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Practical Synthesis of Oligodehydroalanine Derivatives by Repetition of Stepwise Elongation of Serine Derivative and β-Elimination

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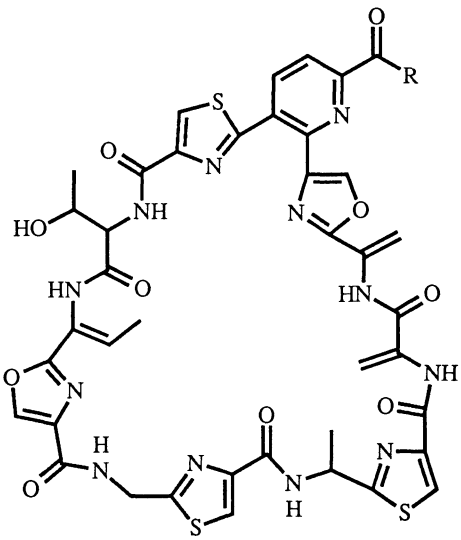
Facile and practical synthesis of various oligodehydroalanine and its amide derivatives, which compose most of the thiostrepton peptide antibiotics, were first accomplished by repetition of the stepwise elongation of serine derivative and then β-elimination.

In recent years, various kinds of thiostrepton peptide antibiotics, which have a characteristic macrocyclic structure, have been isolated from the cultures of various *Streptomyces* (*St.*) strains.[1] For example, the structure of similar peptides A10255G and J,[2] obtained from *St. gardneri*, is illustrated in Fig. 1. All of such peptides are characterized by comprising polythiazole and/or polyoxazole-dehydropeptide substructure. Futhermore, interestingly enough, a wide variety of linear oligodehydroalanines or their amide segments link invariably to the macrocyclic peptide ring. So far, the syntheses of the protected dehydroalanine(ΔAla) by two methods, that is, the β-elimination of serine (Ser) derivatives[3,4] and the Hofmann degradation of diaminopropanates,[5] have been reported. However, the effective synthesis of the oligo- dehydroalanine derivative has not been reported, because the formed ΔAla derivative and its peptide are very labile and readily polymerize during the isolation.



A10255G and **J**

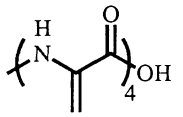
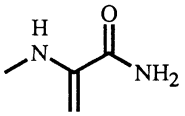
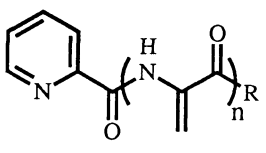
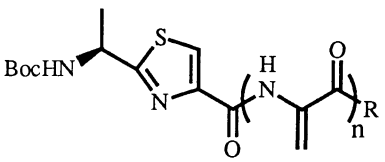
G: R=  **J:** R= 

Fig. 1.

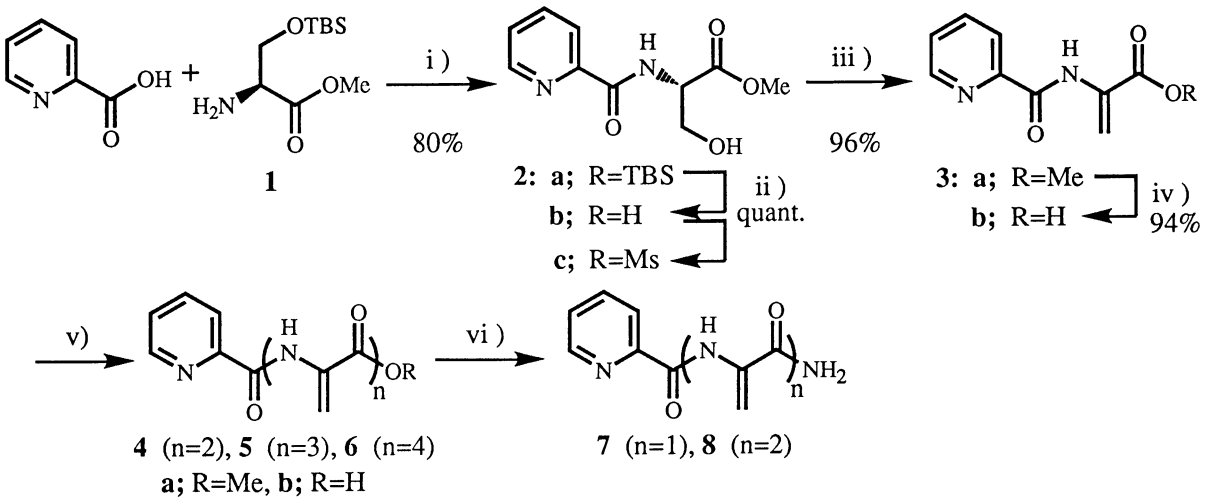


a; R=OH, **b;** R=NH_2
n=1, 2, 3, 4



a; R=OH, **b;** R=NH_2
n=1, 2

Fig. 2.



i) H-Ser(TBS)-OMe (**1**), DCC, HOBt, DMF, r.t., 6 h, ii) 70% AcOH, r.t., 12 h, iii) (a) MsCl, Et_3N, CH_2Cl_2, 35 °C, 15 min (b) Sonication, Et_3N, CH_2Cl_2, 35 °C, 15 min, iv) 1M LiOH, H_2O / dioxane, 0 °C, 15 min, v) Repeated twice, three, and four times the coupling of **3b**, **4b**, and **5b** with **1** and β-elimination, vi) (a) DCC, HOSu, THF, 0 °C, 30 min (b) NH_4OH, 0 °C, 10 min.

Scheme 1.

In this paper, we demonstrate a useful synthetic method for various oligodehydroalanines and their amides coupled with the carbonyl groups of picolinic acid (Pic-OH) and (*S*)-2-(1-*t*-butoxycarbonylamino)ethylthiazole-4-carboxylic acid, as shown in Fig. 2.

First, the coupling of Pic-OH with Ser derivatives and subsequent base-catalyzed β-elimination were examined exclusively. That is, H-Ser(TBS)-OMe (**1**), derived by the *O*-protection of H-Ser-OMe with *t*-butyldimethylsilyl chloride (TBSCl), was found to readily couple with Pic-OH in DMF in the presence of 1-hydroxybenzotriazole (HOBt) by the dicyclohexylcarbodiimide (DCC) method to give Pic-Ser(TBS)-OMe (**2a**) in 80% yield, whereas, in the similar case with H-Ser-OMe, the yield was less than 20%. After removal of TBS group with 70% AcOH, the mesylation of the obtained Pic-Ser-OMe (**2b**) with methanesulfonyl chloride (MsCl) in the presence of Et_3N yielded Pic-Ser(Ms)-OMe (**2c**) as the intermediate, which was then subjected to the β-elimination with Et_3N under sonication. As a result, the effective β-elimination of mesyloxy group of

Table 1. The yields and ^1H NMR data of **3-8**

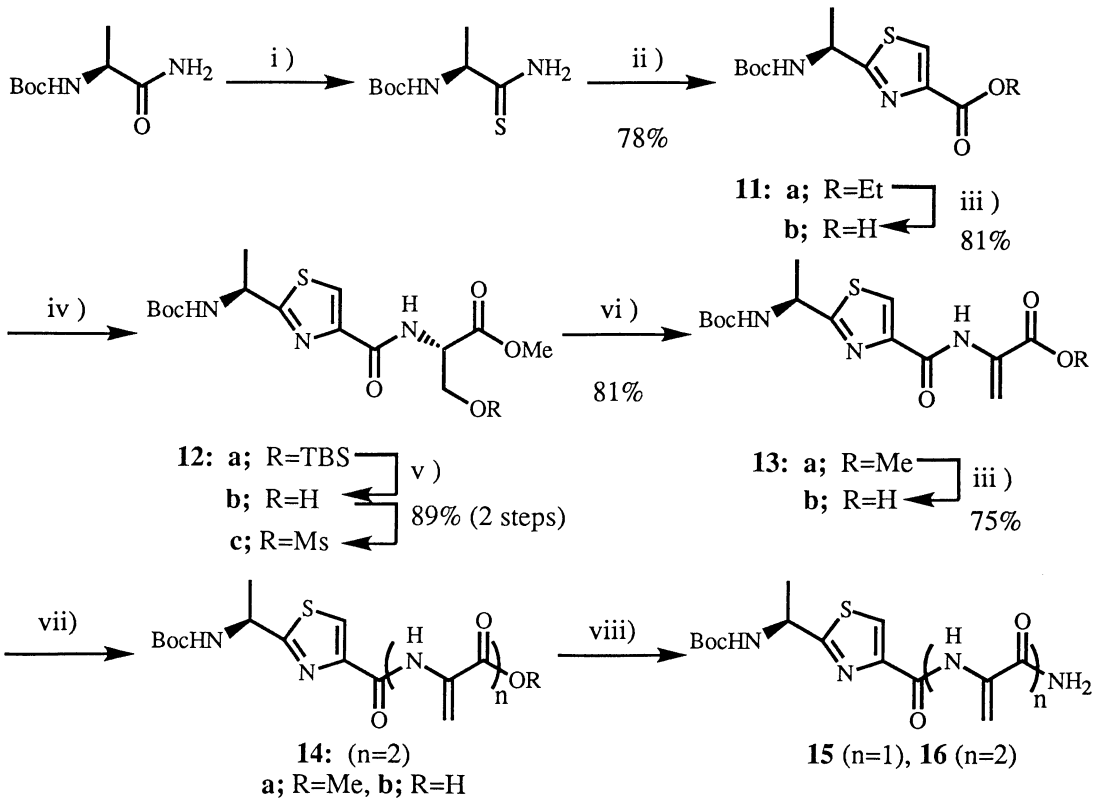
Compd No.	Yield / %	^1H NMR, δ[a] vinyl-H (J_{Hz})	Compd No.	Yield / %	^1H NMR, δ[a] vinyl-H (J_{Hz})
3a	96	6.02 d (1.8), 6.82 s	**6a**	71	5.33-5.58 m (3H), 6.03 s, 6.65 s, 6.66 d (2.0), 6.74 d (2.9), 6.82 d (2.0)
4a	90	5.48 s, 6.00 s, 6.72 s, 6.78 s			
5a	82	5.49 dd (0.7, 2.4), 5.56 dd (1.0, 2.0), 6.01 d (0.7), 6.64 s, 6.72 d (2.4), 6.89 d (2.0)	**7**	40	5.78 s, 6.57 s
			8	45	5.54 s (2H), 6.53 s (2H)

a) Measured in $CDCl_3$.

2c with Et_3N in CH_2Cl_2 proceeded very smoothly under weak basic conditions to give Pic-ΔAla-OMe (**3a**) in 96% yield without polymerization during the reaction and the purification. Subsequently, hydrolysis of ester **3a** with 1M-LiOH gave the corresponding free acid (**3b**). Thus, similar stepwise elongation of **3b** with **1**, followed by the consecutive deprotection, mesylation, and β-elimination repeatedly twice, three and four times gave Pic-di (**4b**; n=2)-, tri (**5b**; n=3)-, and tetradehydroalanines (**6b**; n=4) via the corresponding methyl esters (**4a**, **5a**, and **6a**), respectively. Furthermore, the amidation of **3b** with NH_4OH in the presence of 1-hydroxysuccinimide (HOSu) by the DCC method gave the corresponding Pic-ΔAla-NH_2 (**7**). The amidation of **4b** also gave the expected amide **8** (Scheme 1). The compounds **3-8** purely isolated were found to be very stable. The structures of the all products thus obtained were supported by the ^1H NMR spectral data and the satisfactory results of elemental analyses.

In the ^1H NMR spectra of the synthesized oligodehydroalanines (**3a**, **4a**, **5a**, and **6a**) and their amides (**7** and **8**), all of the signals of the two, four, six, and eight protons of the vinyl groups in the dehydroalanine residues appeared in the δ=5.48-6.89 region as singlet, doublet, and double doublet (J= 0.7-2.4 Hz), as summarized in Table 1.

On the other hand, the synthesis of ethyl (*S*)-2-(1-BocNH)ethylthiazole-4-carboxylate (**11**) as another



i) Lawesson's reagent, DME, r.t., 24h, ii) (a) $BrCH_2COCOOEt$, DME, 0 °C, 15 min (b) TFAA, pyridine, DME, 0 °C, 30 min, iii) 1M LiOH, H_2O / dioxane, r.t., 6 h, iv) **1**, DCC, HOBt, DMF, r.t., 6 h, v) 70 % AcOH, r.t., 12 h, vi) (a) MsCl, Et_3N, CH_2Cl_2, 35 °C, 15 min (b) Sonication, Et_3N, CH_2Cl_2, 35 °C, 15 min, vii) Repeated the coupling of **13b** with **1** and then β-elimination, viii) (a) DCC, HOSu, THF, 0 °C, 30 min (b) NH_4OH, 0 °C, 10 min.

Scheme 2.

substrate in the synthesis of its thiazole-4-carbonyl-oligodehydroalanines was examined, according to the method of Schmidt *et al.*[6] Namely, the thiocarbonylation of Boc-L-Ala-NH_2 with Lawesson's reagent gave the corresponding thioamide. Subsequent cyclization of the thioamide with ethyl bromopyruvate in dimethylethane (DME) in the presence of $KHCO_3$, followed by the oxidation with trifluoroacetic acid anhydride (TFAA) in the presence of pyridine gave (*S*)-**11a**.[7,8]

After ester hydrolysis with l M-LiOH, as in the case of **2a-c**, the obtained free acid [**11b:** Mp 128-129 °C. δ=8.32 (s, 1H, ring-H), 12.87 (br s, 1H, -COOH)] was coupled with **1** to give dipeptide (**12a**), which was successively deprotected [**12b:** Mp 142-143 °C. δ=2.90 (br s, 1H, -OH), 8.04 (s, 1H, ring-H)], mesylated (**12c**), and then the mesyloxy group was eliminated to give 2-(1-BocNH)ethylthiazole-4-carbonyl-ΔAla-OMe [**13a:** Mp 120-121 °C. δ=5.79 (d, 1H, vinyl-H, *J*=1.5 Hz), 6.57 (s, 1H, vinyl-H), 8.05 (s, 1H, ring-H)].

Furthermore, after ester hydrolysis with l M-LiOH, stepwise elongation of the obtained acid [**13b**, Mp 148-149 °C. δ=5.80 (s, 1H, vinyl-H), 6.50 (s, 1H, vinyl-H), 10.50 (br s, 1H, -COOH)] with **1** and then β-elimination were repeated to give 2-(1-BocNH)ethylthiazole-4-carbonyl-didehydroalanines **14a** [Mp 121-122 °C. δ= 5.41 (t, 1H, vinyl-H, *J*=2.0 Hz), 5.94 (d, 1H, vinyl-H, *J*=1.1 Hz), 6.62 (s, 1H, vinyl-H), 6.67 (d, 1H, vinyl-H, *J*=2.2 Hz)] and **14b** [Mp 183-184 °C. δ=5.79 (s, 1H, vinyl-H), 5.84 (s, 1H, vinyl-H), 6.00 (s, 1H, vinyl-H), 6.45 (s, 1H, vinyl-H), 8.32 (s, 1H, ring-H), 12.50 (br s, 1H, -COOH)] (Scheme 2). Finally, the amidations of both **13b** and **14b** with NH_4OH by the DCC method were similarly carried out to give the expected amides **15** (n=l)[9] and **16** (n=2)[9] in 44% and 38% yields, respectively.

In conclusion, it is noteworthy that the synthesis of stable oligodehydroalanine derivatives were first achieved, and this synthetic method is applicable to the synthesis of the other dehydropeptides containnig a dehydroamino acid residue.

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7) (*R*)-**11a**: Mp 89.5 °C. $[\alpha]_D^{20}$ 38.6° (c 0.67, CH_2Cl_2).[6]

8) (*S*)-**11a**: Mp 87-88 °C. $[\alpha]_D^{26}$ -43.2° (c 0.67, CH_2Cl_2). δ=1.40 (t, 3H, $-CH_2CH_3$, *J*=7.0Hz), 1.44 (s, 9H, Boc), 1.62 (d, 3H, $-CH_3$, *J*=6.8 Hz), 4.42 (q, 2H, $-CH_2CH_3$, *J*=7.0 Hz), 4.90-5.35 (m, 2H, NH and α-H), 8.08 (s, 1H, ring-H).

9) **15:** Mp 138-139 °C. $[\alpha]_D^{26}$ -30.0° (c 0.14, MeOH). δ=1.45 (s, 9H, Boc), 1.53 (d, 3H, CH_3, *J*=7.0 Hz), 4.85-5.01 (m, 1H, α-H), 5.76 (s, 1H, vinyl-H), 6.51 (s, 1H, vinyl-H), 7.67 (br s, 1H, NH_2's NH), 7.89 (br d, 1H, Ala's NH *J*=7.9 Hz), 8.14 (br s, 1H, NH_2's NH), 8.34 (s, 1H, ring-H), 9.94 (br s, 1H, ΔAla's NH). **16:** Mp 159-160 °C. $[\alpha]_D^{26}$ -3.45° (c 0.29, MeOH). δ=1.43 (s, 9H, Boc), 1.53 (d, 3H, CH_3, *J*=7.0 Hz), 4.85-5.01 (m, 1H, α-H), 5.73 (s, 2H, vinyl-H), 6.05 (s, 1H, vinyl-H), 6.44 (s, 1H, vinyl-H), 7.52 (br s, 1H, NH_2's NH), 7.94 (br s, 1H, NH_2's NH), 8.10-7.75 (m, 1H, Ala's NH), 8.35 (s, 1H, ring-H), 9.45 (br s, 1H, ΔAla's NH), 9.89 (br s, 1H, ΔAla's NH).

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