A NEW CONCISE APPROACH TO THE ENANTIOSELECTIVE SYNTHESIS OF THE HYDROXYAMINO ACID MOIETY OF AI-77-B

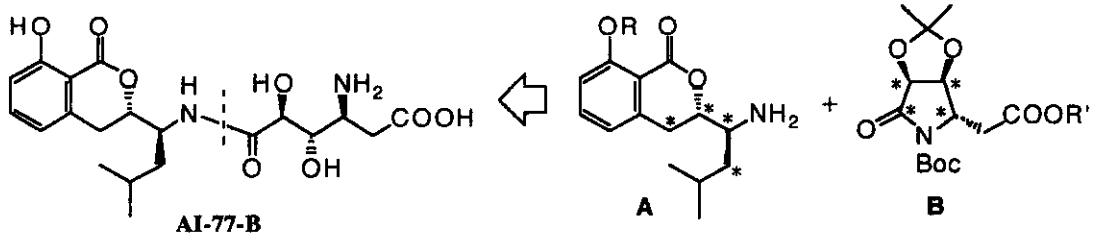
Hiyoshizo Kotsuki,* Mitsuhiro Iwasaki, and Masamitsu Ochi

Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Abstarct---The hydroxyamino acid moiety of AI-77-B has been prepared from D-ribose in an optically pure form via stereoselective alkylation of *N*-acylpyrrolidinium ion intermediates as the key step.

In the course of our synthetic efforts toward AI-77-B, a gastroprotective substance isolated from a culture broth of *Bacillus pumilus* AI-77,[1] we have recently disclosed an efficient entry to the amino-dihydroisocoumarin moiety **A** by using chiral triflate technology[2] and also a new powerful method for the final stage to condense **A** with *N*-Boc-lactams such as **B** by applying high pressure chemistry (Scheme 1).[3]

Scheme 1



Although there are several reports on the synthesis of AI-77-B including its fragments,[4-8] most of the works utilize naturally occurring amino acids as the chiral sources. Our strategy to the construction of **A** and **B** is based on an advantageous structure of D-ribose as an abundant starting material· asterisks indicate that the carbon atoms should be derived from D-ribose. In this paper we wish to describe a simple and enantioselective approach to the *N*-Boc-lactam **B**.

Scheme 2

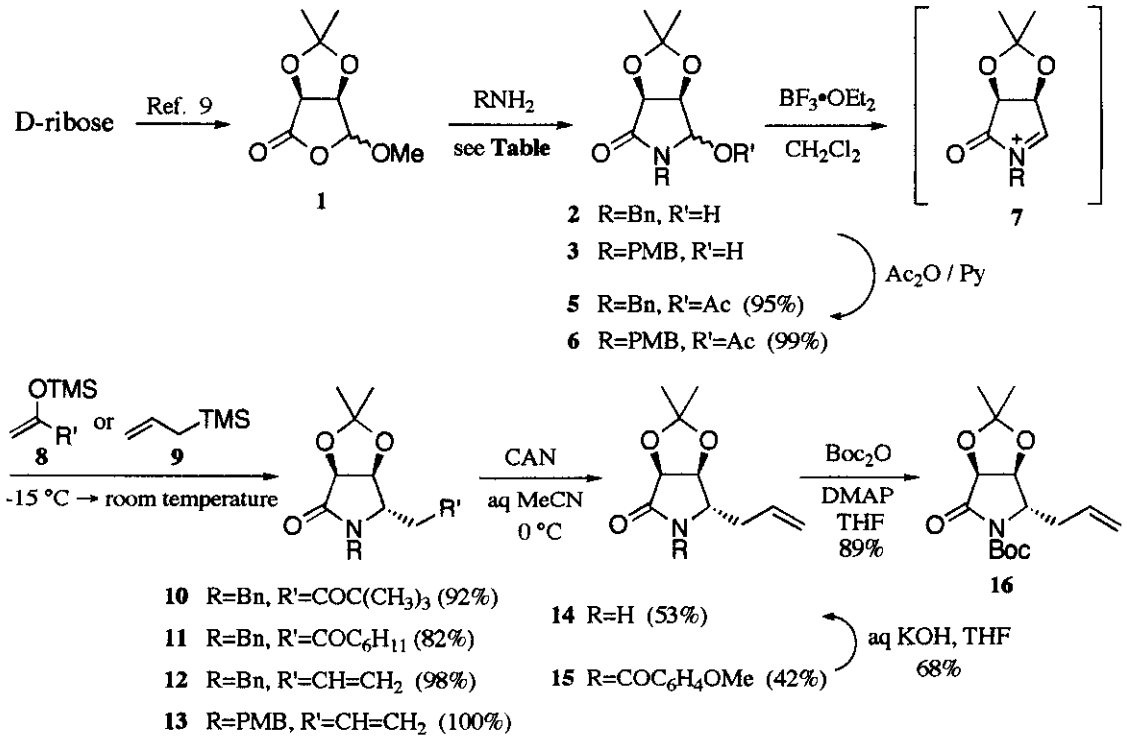
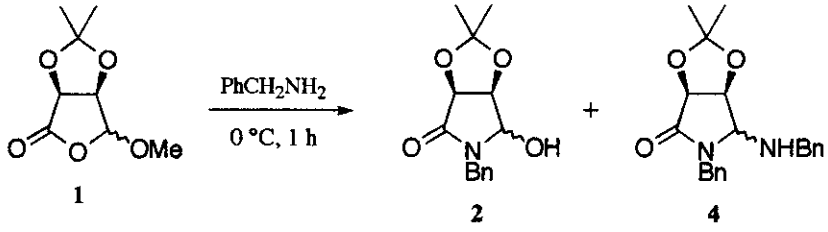


Table. Solvent effect on the formation of lactams from **1**



Solvent	Benzylamine (equiv.)[a)]	**2** . **4**	Total yield, %
MeCN	1 8	4 · 6	92
AcOEt	1.7	4 : 3	75
Et_2O	1.5	7 · 3	99
EtOH	1.0	>10 : 0	95

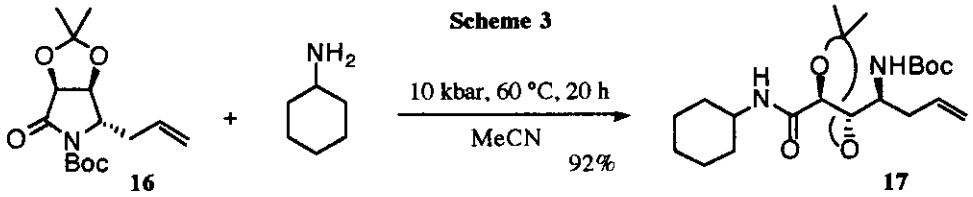
a) Benzylamine was added until all of the starting material was consumed.

Scheme 2 illustrates the synthesis of **16** as a synthon of the fragment **B**. The lactol (**1**), readily available from D-ribose according to the literature procedure,[9] was converted into lactams (**2**) and (**3**) by treatment with benzylamine or *p*-methoxybenzylamine. Interestingly, in this case, the product distribution was affected by the solvent used, as summarized in the Table. Thus, in ethanol the desired *N*-benzyl-lactam (**2**) was obtained exclusively. On the contrary, the use of the other solvent caused a significant side reaction giving aminal (**4**). The lactams (**2**) and (**3**) were converted into the corresponding acetates (**5**) and (**6**) to carry out the following alkylation.

The next stage of our plan for introducing an acetic acid unit onto the lactam ring was designed to exploit the intrinsic nature of **5** and **6** to form the *N*-acylpyrrolidinium ion intermediate (**7**) during Lewis acid-promoted alkylation.[10] In analogy to the literature method,[11] **10** and **11** were prepared from **5** by the action of **8** with BF_3-etherate[12] in a complete stereoselectivity. Unfortunately, however, all attempts to perform subsequent Baeyer-Villiger oxidation under a variety of conditions were unsuccessful. As a more concise route, we also examined the alkylation using ketene acetals such as CH_2=COTMS(OBu^t), but no detectable amounts of the desired adducts were obtained. Then we turned our attention to the use of allylsilane (**9**) under similar conditions, providing **12** and **13** in almost quantitative yields. The stereochemical course of this reaction was clearly confirmed by the nmr data, $J_{4,5} = 0$ Hz, indicating the reaction took place from the convex side.

Although deprotection of the benzyl group of **12** was not so easy, oxidative cleavage of the PMB group in **13** using ceric ammonium nitrate (CAN)[13] gave smoothly **14** together with the *N*-benzoyl derivative (**15**) which was further hydrolyzed to **13**. Finally, transformation of **14** to *N*-Boc-lactam (**16**) was proceeded cleanly under normal conditions. In order to realize the feasibility of our general procedure to convert *N*-Boc-lactams into ω-amino-carboxamides at high pressure,[3] **16** was subjected to aminolysis using cyclohexylamine (1 equiv.) at 10 kbar and 60 °C for 20 h to furnish **17** in 92% yield (Scheme 3).

Scheme 3



16 **17**

In conclusion, the hydroxyamino acid fragment (**16**) was assembled from **1** in 72% overall yield *via* 5-step sequence, in which D-ribose was employed as a convenient chiral source. Further synthetic studies on A1-77-B were now in progress in our laboratory.

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