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Practical Synthesis of Oxazoles Incorporated in α-Dehydroamino Acid and Dehydropeptide Structures

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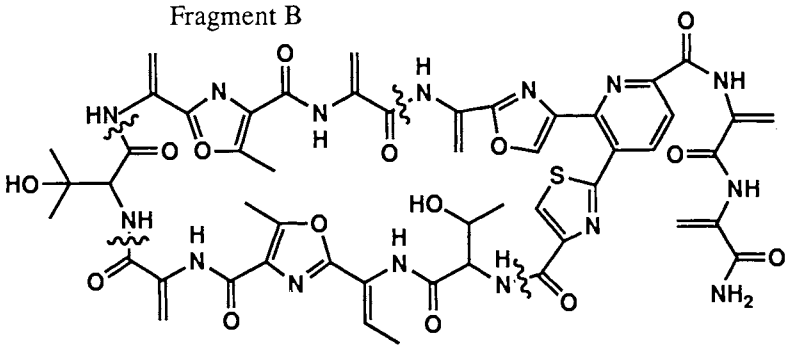
The practical syntheses of a few oxazole α-dehydroamino acids and their dehydrodi- and tripeptides, which are important moieties and segments of berninamycin A, macrocyclic peptide antibiotic, were first accomplished.

Antibiotic berninamycin A (**1**),[1,2] obtained from the culture of *Streptomyces bernensis*, is a macrocyclic peptide containing oxazole dehydropeptide segments composed of 2-(1-aminoalkenyl)-5-methyloxazole-4-carboxylic acid residue. The peptide (**1**) has unique substructures, [-L-Thr-(Z)-2-(1-aminopropenyl)-5-methyloxazole-4-carbonyl-ΔAla-] (Fragment A) and [-2-(1-aminoethenyl)-5-methyloxazole-4-carbonyl-ΔAla-] (Fragment B) (ΔAla=dehydroalanine residue) (Fig. 1). The interesting structure of **1** prompted us to study the synthesis of these fragments and their structure-bioactivity relationship. In addition, this synthetic study would contribute to the synthesis of other naturally occurring dehydropeptides containing dehydrothiazole-4-carboxylic acid moiety.[3]

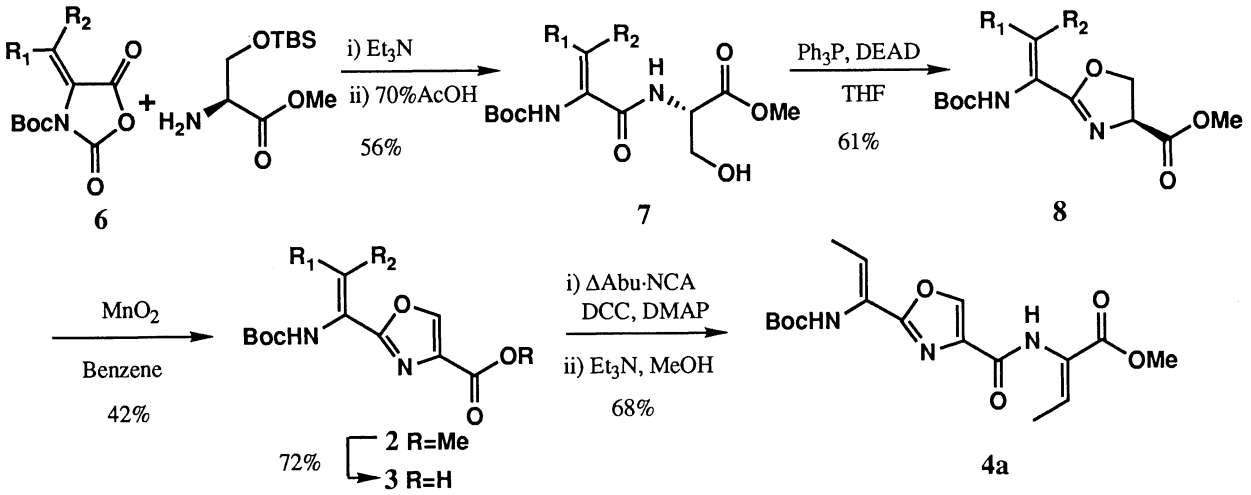


Berninamycin A (**1**)

Fig. 1.

Although the synthetic methods for 2-(1-aminoalkyl)oxazoline-[4,5] and oxazole-4-carboxylate derivatives[4] have been recently reported, there is no report on the syntheses of 2-(1-aminoalkenyl)-oxazole-4-carboxylic acid and its dehydropeptide derivatives. Here, we report the practical and general synthesis of t-butoxycarbonyl (Boc)-(Z)-2-(1-aminoalkenyl)-5-methyloxazole-4-carboxylates (**2**: R=Me, **3**: R=H), Boc-(Z)-2-(1-aminopropenyl)oxazole-4-carbonyl-ΔAbu-OMe (**4**), (ΔAbu=2-amino-2-butenoic acid residue), Boc-N,O-isopropylidene-L-Thr-(Z)-2-(1-aminopropenyl)-5-methyloxazole-4-carbonyl-ΔAA-OMe (**5**: **a**; ΔAA=ΔAbu, **b**; ΔAA=ΔAla).

In order to synthesize **2-4**, N-carboxy-α-dehydroamino acid anhydrides (**6a-d**) (ΔAA·NCA **6**: **a**; ΔAbu, **b**; ΔVal, **c**; ΔLeu, **d**; ΔPhe) were prepared by the cyclization of N-benzyloxycarbonyl-α-



a; R_1=CH_3, R_2=H, b; R_1=R_2=CH_3, c; R_1=$(CH_3)_2CH$, R_2=H, d; R_1=Ph, R_2=H

Scheme 1.

dehydroamino acid with $SOCl_2$.[6] The coupling reaction of **6** with H-Ser(TBS)-OMe (TBS=t-butyldimethylsilyl) in the presence of Et_3N, followed by the deprotection with 70% AcOH, gave Boc-ΔAA-Ser-OMe (**7a-d**).

According to the method of Galeotti et al,[4] the compounds **7a-d** were cyclized with Ph_3P and diethyl azodicarboxylate (DEAD) to give Boc-(Z)-2-(1-aminoalkenyl)oxazoline-4-carboxylic acid methyl ester (**8a-d**). Subsequent oxidation of the oxazoline ring was attempted by using NiO_2[5] or MnO_2.[7] In the case using NiO_2, the yield of **2a-d** was less than 25%, but in the case of MnO_2 the yield was 39-45% (Table 1).

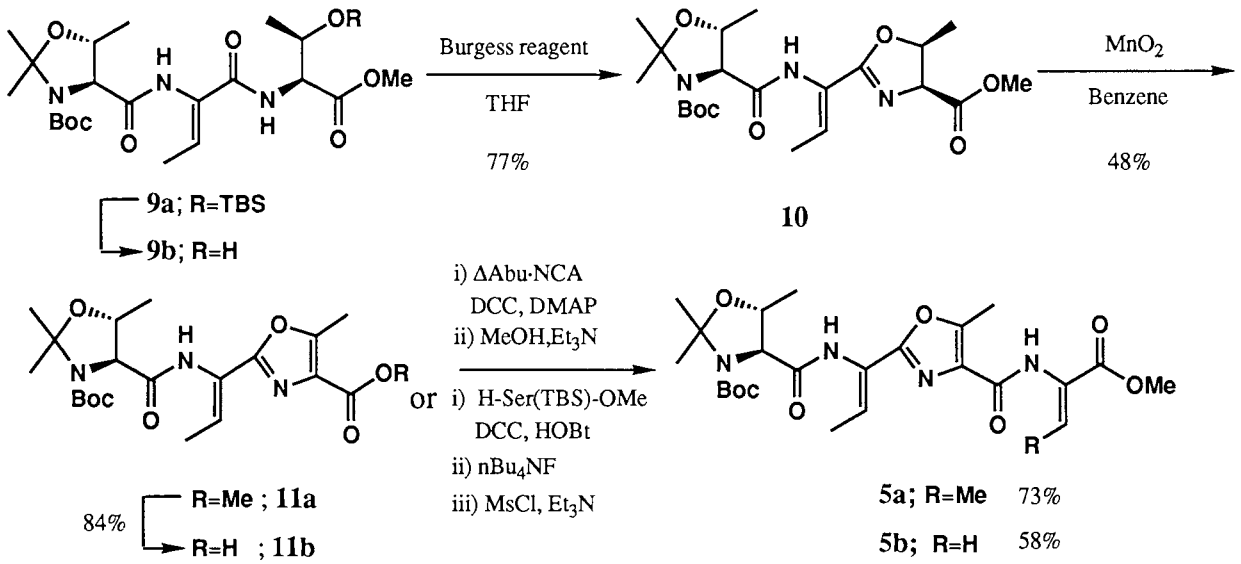
Hydrolysis of **2a** with 1M LiOH gave **3a** [yield 72%, mp 128-129 °C. ^{1}H NMR: δ=8.88 (br s, 1H, -COOH)], which was coupled with ΔAbu·NCA (**6a**) with DCC in the presence of 2,4-dimethylaminopyridine (DMAP) and then methanolysis gave the expected **4**[8] in 68% yield (Scheme 1).

Table 1. The Yields, Melting Points, and ^{1}H NMR Data of **2a-d**

Compd. No.	Yield / %[a]	Mp / °C[b]	^{1}H NMR, δ ($CDCl_3$)	
			Ring-H	-CH= (J/Hz)
2a	43	131-132	8.15 s	6.60q (7.3)
2b	39	86-87	8.18 s	———
2c	45	105-106	8.16 s	6.39d (10.1)
2d	41	195-196	8.15 s	7.63-6.93m (+Ph)

a) Obtained by using MnO_2.

b) Colorless needles from hexane-ethyl acetate.



Scheme 2.

The synthesis of Fragment A was achieved as shown in Scheme 2. The stepwise coupling reactions of **6a** with Boc-N,O-isopropylidene-Thr-OH and then H-Thr(TBS)-OMe in the presence of Et_3N was performed in one-pot to give the corresponding Thr-ΔAbu-Thr(TBS) derivative (**9a**),[9] whose TBS group was then deprotected with n-Bu_4NF to give the corresponding free alcohol (**9a**).[9] Subsequent cyclization of **9b** with the Burgess reagent [methyl N-(triethylammoniosulfonyl)carbamate],[10] in place of Ph_3P and DEAD proceeded smoothly to give the corresponding (Z)-2-(1-aminopropenyl)-5-methyloxazoline-4-carboxylic acid methyl ester (**10**).[11] The oxidation of the oxazoline ring of **10** with MnO_2, followed by the ester hydrolysis with 1M-LiOH, gave Boc-N,O-isopropylidene-Thr-(Z)-2-(1-aminopropenyl)-5-methyloxazole-4-carboxylic acid **11b**[12] via **11a**.[12] Finally, the coupling reaction of **11b** with **6a** and subsequent methanolysis gave **5a**.[13] Condensation of **11b** with H-Ser(TBS)-OMe, deprotection of TBS group, mesylation, and elimination with a base gave the Fragment A **5b**.[13]

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8) **4a**: Mp 229.0-229.5 °C. (Colorless needles). ^1H NMR ($CDCl_3$): δ=8.10 (s, 1H, ring-H), 6.95 (br s, 1H, NH), 6.86 (br s, 1H, NH), 6.60 (q, 1H, -CH=, J=7.03 Hz), 6.58 (q, 1H, -CH=, J=7.03 Hz), 3.89 (s, 3H), 1.92 (d, 3H, J=7.03 Hz), 1.88 (d, 3H, J=7.03 Hz), 1.45 (s, 9H), 0.86 (s, 9H), 0.05 (s, 6H).

9) **9a:** $[\alpha]_D^{25}$ 27.8° (c 0.9, MeOH). Colorless syrup. ^{1}H NMR ($CDCl_3$) : δ=7.67 (br s, 1H, NH), 6.72 (br d, 1H, NH, J=8.79 Hz), 6.45 (q, 1H, -CH=, J=7.3 Hz), 4.63-3.89 (m, 4H), 3.72 (s, 3H), 1.85 (d, 3H, J=7.3 Hz), 1.63 (s, 6H), 1.45 (d, 3H, J=9.23 Hz), 1.41 (s, 9H), 1.22 (d, 3H, J=6.15 Hz). **9b:** $[\alpha]_D^{25}$ 9.1° (c 0.34, MeOH). Mp 183-184 °C (Colorless needles). ^{1}H NMR ($CDCl_3$): δ=7.76(br s, 1H, NH), 7.20 (br d, 1H, NH, J=9.23 Hz), 6.92 (q, 1H, -CH=, J=7.08 Hz), 4.70-4.64 (m, 1H), 4.44-4.16 (m, 2H), 3.93 (d, 1H, J=8.13 Hz), 3.75 (s, 3H), 2.46 (br s, 1H, OH), 1.76 (d, 3H, J=7.08Hz), 1.61 (s, 6H), 1.47 (d, 3H, J=5.7 Hz), 1.45 (s, 9H), 1.25 (d, 3H, J=6.3 Hz).

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11) **10:** $[\alpha]_D^{25}$ 4.1° (c 1.68, MeOH). Colorless syrup. ^{1}H NMR ($CDCl_3$) : δ=7.55 (br s, NH, 1H), 6.55 (q, 1H, -CH=, J=7.08 Hz), 5.04-4.88 (m, 1H), 4.83 (d, 1H, J=9.80 Hz), 4.40-3.93 (m, 2H), 3.74 (s, 3H), 1.84 (d, 3H, J=7.33 Hz), 1.64 (s, 6H), 1.46 (d, 3H, J=5.86 Hz), 1.45(s, 9H), 1.32 (d, 3H, J=6.35 Hz).

12) **11a:** $[\alpha]_D^{25}$ -3.7° (c 0.47, MeOH). Colorless syrup. ^{1}H NMR ($CDCl_3$) : δ=7.56 (br s, 1H, NH), 6.70 (q, 1H, -CH=, J=7.33 Hz), 4.37-4.20 (m, 1H), 4.01 (d, 1H, J=7.8 Hz), 3.88 (s, 3H), 2.61 (s, 3H), 1.84 (d, 3H, J=7.33 Hz), 1.64 (s, 6H), 1.46 (d, 3H, J=6.35 Hz), 1.45 (s, 9H). **11b:** $[\alpha]_D^{25}$ -1.6° (c 0.51, MeOH). Mp 275-276 °C (Colorless prisms). ^{1}H NMR (DMSO-d_6) : δ=9.82 (br s, 1H, -COOH), 7.36 (br s, 1H, NH), 6.50 (q, 1H, -CH=, J=7.03 Hz), 4.40-3.98 (m, 2H), 2.63 (s, 3H), 1.89 (d, 3H, J=7.03 Hz), 1.62 (s, 6H), 1.56 (d, 3H, J=6.27 Hz), 1.44 (s, 9H).

13) **5a:** $[\alpha]_D^{25}$ -1.0° (c 0.60, MeOH). Mp 83-84 °C (Colorless needles). ^{1}H NMR ($CDCl_3$) : δ=8.15 (br s, 1H, NH), 7.53 (br s, 1H, NH), 6.92 (q, 1H, -CH=, J=7.25 Hz), 6.63 (q, 1H, -CH=, J=7.25 Hz), 4.37-4.04 (m, 1H), 3.95 (d, 1H, J=8.25 Hz), 3.77 (s, 3H), 2.63 (s, 3H), 1.92 (d, 3H, J=7.25 Hz), 1.87 (d, 3H, J=7.25 Hz), 1.66 (s, 6H), 1.52 (d, 3H, J=6.8 Hz), 1.45 (s, 9H). **5b:** $[\alpha]_D^{25}$ -38.4° (c 0.60, MeOH). Mp 189-190 °C (Colorless needles). ^{1}H NMR ($CDCl_3$) : δ=9.09 (br s, 1H, NH), 7.46 (br s, 1H, NH), 6.71 (q, 1H, -CH=, J=7.25 Hz), 6.65 (s, 1H, -CH=), 5.91 (d, 1H, -C=(H,H), J=1.31 Hz), 4.44-4.28 (m, 1H), 4.01 (d, 1H, J=7.91 Hz), 3.83 (s, 3H), 2.61 (s, 3H), 1.90 (d, 3H, J=7.25 Hz), 1.65 (s, 6H), 1.55 (d, 3H, J=6.15 Hz), 1.44 (s, 9H).

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