CHEMISTRY LETTERS, pp. 49-52, 1992.

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

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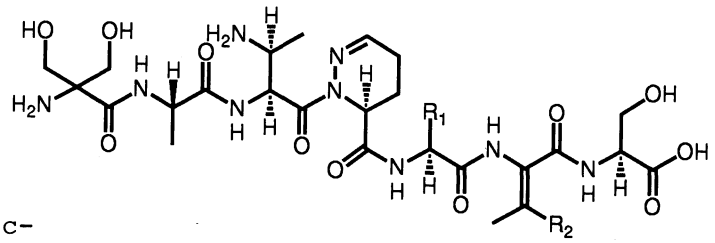
The stereoselective synthesis of (S,S)-2,3-diaminobutyric acid (Dab), which is one of the four uncommon α-amino acid residues of antrimycins (**1a**) and cirratiomycins (**1b**), was accomplished. Furthermore, N-terminal tripeptide segment of **1** containing Dab residue was also synthesized.

Antrimycins (**1a**)[1] and cirratiomycins (**1b**),[2] produced by Streptomyces (St.) xanthocidicus MG125-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 dehydrotripeptides[3] 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**.

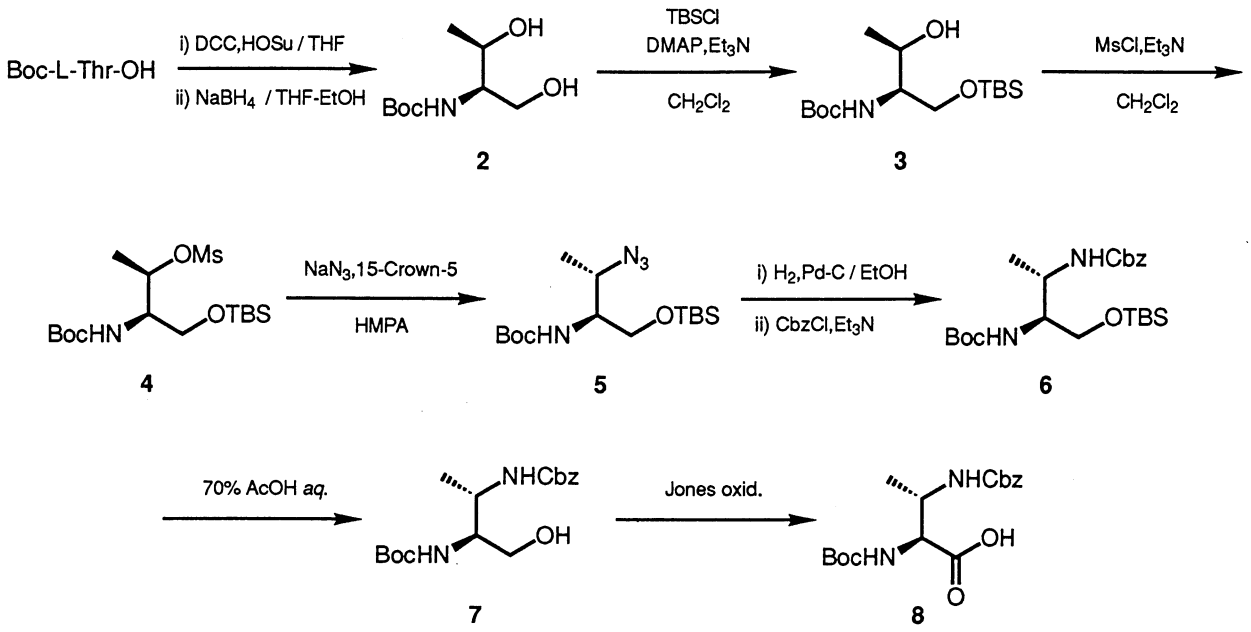


1a: Antrimycins R_1=Me, Et, n-Pr, i-Bu, R_2=Me, Et
1b: Cirratiomycins R_1=Me, i-Bu, R_2=Et

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 lavendomycin, 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



Scheme 1.

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**). Fyrthermore, 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.

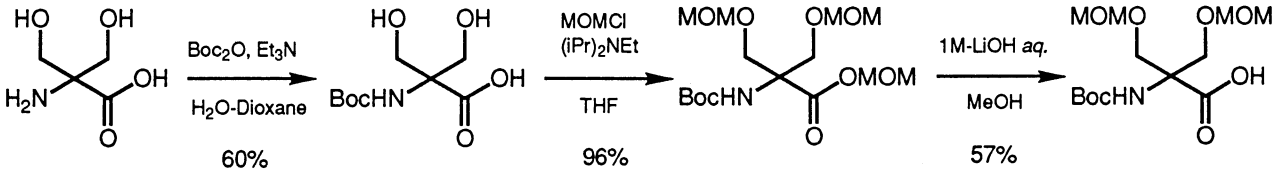
The yields and specific rotations of the all compounds (**2-7** and **8**), thus obtained, are summarized in Table 1. It can be seen that the yields of the all products are very high and reach ca. 84%. Moreover, the structures of the newly obtained compounds could be determined by the spectroscopical (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 $(Boc)_2O$ 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 %	$[\alpha]_D^{25}$/° (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)

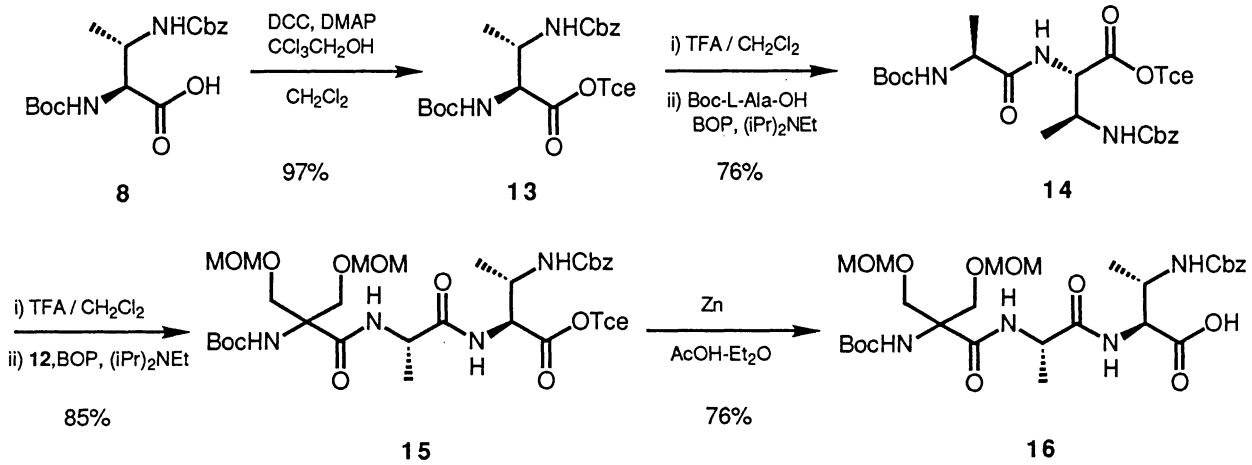
group by treatment with chloromethylmethyl ether (MOMCl) in the presence of diisopropylethylamine [$(i\text{-Pr})_2$NEt] in THF at room temperature overnight to afford the corresponding HMSer $(MOM)_2$ ester (**11**). Selective ester hydrolysis was performed using 1 M-LiOH in MeOH at room temperature for 6 h to give the expected α-free acid (**12**) (Scheme 2), which was then subjected to the following stepwise condensations.



9 **10** **11** **12**

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 CH_2Cl_2 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 CF_3COOH (TFA) in CH_2Cl_2 at room temperature for 40 min and coupling with L-alanine (Boc-Ala-OH) in the presence of BOP[8] and $(i\text{-Pr})_2$NEt 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 acids[4)] 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.

This research was financially supported by a Grant-in-Aid from the Ministry of Education, Science and Culture, to whom grateful acknowlegment is made.

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(Received October 18, 1991)