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# Synthesis of a Common Main Skeleton of Thiostrepton Peptide Antibiotics, A10255G and J

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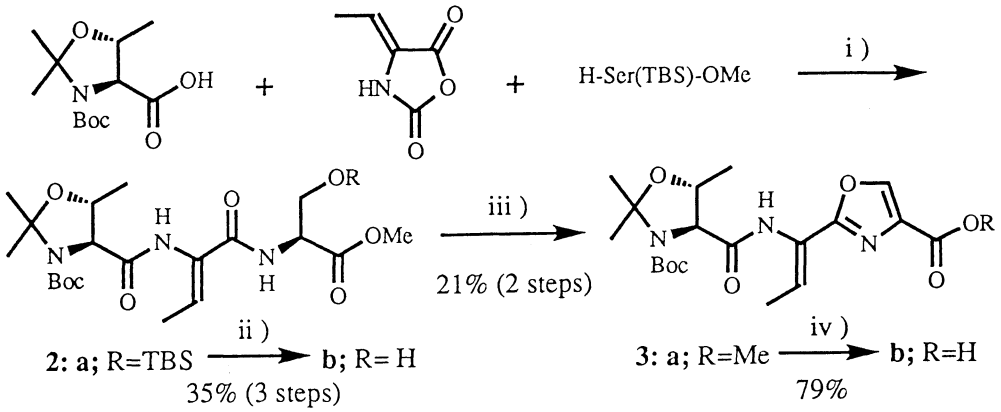
The synthesis of a common main skeleton of thiostrepton peptides, A10255G and J, containing a few kinds of unusual amino acids is described.

In the preceding paper,[1] we have reported the syntheses of various polydehydroalanines, found in most thiostrepton macrocyclicpeptide antibiotics, for example, A10255G and J (**1**).[2] In the course of the total synthesis of the two natural products, besides the syntheses of a few component segments, the convenient synthesis of the common main skeleton of **1** was accomplished.

First, in order to synthesize the oxazole-4-carboxylic acid containing N-terminal dipeptide of **1**, one-pot reaction of *N*-carboxy-2-amino-2-butenoic acid anhydride (ΔAbu·NCA)[3] with Boc-*N*,*O*-isopropylidene-Thr-OH and then H-Ser(TBS)-OMe (TBS=*t*-butyldimethylsilyl) in the presence of 4-dimethylaminopyridine (DMAP) by the usual DCC method gave the protected Thr-ΔAbu-Ser(TBS)-OMe [**2a**: $^1$H NMR ($CDCl_3$) δ=6.52 (q, 1H, =CH-, *J*=7.03 Hz)]. According to the method of Galeotti *et al.*[4] and by the our method,[5] after removal of TBS group by using *n*-$Bu_4NF$, the cyclization of the obtained Thr-ΔAbu-Ser-OMe [**2b**: δ=6.86 (q, 1H, =CH-, *J*=7.03 Hz), 2.01 (br s, 1H, -OH)] with $Ph_3P$ and diethyl azodicarboxylate (DEAD), followed by the ring oxidation of the formed oxazoline with $MnO_2$, gave the corresponding oxazole methyl ester [**3a**: δ=6.70 (q, 1H, =CH-, *J*=7.25 Hz), 8.14 (s, 1H, ring-H)]. Hydrolysis of **3a** with 1 M LiOH gave the free acid [**3b**: δ=6.43 (q, 1H, =CH-, *J*=7.25 Hz), 8.58 (s, 1H, ring-H), 12.80 (br s, 1H, -COOH)] (Scheme 1).

On the other hand, the *N*-component tripeptide (**7**) containing two thiazole rings was derived mainly from

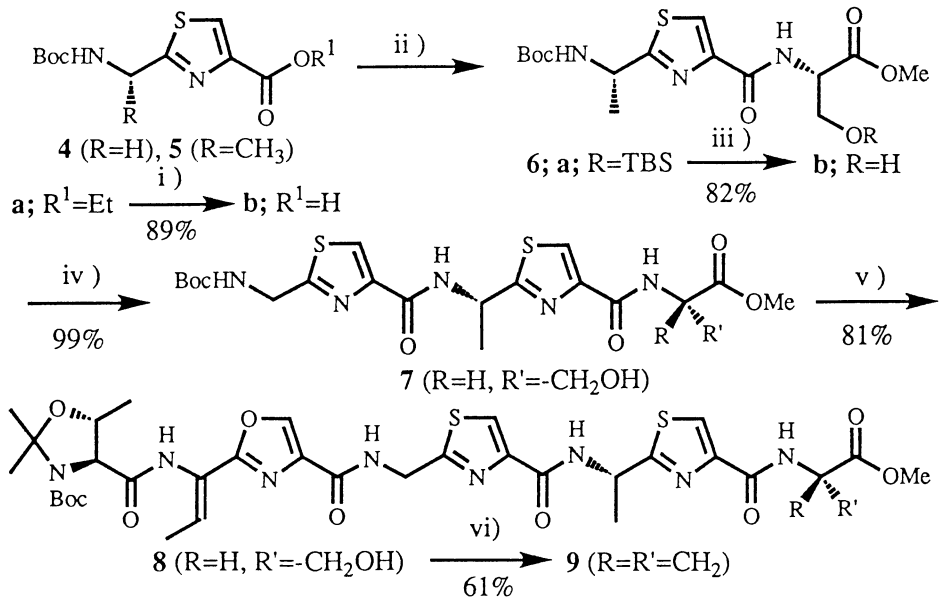



i) DCC, DMAP, $Et_3N$, $CH_2Cl_2$, 0 °C, 36 h, ii) *n*-$Bu_4NF$, THF, 0 °C, 30 min, iii) (a) $Ph_3P$, DEAD, THF, r.t., 10 min (b) $MnO_2$, benzene, r.t., 72 h, iv) 1M LiOH, $H_2O$ / dioxane, 0 °C, 6 h.

Scheme 1.

two moieties, (*S*)-2-(1-BocHN)alkylthiazole-4-carboxylic acids [**4b**: δ=8.34 (s, 1H, ring-H) and **5b**: δ=8.32 (s, 1H, ring-H)] via the corresponding esters [**4a** (R=H) and **5a** (R=Me)], which were prepared by the methods reported by U. Schmidt *et al.* [6]

The coupling of **5b** with H-Ser(TBS)-OMe, followed by the deprotection of the TBS group of the obtained **6a** gave the corresponding dipeptide [**6b**: δ=2.90 (br s, 1H, -OH), 8.04 (s, 1H, ring-H)]. After deprotecting the Boc group, the formed *N*-free dipeptide was coupled with **4b** by using BOP[7] to give **7** [Mp 133-134 °C, $[\alpha]_D^{26}$ 23.84° (c 1.98, MeOH). δ=8.05 and 8.07 (each 1H, s, ring-H)], which was similarly coupled with **3b** to give the pentapeptide [**8**: Mp 126-127 °C, $[\alpha]_D^{26}$ -8.33° (c 0.36, MeOH). δ=8.07, 8.10 and 8.14 (each 1H, s, ring-H)]. Finally, the *C*-terminal Ser residue of **8** was dehydrated by mesylation with mesyl chloride (MsCl) and then β-elimination with $Et_3N$ under sonication to give the expected main skeletal pentapeptide (**9**) [8][ δ=5.93 (d, 1H, =CH-, *J*=1.30 Hz), 6.56 (q, 1H, =CH-, *J*=7.40 Hz), 6.71 (s, 1H, =CH- )] in 61% yield (Scheme 2).




i) 1M LiOH, $H_2O$ / dioxane, 0 °C, 6 h, ii) H-Ser(TBS)-OMe, DCC, HOBt, DMF, r.t., 6 h, iii) *n*-$Bu_4NF$, THF, r.t., 12 h, iv) (a) TFA, $CH_2Cl_2$, 0 °C, 30 min (b) **4b**, BOP, (*i*-$Pr)_2NEt$, $CH_3CN$, 0 °C, 3 h, v) (a) TFA, $CH_2Cl_2$, 0 °C, 30 min (b) **3b**, BOP, (*i*-$Pr)_2NEt$, $CH_3CN$, 0 °C, 3 h, vi) (a) MsCl, $Et_3N$, $CH_2Cl_2$, 35 °C, 15 min (b) $Et_3N$, $CH_2Cl_2$, 35 °C, 15 min.

Scheme 2.

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5) C. Shin, Y. Nakamura, and K. Okumura, *Chem. Lett.*, **1993**, 1405.
6) U. Schmidt, P. Gleich, H. Griesser, and R. Utz, *Synthesis*, **1986**, 992.
7) Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate as condensing agent.
8) **9**: Mp 130-131 °C, $[\alpha]_D^{25}$ 2.50° (c 0.40, MeOH). Found: C, 51.82; H, 5.33; N, 13.85%. Calcd for $C_{34}H_{42}N_8O_{10}S_2$; C, 51.89; H, 5.38; N, 14.24%.

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