

Convenient Syntheses of Thiazoles Incorporated with
 α -Dehydroamino Acid and Dehydropeptide Structures

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The convenient syntheses of various thiazole α -dehydro-amino acids, thiazole valine ethyl ester, and their dehydrodi- and tripeptides, which are important moieties and segment of micrococcin P₁ and nosiheptide, macrocyclic peptide antibiotics, were first accomplished.

Micrococcin P₁ (1),¹⁾ obtained from the culture of *Bacillus pumilus*, is a macrocyclic peptide antibiotic containing poly-thiazole ring and thiazole dehydropeptide segments comprised of 2-(1-aminoalkyl)thiazole-4-carboxylic acid (Thz) residue. The similar Thz dehydropeptide segment is also present in an antibiotic nosiheptide.²⁾ Particularly, the peptide (1) has a characteristic skeleton [-L-Thr-(Z)-(Δ Abu)Thz-D-(Val)Thz-] (Δ Abu=2-amino-2-butenic acid residue), as shown in Fig. 1. The interesting structure and bioactivity of 1 prompted us to study the synthesis and relationship between the structure and the bioactivity. We here demonstrate the convenient syntheses of N, O-diprotected-Thr-(Δ Abu)Thz-OR (2: a; R=Et, b; R=H) and its dehydrotripeptide (4) coupled with H-D-(Val)Thz-OEt (3) as the C-terminal component.

At first, we studied in detail on the synthesis of N-benzyloxycarbonyl (Cbz)-(Δ Abu)Thz-OR (8a; R=Et, 9; R=H). The conversion of Cbz-(Z)- Δ Abu-NH₂ (6),³⁾ derived by the amidation of Cbz-(Z)- Δ Abu-OH (5)⁴⁾ with 28% NH₄OH in the presence of N-hydroxysuccinimide (HOSu) and dicyclohexylcarbodiimide (DCC),⁵⁾ with Lawesson's reagent gave the corresponding thioamide (7),⁶⁾ according to the method reported by Bredenkamp et al.⁷⁾ Subsequently, the

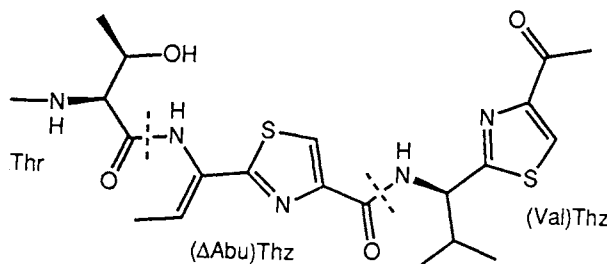
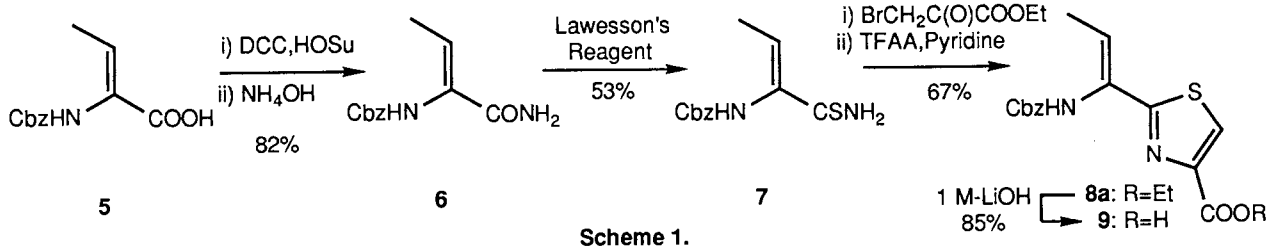


Fig. 1.



obtained **7** was cyclized with ethyl bromopyruvate in the presence of KHCO_3 in dimethoxyethane (DME) at room temperature (r. t.) for 10 min and then with $(\text{CF}_3\text{CO})_2\text{O}$ (TFAA)-pyridine under Ar gas at 0°C for 1 h to give Cbz-(ΔAbu)-Thz-OEt (**8a**). The hydrolysis of **8a** with 1 M-LiOH gave the corresponding acid **9**. In addition, various kinds of α -dehydroamino acids { ΔAA : **b**; ΔVal , **c**; ΔLeu , **d**; ΔPhe , **e**; $\Delta\text{Glu}(\text{OMe})$ } were similarly worked up to give the desired Cbz-(ΔAA)Thz-OEt (**8b-e**) in 58-91% yield, as summarized in Table 1.

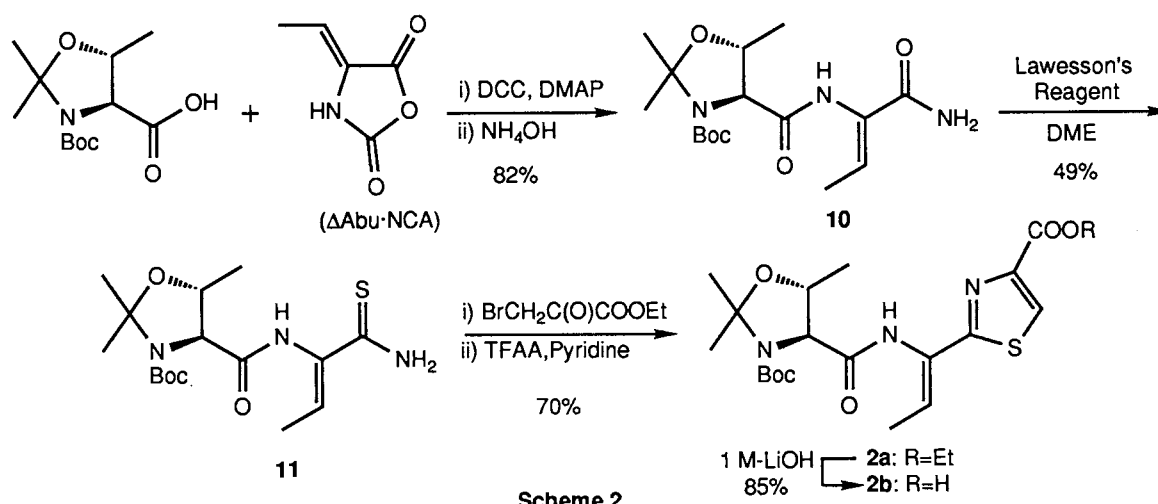
Table 1. The synthesis of Cbz-(ΔAA)Thz-OEt (**8**)

Compound No.	Yield/% ^{a)}	Mp / $^\circ\text{C}$ ^{b)}	^1H NMR, δ (CDCl_3)	
			ring-H	-CH= (J_{Hz})
8a	67	127-128	8.01s	6.55q (7.3)
9	85	204-205	8.33s	6.54q (7.0)
8b	70	111-112	8.06s	—
8c	91	88-89	8.01s	6.41d (9.9)
8d	85	101-100	8.06s	—
8e	58	115-116	8.06s	6.52d (7.0)

a) Calculated from the corresponding thioamide.

b) Colorless needles from ethyl acetate-hexane.

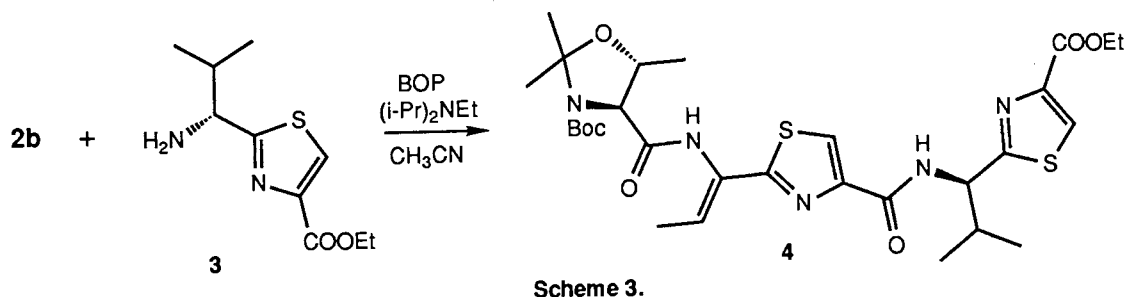
In order to further apply and generalize the above synthetic method, the similar consecutive treatments of N-protected dehydropeptide ester were also tried successfully. That is, to obtain the starting material for the synthesis of **1**, the useful one-pot coupling of N-carboxy 2-amino-2-butenic acid anhydride ($\Delta\text{Abu}\cdot\text{NCA}$), derived from **5** and SOCl_2 ,⁸⁾ with successive N-t-butoxycarbonyl (Boc)-N, O-isopropylidene-Thr-OH in the presence of DCC and dimethylaminopyridine (DMAP) in THF and 28% NH_4OH by the ΔNCA method⁹⁾ was achieved to give N, O-diprotected-Thr- $\Delta\text{Abu}\text{-NH}_2$ (**10**).¹⁰⁾ The similar conversion of **10** with Lawesson's reagent gave the corresponding thioamide (**11**),¹¹⁾ which was cyclized with ethyl bromopyruvate to give the expected **2a**.¹²⁾ Subsequent ester hydrolysis of **2a** with 1 M-LiOH gave **2b**¹²⁾ as the



C-component, according to Scheme 2.

Furthermore, the similar synthesis of Boc-D-(Val)Thz-OEt (**12**) was thoroughly examined, because the synthesis of **12** by this method has not been reported. Quite similarly as in the above cases, the successive amidation (76%), thioamidation (84%), and then thiazolization (73%) of Boc-D-Val-OH was carried out to give **12** [Mp 114-115 °C. $[\alpha]_D^{25}$ 39.28° (c 2.6, MeOH)],¹³ which was in accord with the compound synthesized by Shioiri's method.¹⁴ After N-deprotecting **12** with CF₃COOH by the usual method, the obtained **3** was utilized intact to the next condensation with **2b** as shown in Scheme 3.

Finally, the obtained thiazole-dehydrodipeptide **2b** (0.16 mmol) was coupled with **3** (0.16 mmol) in CH₃CN (10 ml) in the presence of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP) (0.16 mmol) and (i-Pr)₂NEt (0.40 mmol) at r. t. for 3 h to give the expected N-Boc-N,O-isopropylidene-L-Thr-(Z)-(ΔAbu)Thz-D-(Val)Thz-OEt (**4**)¹⁵ almost quantitatively.



References

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- 3) **6**: ¹H NMR (CDCl₃): δ 6.51 (q, 1H, J=7.3 Hz), 6.47 (bs, 1H, NH), 5.92

- (bs, 2H, NH₂), 5.15 (s, 2H).
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 - 6) **7**: ¹H NMR (CDCl₃): δ 7.56 (bs, 2H, NH₂), 6.78 (q, 1H, J=7.0 Hz), 6.46 (bs, 1H, NH), 5.16 (s, 2H).
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 - 10) **10**: [α]_D²⁵ -42.7° (c 1.08, MeOH). ¹H NMR (DMSO-d₆): δ 9.13 (bs, 1H, NH), 6.91 (bs, 2H, NH₂), 6.43 (q, 1H, J=7.3 Hz), 4.25-3.90 (m, 2H), 1.63 (d, 3H, J=7.3 Hz), 1.52 and 1.51 (s x 2, 6H), 1.39 (s, 9H), 1.33 (d, 3H, J=5.9 Hz).
 - 11) **11**: [α]_D²⁶ -41.5° (c 1.20, MeOH). ¹H NMR (C₆D₆ at 70 °C): δ 8.0-6.8 (m, 4H, NH₂, NH, CH=), 4.33 (dq, 1H, J=6.2 and 8.1 Hz), 3.69 (d, 1H, J=8.1 Hz), 1.66 and 1.60 (s x 2, 6H), 1.50 (d, 3H, J=7.7 Hz), 1.32 (s, 9H), 1.25 (d, 3H, J=6.2 Hz).
 - 12) **2a**: [α]_D²⁴ -9.5° (c 1.0, MeOH). ¹H NMR (CDCl₃): δ 8.04 (s, 1H, Thz-H), 7.84 (bs, 1H, J=7.3 Hz), 4.38 (q, 2H, J=7.0 Hz), 4.34 (dq, 1H, J=7.3 and 7.7 Hz), 4.01 (d, 1H, J=7.7 Hz), 1.89 (d, 3H, J=7.3 Hz), 1.67 (s, 6H), 1.45 (s, 9H), 1.45 (t, 3H, J=7.0 Hz), 1.35 (d, 3H, J=7.3 Hz). **2b**: [α]_D²⁵ -8.3° (c 0.75, MeOH). ¹H NMR (CDCl₃): δ 8.54 (bs, 1H, COOH), 8.11 (s, 1H, Thz-H), 8.00 (bs, 1H, NH), 6.57 (q, 1H, J=7.5 Hz), 4.38 (dq, 1H, J=6.4 and 7.5 Hz), 4.05 (d, 1H, J=7.5 Hz), 1.88 (d, 3H, J=7.0 Hz), 1.65 (s, 6H), 1.49 (d, 3H, J=6.4 Hz), 1.46 (s, 9H). Found: C, 53.46; H, 6.45; N, 9.60%. Calcd for C₁₉H₂₇N₃O₆S: C, 53.63; H, 6.40; N, 9.88%.
 - 13) **12**: ¹H NMR (CDCl₃): δ 8.07 (s, 1H, Thz-H), 5.30 (bd, 1H, NH), 4.89 (dd, 1H, J=5.3 and 8.8 Hz), 4.42 (q, 2H, J=8.8 Hz), 2.45 (m, 1H), 1.44 (s, 9H), 1.40 (t, 3H, J=7.0 Hz), 0.98 and 0.91 (d x 2, 6H, J=6.6 and 6.8 Hz).
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 - 15) **4**: [α]_D²⁵ -36.3° (c 0.84, MeOH). ¹H NMR (CDCl₃): δ 8.08 (s, 2H, Thz-H and NH), 8.03 (bd, 1H, NH), 8.02 (s, 1H, Thz-H), 6.61 (q, 1H, J=7.3 Hz), 5.33 (dd, 1H, J=6.6 and 9.0 Hz), 4.53-4.28 (m, 3H), 4.11 (d, 1H, J=7.3 Hz), 2.58 (m, 1H), 1.89 (d, 3H, J=7.3 Hz), 1.65 and 1.64 (s x 2, 6H), 1.47 (t, 3H, J=7.0 Hz), 1.43 (s, 9H), 1.35 (d, 3H, J=7.0 Hz), 1.03 and 1.00 (d x 2, 6H, J=6.6 and 6.8 Hz). Found: C, 55.09; H, 6.68; N, 10.77%. Calcd for C₂₉H₄₁N₅O₇S: C, 54.78; H, 6.50; N, 11.02%.

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