

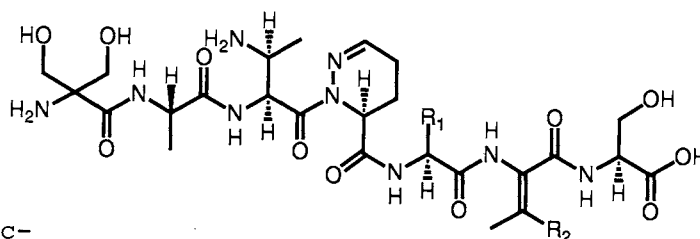
Facile Syntheses of (S,S)-2,3-Diaminobutyric Acid
and the Acid Containing N-Terminal Tripeptide of Antrimycins

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The stereoselective synthesis of (S,S)-2,3-diaminobutyric acid (Dab), which is one of the four uncommon α -amino acid residues of antrimycins (**1a**) and cirratiomycins (**1b**), was accomplished. Furthermore, N-terminal tripeptide segment of **1** containing Dab residue was also synthesized.

Antrimycins (**1a**)¹⁾ and cirratiomycins (**1b**),²⁾ produced by Streptomyces (St.) xanthocidicus MGL25-CF1 and St. cirratus 248-Sg2, respectively, are same dehydroheptapeptide consisted of a common N-terminal tetrapeptide and eight kinds of C-terminal tripeptide segments, as illustrated in Fig. 1. We already reported on the convenient synthesis of the eight kinds of C-terminal dehydrotripeptides³⁾ and, in the preceding paper,⁴⁾ the stereoselective syntheses of (3S)-2,3,4,5-tetrahydropyridazine-3-carboxylic acid (Pya) and the acid containing C-terminal dehydrotetrapeptide of **1**.

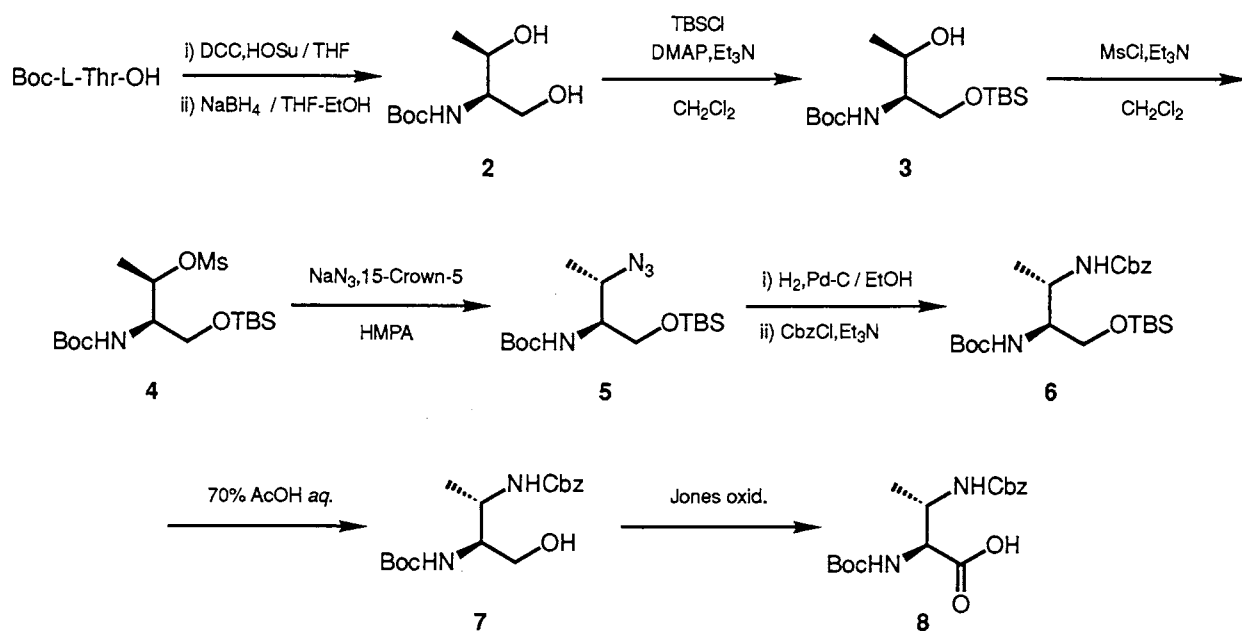


1a: Antrimycins $R_1 = \text{Me, Et, n-Pr, i-Bu}, R_2 = \text{Me, Et}$
1b: Cirratiomycins $R_1 = \text{Me, i-Bu}, R_2 = \text{Et}$

Fig. 1.

We wish to report the convenient syntheses of (S,S)-2,3-diaminobutyric acid (Dab) and the N-terminal tripeptide containing Dab at the C-terminus of **1**. Although the synthesis of the Dab derivative, which is also an important residue of lavandomycin, antrimycin-like linear dehydrohexapeptide,⁵⁾ has been recently reported by Schmidt et al.,⁶⁾ here, a similar synthetic route from L-threonine (Thr) was widely and variously modified.

Consecutive esterification of t-butoxycarbonyl (Boc)-Thr-OH with N-hydroxysuccinimide (HOSu) in THF at 0 °C for 1 h and at room temperature for 5 h by the dicyclohexylcarbodiimide (DCC) method and reduction intact with NaBH_4 under cooling for 30 min gave the corresponding 2-(N-Boc)amino-1,3-diol (**2**). After selective protection of the primary OH group of **2** by



treatment with *t*-butyldimethylchlorosilane (TBSCl) in the presence of 4-dimethylaminopyridine (DMAP) and Et_3N in CH_2Cl_2 at room temperature for 6 h, the secondary OH group of the obtained TBS ether (3) was further treated with MeSO_2Cl (MsCl) in the presence of Et_3N in CH_2Cl_2 under cooling for 30 min and then at room temperature for 4 h to give the expected 3-mesyloxy-1-TBS ether (4). Subsequent Walden's inversion of 4 with NaN_3 in the presence of 15-crown-5 in hexamethylphosphoric triamide (HMPA) at 55 °C for 3 h gave the corresponding 3-azide ether (5). Furthermore, catalytic hydrogenolysis of 5 with 10% Pd/C in EtOH at room temperature for 2 h was performed, followed by the acylation with benzyloxycarbonyl chloride (CbzCl) in the presence of Et_3N , giving 2,3-diamino ether (6). Finally, deprotection of TBS group of 6 by treatment with 70% AcOH aqueous solution gave the corresponding 2,3-diamino alcohol (7), which was then oxidated with Jones reagent in acetone at 0 °C for 1 h to give the expected α,β -diprotected-Dab (8) by nine steps from threonine, according to Scheme 1.

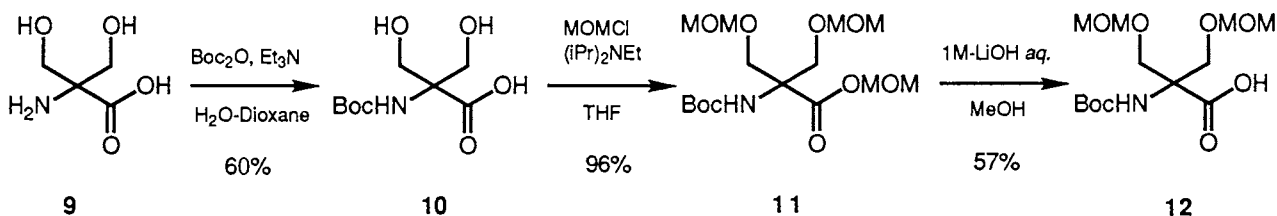
The yields and specific rotations of the all compounds (2-7 and 8), thus obtained, are summarized in Table 1. It can be seen that the yields of the all products are very high and reach ca. 84%. Moreover, the structures of the newly obtained compounds could be determined by the spectroscopical (IR, NMR, $[\alpha]_D$) and satisfactory elemental analyses.

On the other hand, hydroxymethyl serine (HMSer: 9),⁷⁾ which is also an important N-terminal residue of 1, was protected with Boc group using $(\text{Boc})_2\text{O}$ in the presence of Et_3N in H_2O -dioxane at room temperature for 4 h to give 2-(N-Boc)amino-HMSer (10), which was further protected with MOM

Table 1. The yields and specific rotations of 2-7 and 8

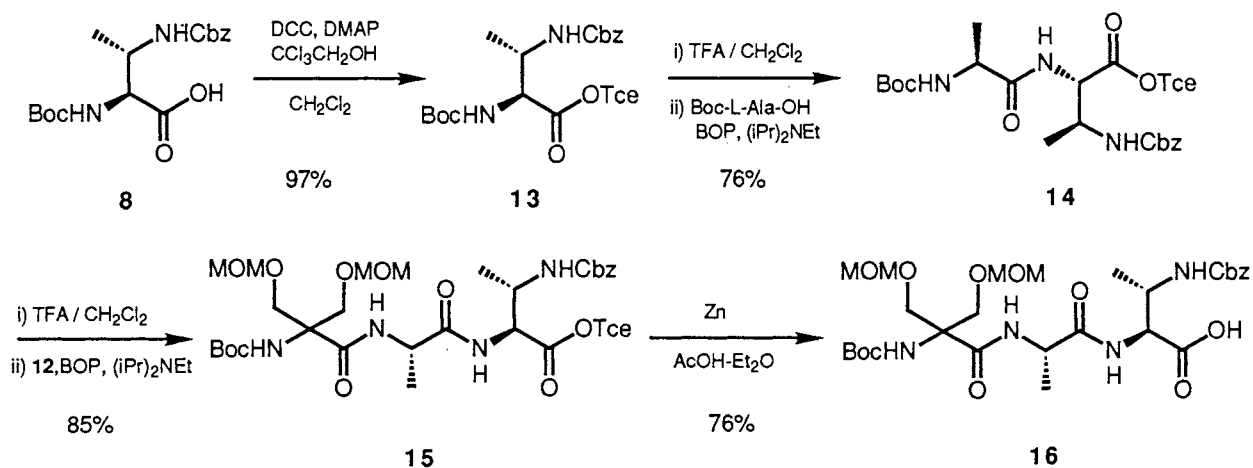
| Compound No. | Yield % | $[\alpha]_D^{25}/^\circ$ (in MeOH) |
|--------------|---------|---------------------------------------|
| 2 | 96 | 1.6 (c 1.22) |
| 3 | 71 | -16.4 (c 1.48) |
| 4 | 88 | -2.0 (c 1.23) |
| 5 | 87 | 13.6 (c 0.75) |
| 6 | 81 | -17.1 (c 1.31) |
| 7 | 90 | -9.8 (c 0.90) |
| 8 | 75 | -27.4 (c 1.04) |

group by treatment with chloromethylmethyl ether (MOMCl) in the presence of diisopropylethylamine [(i-Pr)₂NEt] in THF at room temperature overnight to afford the corresponding HMSer (MOM)₂ ester (11). Selective ester hydrolysis was performed using 1 M-LiOH in MeOH at room temperature for 6 h to give the expected α -free acid (12) (Scheme 2), which was then subjected to the following stepwise condensations.



Scheme 2.

According to Scheme 3, in order to elongate stepwisely the N-terminus of Dab (8), the compound 8 was treated with trichloroethanol (TceOH) in the presence of DMAP in CH₂Cl₂ by the DCC method to give Dab Tce ester {13: $[\alpha]_D^{25}$ -29.8° (c 0.96 in MeOH)}. Subsequently, successive deprotection of Boc group in 13 with CF₃COOH (TFA) in CH₂Cl₂ at room temperature for 40 min and coupling with L-alanine (Boc-Ala-OH) in the presence of BOP⁸⁾ and (i-Pr)₂NEt for 4 h gave the expected dipeptide, Boc-Ala-Dab(Cbz)-OTce {14: $[\alpha]_D^{25}$ -42.0° (c 1.10 in MeOH)}. Finally, quite similarly in the case of 13, the coupling of 14 with 12 was worked up to give Boc-HMSer(MOM)₂-Ala-Dab(Cbz)-OTce {15: $[\alpha]_D^{25}$ -20.1° (c 1.26 in MeOH)}, which was soon hydrolyzed with Zn powder in a mixture of AcOH and diethyl ether at room temperature for 5 h to give Boc-HMSer(MOM)₂-Ala-Dab(Cbz)-OH {16: $[\alpha]_D^{25}$ -16.9°



Scheme 3.

(0.81 in MeOH)}.

In conclusion, the complete syntheses of the four uncommon α -amino acids (HMSer, Dab, Pya,⁴⁾ and eight kinds of α -dehydroamino acids⁴⁾ and two fragments, N-terminal tripeptide and C-terminal tetrapeptide,⁴⁾ of antrimycin containing the obtained four acids will be available for the total syntheses of all antrimycins in near future.

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