SYNTHESIS OF ARPHAMENINE A AND *EPI*-ARPHAMENINE A

Sir:

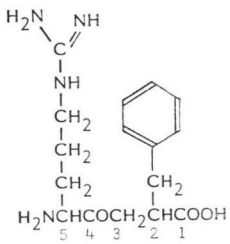
Arphamenine A (**1a**), produced from *Chromobacterium violaceum* BMG361-CF4 as an amino peptidase B inhibitor[1,2], is the first naturally occurring carba analog of peptide and *epi*-arphamenine A (**1b**) is the artifact arising from the epimerization at C-2.

Here we describe the synthesis of optically active arphamenine A (**1a**) and *epi*-arphamenine A (**1b**). Since in these compounds epimerization at C-2 should be inevitable, the C-1 ~ C-3 portion was synthesized by "malonic ester synthesis" which gave the diastereomers (**1a** and **1b**).

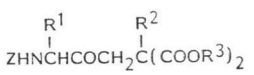
Bromomethylketone **3** [mp 137°C, $[\alpha]_{365}^{20}$ −25° (*c* 0.75, $CHCl_3$)] was prepared in 85% yield from the corresponding diazoketone **2**[3] by the reaction with 1.5 equivalents of HBr in ether. The sodium salt (1.2 equivalents) of a malonic tetrahydropyranyl (THP) ester **4**, which was prepared from the corresponding malonate[4] and NaH in a mixture of DMF and HMPA, was allowed to react with **3** at room temperature for 2 hours to give the crude diester derivative **5**. Removal of the THP group with 1.5 equivalents of 1 N HCl at room temperature for 2 hours, followed by decarboxylation in pyridine at 100°C for 15 minutes under argon afforded a mixture of the mono acids (**6a** and **6b**) in 78% yield (from **3**). The THP group was removed without decomposition and racemization of the arginine moiety. The mixture was chromatographed on a silica gel column with $CHCl_3$ - MeOH (50: 1) to yield two diastereomers, **6a** and **6b**, which showed Rf 0.24 and 0.15 on TLC in the same solvent system. **6a**: $[\alpha]_D^{25}$ +21° (*c* 0.6, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 5.01 (2H, s, CH_2Ph), 5.03 and 5.24 (2H in total, AB-q, J=12.5 Hz, CH_2Ph), 5.18 (2H, s, CH_2-Ph). **6b**: $[\alpha]_D^{25}$ +16° (*c* 0.4, $CHCl_3$); ^1H NMR (80 MHz, $CDCl_3$) δ 5.01, 5.08 and 5.18 (each 2H, s, CH_2Ph).

Catalytic hydrogenation of compound **6a** on Pd-black under 3 atm hydrogen, followed by chromatography on Sephadex LH-20 with 0.01 N HCl gave arphamenine A (**1a**) monohydrochloride [Rf 0.26 on TLC (phenol - water, 3: 1); $[\alpha]_D^{25}$ +23.5° (*c* 1.0, water)], while **6b** gave *epi*-arphamenine A (**1b**) monohydrochloride [Rf 0.17 on TLC in the same solvent system; $[\alpha]_D^{25}$ +19.0° (*c* 0.75, water)]. These synthetic compounds were in all respects identical with the natural products obtained by extraction from fermentation broths[1,2]. Epimerization at C-2 is inevitable, and in all these compounds obtained by synthesis or fermentation, the presence of a small amount of the other diastereomer was shown by thin-layer chromatography.

Recently, two procedures affording carba analogs of dipeptides through Grignard reaction[5,6] and a modified Dakin-West reaction[6,7] have been reported. We thought, however, that these procedures might present some difficulties in the synthesis of chemically labile arphamenines. Our procedure described above could be applied to the synthesis of a variety of peptide carba analogs with great simplicity, even in large scale production.



2 **3** **4**



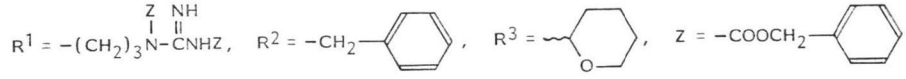
5

6a 2*R*,5*S*-Isomer

6b 2*S*,5*S*-Isomer

1a Arphamenine A (2*R*,5*S*-isomer)

1b *epi*-Arphamenine A (2*S*,5*S*-isomer)



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