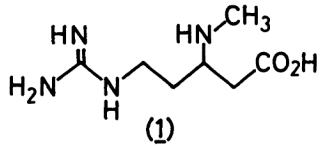
CHEMISTRY LETTERS, pp.589-590, 1978. Published by the Chemical Society of Japan

# SYNTHESIS OF $N^{\beta}$-METHYL-L-β-ARGININE, A COMPONENT AMINO ACID IN A NEW ANTIBIOTIC LL-BM547β

Shinya NOMOTO and Tetsuo SHIBA
Department of Chemistry, Faculty of Science, Osaka University, Toyonaka, Osaka 560

First synthetic method for preparation of N-methyl guanidino β-amino acid was established. Thus, $N^{\beta}$-methyl-L-β-arginine, a component of the antibiotic LL-BM547β, was synthesized from $N^{\gamma}$-*t*-butoxycarbonyl-$N^{\alpha}$-tosyl-L-α,γ-diaminobutyric acid through a successive reaction of $N^{\alpha}$-methylation of tosylamino group with diazomethane, the Arndt-Eistert synthesis, and guanidination of the ω-amino group. The synthetic product was identical with the natural amino acid with respect to a specific rotation and NMR spectrum.

The antituberculous peptides, viomycin,[1] capreomycins[2] and tuberactinomycins,[3] bear commonly L-β-lysine or γ-hydroxy-L-β-lysine as a branch attached to analogous cyclic pentapeptide moieties. Recently, $N^{\beta}$-methyl-L-β-arginine (1) as a new amino acid at the corresponding branch position was found by W. J. McGahren *et al.*[4] in the hydrolyzate of antibiotic LL-BM547β whose cyclic peptide moiety was the same as that of tuberactinomycin A and B (viomycin).[3] In this communication we wish to report a synthesis of this new guanidino amino acid (1).



(1)

In the synthetic procedure (Fig.1), N-methylation of tosylamino group must precede the Arndt-Eistert reaction, since a tosylamino group is reactive enough toward a mixed anhydride of an intermediate in the latter reaction. On the other hand, guanidination of ω-amino group should be carried out preferably after the Arndt-Eistert synthesis to avoid a possible lactam formation which actually occurred in the activation of carboxyl group in arginine.

After *t*-butoxycarbonylation of γ-amino group in $N^{\alpha}$-tosyl-L-α,γ-diaminobutyric acid (2),[5] selective $N^{\alpha}$-methylation of $N^{\alpha}$-tosyl-$N^{\gamma}$-*t*-butoxycarbonyl derivative 3 was performed by the use of diazomethane in ether at 0°C for 10 h to give an oily N-methylated product 4, pmr ($CDCl_3$): δ2.82 (s, 3H, $N^{\alpha}$-$CH_3$), 5.10 (br.t, 1H, γ-NH). This new procedure employing diazomethane for N-tosylamino acid provides a mild and simple method for preparation of N-monomethyl amino acid derivatives compared to the hitherto method with methyl iodide and alkali. Saponification of the ester group in 4 afforded a crystalline carboxylic acid 5 in 89% yield, mp 122-3°C. The Arndt-Eistert reaction for 5 was conducted as previously reported[6] to give an oily β-ornithine derivative 6, which was then saponified to afford a crystalline carboxylic acid 7, yield, 87%, mp 125-7°C.

In the next step of the synthesis, *t*-butoxycarbonyl group of 7 was selectively

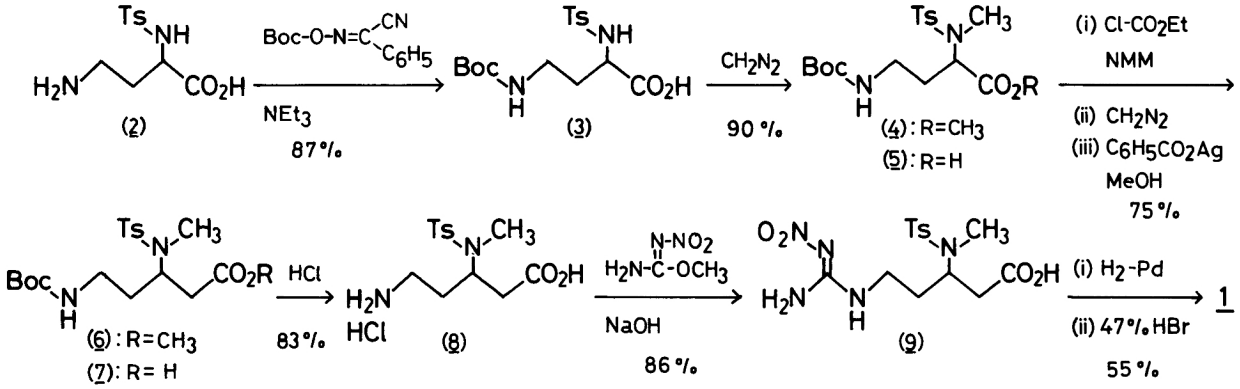



Fig. 1

Abbreviations ; Boc : t-butoxycarbonyl , Ts : tosyl , NMM : N-methylmorpholine.

removed with 4N HCl in THF, product (8) being precipitated from the reaction mixture, mp 209°C (dec). Compound 8 was then treated with O-methyl-N-nitroisourea in 2N NaOH at 0°C for 1 h to yield a crystalline $N^{\beta}$-methyl-β-arginine derivative 9, mp 222-3°C. Finally, the nitro group in 9 was removed by catalytic reduction in acetic acid and then the product, without being isolated, was heated under reflux in 47% HBr for 3 h to remove the tosyl group. The product was applied to a column (1.9 x 30 cm) of Amberlite IRC 120 ($H^+$ form) and eluted with 3N HCl to afford the expected amino acid dihydrochloride, being positive for both Sakaguchi and ninhydrin reactions, as an oily material as reported.[4] It showed a specific rotation [+18° ($H_2O$); lit.[4] +20° ±2 ($H_2O$)] and an NMR spectrum in good agreements with those of the natural $N^{\beta}$-methyl-L-β-arginine.[4] Furthermore, a crystalline diflavianate of the synthetic product was identified by elemental analysis, Found: C, 39.68; H, 3.41; N, 13.65; S, 7.88%. Calcd. for $C_7H_{16}N_4O_2 \cdot 2\ (C_{10}H_6N_2O_8S)$: C, 39.71; H, 3.46; N, 13.72; S, 7.85%.

This novel synthesis may offer an assured method for syntheses of other N-methyl guanidino amino acids such as blastidic acid[7] and stendomycidine[8] which are involved in biologically important natural products.

## References

1) T. Noda, T. Take, A. Nagata, T. Wakamiya, and T. Shiba, J. Antibiotics, 25, 427 (1972).
2) S. Nomoto, T. Teshima, T. Wakamiya, and T. Shiba, J. Antibiotics, 30, 955 (1977).
3) H. Yoshioka, T. Aoki, H. Goko, K. Nakatsu, T. Noda, H. Sakakibara, T. Take, A. Nagata, J. Abe, T. Wakamiya, T. Shiba, and T. Kaneko, Tetrahedron Lett., 1971, 2043.
4) W. J. McGahren, G. O. Morton, M. P. Kunstmann, and G. A. Ellestad, J. Org. Chem., 42, 1282 (1977).
5) J. Rudinger, K. Poduska, and M. Zaoral, Collect. Czech. Chem. Commun., 25, 2022 (1960).
6) T. Wakamiya, H. Uratani, T. Teshima, and T. Shiba, Bull. Chem. Soc. Jpn., 48, 2401 (1975).
7) N. Otake, S. Takeuchi, T. Endo, and H. Yonehara, Tetrahedron Lett., 1965, 1411.
8) M. Bodanszky, G. Marconi, and A. Bodanszky, J. Antibiotics, 22, 40 (1969).

(Received April 1, 1978)