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

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The convenient syntheses of various thiazole α-dehydroamino acids, thiazole valine ethyl ester, and their dehydrodi- and tripeptides, which are important moieties and segment of micrococcin P_1 and noshiheptide, macrocyclic peptide antibiotics, were first accomplished.

Micrococcin P_1 (**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)-(ΔAbu)Thz-D-(Val)Thz-] (ΔAbu= 2-amino-2-butenoic acid residue), as shown in Fig. 1. The interesting structure and bioactivity of **1** prompted us to study the synthesis and correlationship between the structure and the bioactivity. We here demonstrate the convenient syntheses of N, O-diprotected-Thr-(ΔAbu)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.

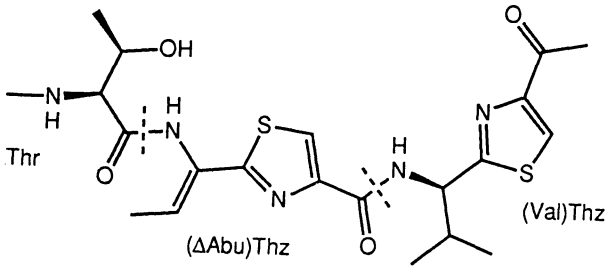
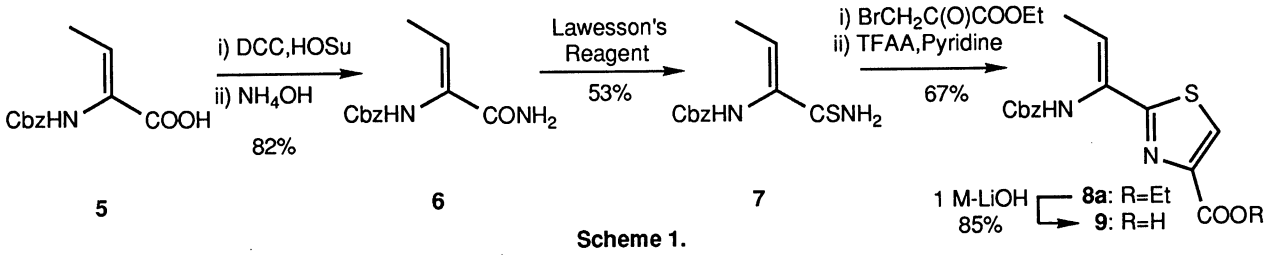


Fig. 1.

At first, we studied in detail on the synthesis of N-benzyloxycarbonyl (Cbz)-(ΔAbu)Thz-OR (**8a**; R=Et, **9**; R=H). The conversion of Cbz-(Z)-ΔAbu-NH_2 (**6**),[3] derived by the amidation of Cbz-(Z)-ΔAbu-OH (**5**)[4] with 28% NH_4OH 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



Scheme 1.

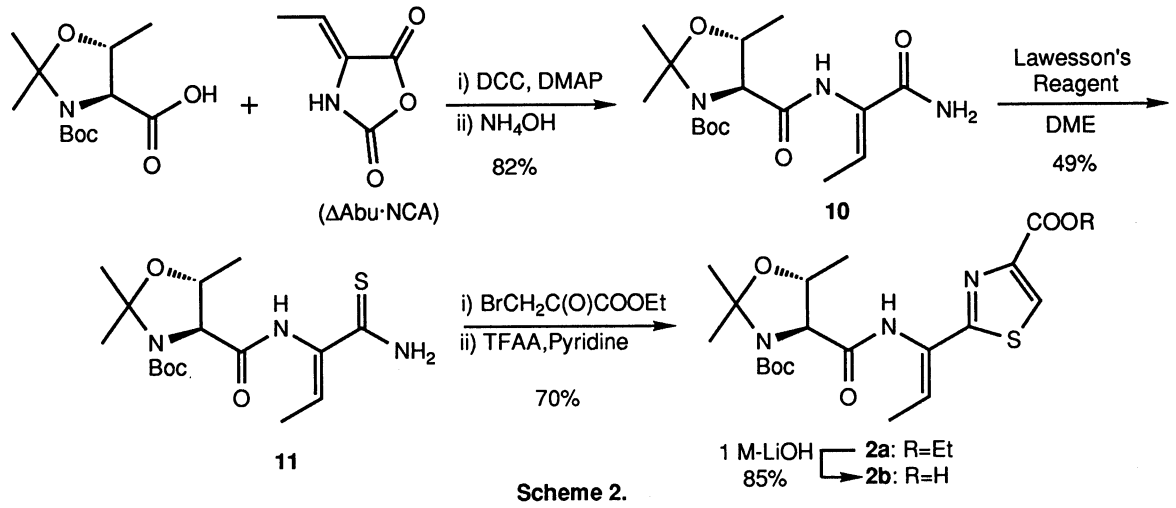
obtained **7** was cyclized with ethyl bromopyruvate in the presence of $KHCO_3$ in dimethoxyethane (DME) at room temperature (r. t.) for 10 min and then with $(CF_3CO)_2O$ (TFAA)-pyridine under Ar gas at 0 °C for 1 h to give Cbz-(ΔAbu)-Thz-OEt (**8a**). The hydrolysis of **8a** with 1 M-LiOH gave the corresponding acid **9**. In addition, various kinds of α-dehydroamino acids {ΔAA: **b**; ΔVal, **c**; ΔLeu, **d**; ΔPhe, **e**; ΔGlu(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 /°C[b]	^{1}H 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-butenoic acid anhydride (ΔAbu·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 method[9] was achieved to give N, O-diprotected-Thr-ΔAbu-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

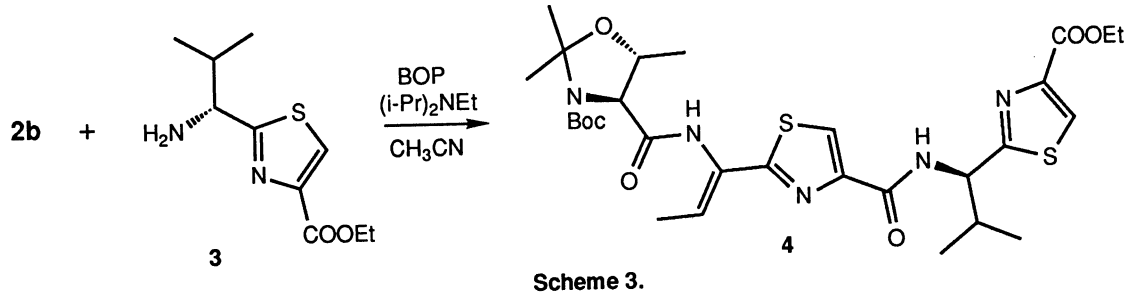


Scheme 2.

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 thiazolation (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 CF_3COOH by the usual method, the obtained **3** was utilized intact to the next condensation with **2b** as shown in Scheme 3.

Fianlly, the obtained thiazole-dehydrodipeptide **2b** (0.16 mmol) was coupled with **3** (0.16 mmol) in CH_3CN (10 ml) in the presence of benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophophate (BOP) (0.16 mmol) and $(i\text{-}Pr)_2NEt$ (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.



Scheme 3.

References

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2) C. Pascard, A. Ducruix, J. Lunel, and T. Prange, J. Am. Chem. Soc., **99**, 6418 (1977).
3) **6**: ^1H NMR ($CDCl_3$): δ 6.51 (q, 1H, J=7.3 Hz), 6.47 (bs, 1H, NH), 5.92

(bs, 2H, NH_2), 5.15 (s, 2H).

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6) **7**: ^{1}H NMR ($CDCl_3$): δ 7.56 (bs, 2H, NH_2), 6.78 (q, 1H, J=7.0 Hz), 6.46 (bs, 1H, NH), 5.16 (s, 2H).

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10) **10**: $[\alpha]_D^{25}$ -42.7° (c 1.08, MeOH). ^{1}H NMR (DMSO-d_6): δ 9.13 (bs, 1H, NH), 6.91 (bs, 2H, NH_2), 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**: $[\alpha]_D^{26}$ -41.5° (c 1.20, MeOH). ^{1}H NMR (C_6D_6 at 70 °C): δ 8.0-6.8 (m, 4H, NH_2, 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**: $[\alpha]_D^{24}$ -9.5° (c 1.0, MeOH). ^{1}H NMR ($CDCl_3$): 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**: $[\alpha]_D^{25}$-8.3° (c 0.75, MeOH). ^{1}H NMR ($CDCl_3$): 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 $C_{19}H_{27}N_3O_6S$: C, 53.63; H, 6.40; N, 9.88%.

13) **12**: ^{1}H NMR ($CDCl_3$): 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**: $[\alpha]_D^{25}$ -36.3° (c 0.84, MeOH). ^{1}H NMR ($CDCl_3$): 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 $C_{29}H_{41}N_5O_7S$: C, 54.78; H, 6.50; N, 11.02%.

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