

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

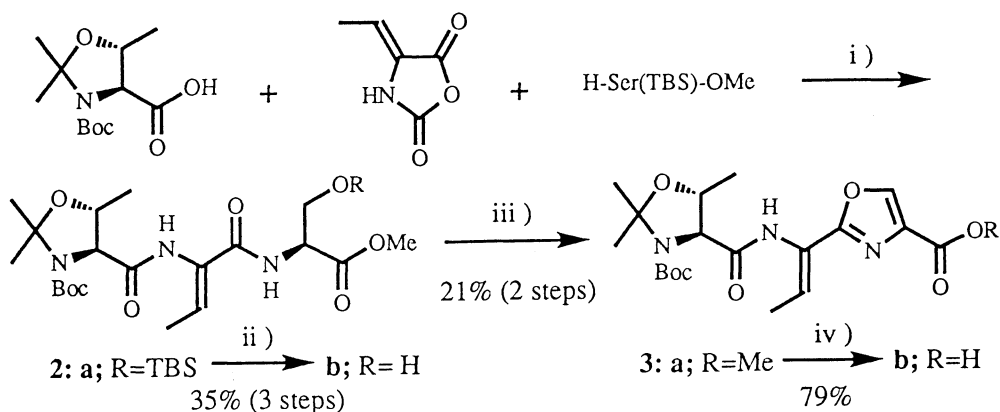
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The synthesis of a common main skeleton of thiostrepton peptides, A10255G and J, containing a few kinds of unusual amino acids is described.

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-butenic acid anhydride (Δ Abu-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- Δ Abu-Ser(TBS)-OMe [**2a**: ¹H NMR (CDCl₃) 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*-Bu₄NF, the cyclization of the obtained Thr- Δ Abu-Ser-OMe [**2b**: δ =6.86 (q, 1H, =CH-, *J*=7.03 Hz), 2.01 (br s, 1H, -OH)] with Ph₃P and diethyl azodicarboxylate (DEAD), followed by the ring oxidation of the formed oxazoline with MnO₂, 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

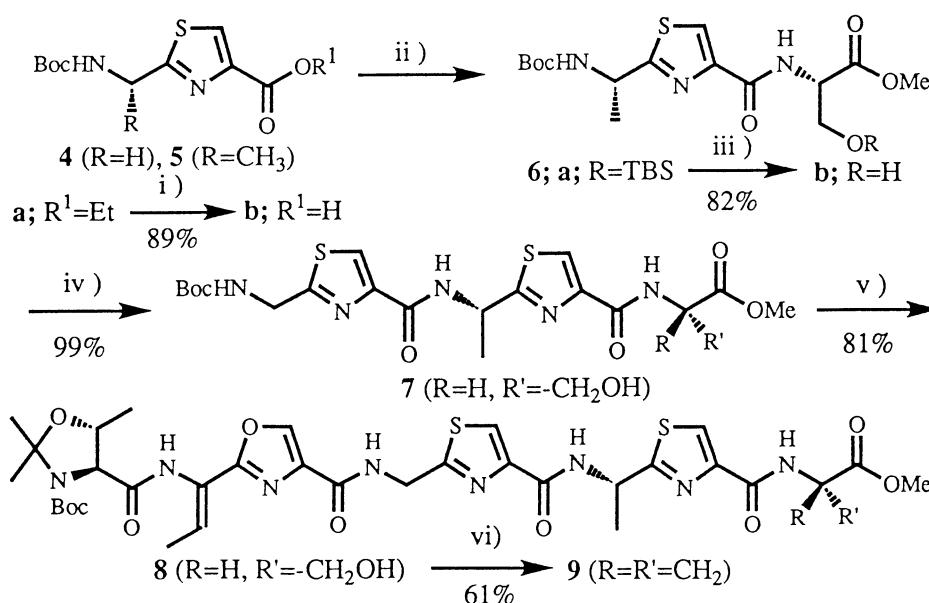


i) DCC, DMAP, Et₃N, CH₂Cl₂, 0 °C, 36 h, ii) *n*-Bu₄NF, THF, 0 °C, 30 min, iii) (a) Ph₃P, DEAD, THF, r.t., 10 min (b) MnO₂, benzene, r.t., 72 h, iv) 1M LiOH, H₂O / dioxane, 0 °C, 6 h.

Scheme 1.

two moieties, (*S*)-2-(1-BocHN)alkylthiazole-4-carboxylic acids [**4b**: $\delta=8.34$ (s, 1H, ring-H) and **5b**: $\delta=8.32$ (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**: $\delta=2.90$ (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 BOP⁷⁾ to give **7** [Mp 133-134 °C, $[\alpha]_D^{26}$ 23.84° (c 1.98, MeOH). $\delta=8.05$ 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). $\delta=8.07$, 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 Et₃N under sonication to give the expected main skeletal pentapeptide (**9**)⁸⁾ [$\delta=5.93$ (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, H₂O / dioxane, 0 °C, 6 h, ii) H-Ser(TBS)-OMe, DCC, HOBT, DMF, r.t., 6 h, iii) *n*-Bu₄NF, THF, r.t., 12 h, iv) (a) TFA, CH₂Cl₂, 0 °C, 30 min (b) **4b**, BOP, (*i*-Pr)₂NEt, CH₃CN, 0 °C, 3 h, v) (a) TFA, CH₂Cl₂, 0 °C, 30 min (b) **3b**, BOP, (*i*-Pr)₂NEt, CH₃CN, 0 °C, 3 h, vi) (a) MsCl, Et₃N, CH₂Cl₂, 35 °C, 15 min (b) Et₃N, CH₂Cl₂, 35 °C, 15 min.

Scheme 2.

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- 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 C₃₄H₄₂N₈O₁₀S₂; C, 51.89; H, 5.38; N, 14.24%.

(Received March 28, 1994)