)$_2$NEt/$CHCl_3$, ii) TFA, iii) TPSCl, imidazole

using the BOP[16] method proceeded to give the compound (**21**).[17] Finally, the Ip group of **21** was deprotected with TFA and then protected the formed OH group with TPS-Cl to give the expected derivative (**22**) of **5**, as shown in Scheme 3.

In conclusion, it is worth noting that a useful synthesis of the main central skeleton of thiostrepton-type

antibiotics such as berninamycins, sulfomycin I, A 10225, and thioxamycin and so on, was first accomplished by a novel synthetic method. Further investigations on the total synthesis of sulfomycin, A 10255 , and berninamycins are currently under way in our laboratory..

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13. Compound (**13**). Yield 64%. Colorless syrup. $[\alpha]_D^{24}$ –9.09° (*c* 0.66, $CHCl_3$). IR (KBr) 2984, 2935, 2834, 1716, 1508 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz, 60 °C) δ=1.42 (t, 3H, C*H*$_3$CH$_2$, *J*=7.3 Hz), 1.56, 1.77 (each s, 6H, Ip's CH_3 x 2), 3.37 (s, 6H, OMe), 4.13-4.31 (m, 2H, Ser's β-H), 4.45 (q, 2H, CH$_3$C*H*$_2$, *J*=7.3 Hz), 4.49 (m, 1H, Ser's α-H), 4.88 (s, 1H, CH), 5.14 (ABq, 2H, Cbz's CH_2, *J*=12.2 Hz), 5.27, 6.29 (each s, 2H, vinyl's H x 2), 7.20 (m, 5H, Cbz's Ph), 7.60, 8.08 (each d, 2H, pyridine's H, *J*=8.4 Hz), 8.23 (s, 1H, thiazole's H), 9.00 (br s, NH). *Anal*. Calcd for $C_{39}H_{34}N_4O_8S$: C, 59.00; H, 5.61; N, 9.17. Found: C, 58.53; H, 5.33; N, 9.23
14. Compound (**19**). Yield 64%. Colorless syrup. $[\alpha]_D^{27}$ +45.6° (*c* 0.88, $CHCl_3$). IR (KBr) 3400, 3067, 2987, 2955, 2963, 2778, 2756, 2370, 1717, 1667 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ=0.96 (s, 9H, TPS's *t*-Bu), 1.43 (t, 3H, C*H*$_3$CH$_2$, *J*=7.1 Hz), 3.34, 3.38 (each s, 6H, OMe x 2), 3.72-4.31 (m, 3H, oxazole's α, β-H), 4.46 (q, 2H, CH$_3$C*H*$_2$, *J*=7.1 Hz), 5.08 (s, 2H, Cbz's CH_2), 5.31 (s, 1H, C*H*(OMe)2, 5.59 (m, 1H, NH), 7.23-7.63 (m, 15H, TPS's Ph x 2, Cbz's Ph), 7.85 (d, 1H, pyridine ring-H, *J*=8.0 Hz), 7.96 (d, 1H, pyridine's H, *J*=8.0 Hz), 8.22 (s, 1H, thiazole's H), 8.29 (s, 1H, oxazole's H). *Anal*. Calcd for $C_{43}H_{46}N_4O_8SSi$: C, 64.00; H, 5.75; N, 6.94. Found: C, 63.78; H, 5.55; N, 6.79.
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16. BOP=(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate.
17. Compound (**21**). Yield 48%. Colorless syrup. $[\alpha]_D^{27}$ –84.4° (*c* 0.45, $CHCl_3$). IR (KBr) 3886, 3856, 3778, 3754, 3604, 3608, 3424, 3196, 3970, 2932, 2860 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz, 60 °C) δ=0.82, 0.90 (each s, 18H, TPS's *t*-Bu), 1.34 (t, 3H, C*H*$_3$CH$_2$, *J*=7.3 Hz), 1.51-l.77 (m, 6H, Ip's CH_3 x 2), 2.47 (s, 3H, oxazole's CH_3), 3.28, 3.33 (each s, 6H, OMe x 2), 3.83-4.23 (m, 8H, Ser's α-H, β-H, oxazole's α-H x 2, β-H x 2), 4.34 (q, 2H, CH$_3$C*H*$_2$, *J*=7.3 Hz), 4.72 (m, 1H, Ser's α-H), 5.19 (s, 2H, Cbz's CH_2), 5.23 (s, 1H, CH), 6.17-6.26 (m, 1H, NH), 7.19-7.65 (m, 26H, Cbz's Ph, TPS's Ph x 2, NH), 7.80 (d, 1H, pyridine's H, *J*=9.0 Hz), 8.45 (d, 1H, pyridine's H, *J*=9.0 Hz), 8.09 (s, 1H, thiazole's H), 8.18 (s, 1H, oxazole's H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ=11.56, 14.19, 14.29, 14.30, 19.01, 19.03, 19.08, 19.12, 21.03, 23.93, 25.31, 26.61, 26.73, 51.85, 52.52, 53.71, 53.82, 54.12, 54.31, 54.68, 60.37, 61.47, 63.99, 64.12, 66.08, 66.27, 66.75, 67.67, 76.75, 77.00, 77.25, 95.54, 103.88, 120.04, 127.51, 127.54, 127.69, 128.02, 128.34, 128.62, 128.66, 129.46, 129.69, 132.72, 133.07, 133.11, 135.40, 135.43, 135.50, 135.57, 138.79, 138.84, 148.02, 148.38, 151.74, 154.81, 155.09, 158.04, 161.23, 164.42, 168.93. *Anal*. Calcd for $C_{72}H_{81}N_7O_{13}SSi_2$: C, 64.50; H, 6.09; N, 7.31. Found: C, 64.19; H, 5.96; N, 7.22.