CHEMISTRY LETTERS, pp. 697-700, 1987. 

# Total Synthesis of (-)-Anisomycin[1)]

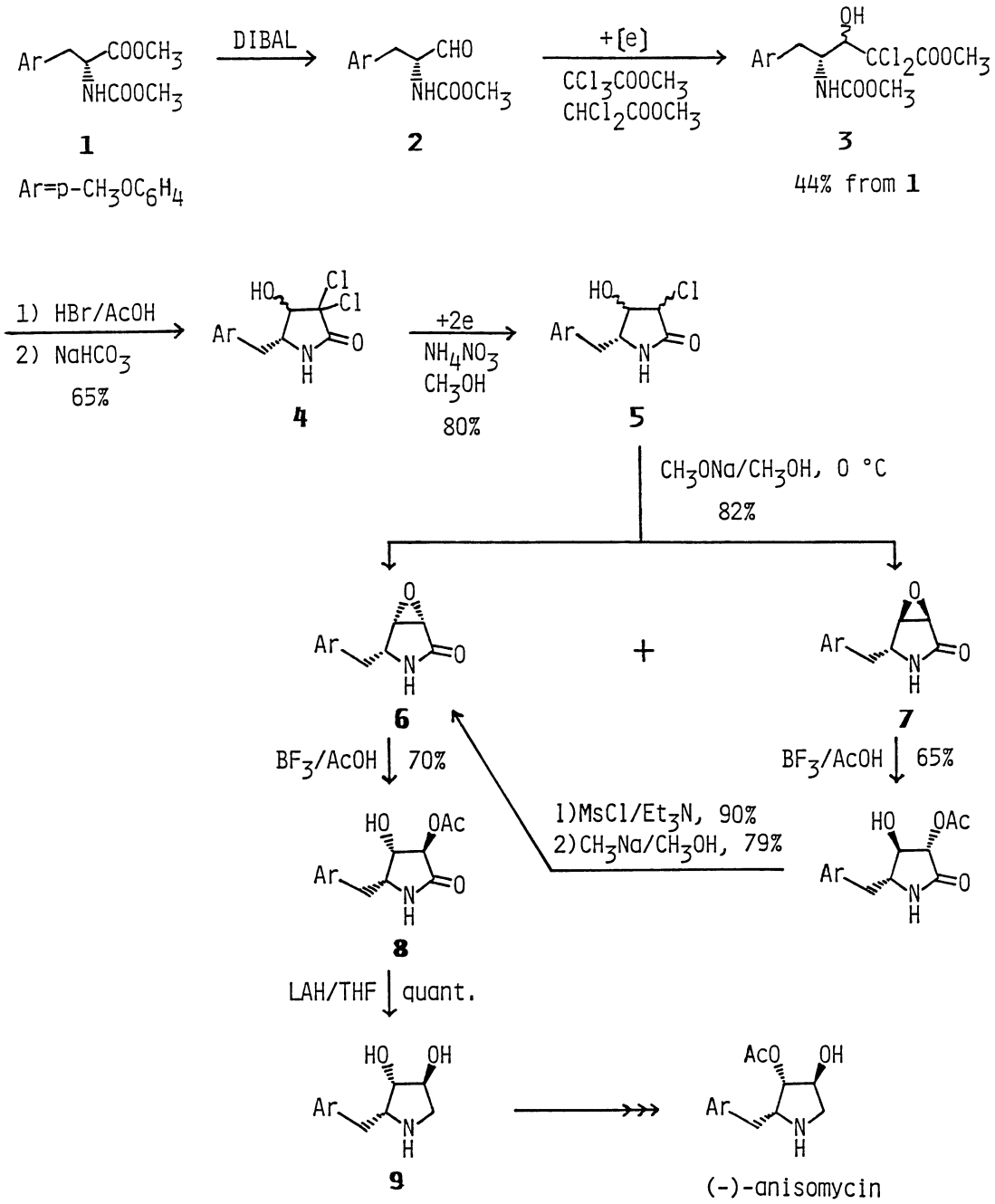
Tatsuya SHONO* and Naoki KISE
Department of Synthetic Chemistry, Faculty of Engineering,
Kyoto University, Yoshida, Sakyo, Kyoto 606

Antibiotic (-)-anisomycin was synthesized starting from D-tyrosine using the addition of electrogenerated dichloro-(methoxycarbonyl)methyl anion to aldehyde 2 as a key reaction.

The antibiotic anisomycin[2)] is a fermentation product of various *Streptmyces* species and possesses wide activity against pathogenic protozoa and fungi.[3)] Anisomycin and deacetylanisomycin are used as fungicides to eradicate bean mildew.[4)] The structure of anisomycin has been determined by X-ray investigation[5)] and the absolute configuration by chemical correlation.[6)] Although some methods for the total synthesis of (-)-anisomycin[7)] have already been studied,[9)] these methods required multistage and were not necessarily satisfactory. We wish to report herein the synthesis of (-)-anisomycin from D-tyrosine in which the addition of electrogenerated dichloro(methoxycarbony)-methyl (DMM) anion to an aldehyde is used as a key reaction (Scheme 1).[10)]

The optically active aldehyde 2[11)] was obtained by the reduction of protected D-tyrosine 1 with DIBAL.[12)] The addition reaction of the electrogenerated DMM anion to aldehyde 2 was carried out according to our method.[13,14)] The adduct 3 was hydrolysed with acid and then treated with sodium bicarbonate to give γ-lactam 4 as a mixture of *cis* and *trans* isomers. Selective reduction of 4 to monochloride 5 was accomplished by cathodic reduction.[15,16)] Treatment of the isomeric mixture of 5 with sodium methoxide at 0 °C afforded α,β-epoxy-γ-lactams 6[17)] and 7 in about 1:1 ratio. After separation of 6 and 7 by column chromatography on

silica gel, 7 could easily be converted to 6. Thus, treatment of 7 with catalytic amount of $BF_3$-HOAc in acetic acid followed by mesylation and treatment with




Scheme 1.

a base gave 6. *cis*-Epoxide 6 gave (-)-deacetylanisomycin 9[18] through treatment with $BF_3$-HOAc and LAH reduction of the resulting acetate 8.[20] Three methods have

already been reported for transformation of 9 to (-)-anisomycin.[8b,9a,b]

One of the authors (T.S.) wishes to thank the Ministry of Education, Science, and Culture, Japan, for the Grant-in-Aid for Scientific Research (B) (Grant No. 59470079).

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10) Satisfactory spectroscopic and elemental analyses were obtained for all products.

11) Since the aldehyde 2 was readily racemized, it was used without purification.

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14) The mixture of 2 (10 mmol), methyl trichloroacetate (10 mmol), and methyl dichloroacetate (20 mmol) was dissolved in DMF (60 ml) containing $Et_4NOTs$ (10 g) and electrochemically reduced by using a cell equipped with carbon rod electrodes and a ceramic diaphragm (0.1 A, 20 m*F*).

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16) The electroreduction of 4 (5 mmol) was carried out by using a Pt cathode and a carbon rod anode at 0 °C in 0.2 M $NH_4NO_3$/methanol (40 ml). The cathodic and anodic chambers were divided by a ceramic diaphragm and 3 *F*/mol of electricity was passed (0.2 A).

17) 6: mp 141-142 °C.

18) 9: mp 172-174 °C (lit.[19] 176-178 °C); $[\alpha]_D^{20}$ -20° (c 1.0, ethanol) (lit.[19] -20°); 400 MHz $^1H$ NMR ($CDCl_3$-$d_6$ DMSO) δ 2.64 (1H, dd, *J*=2.5, 12.2 Hz), 2.71 (1H, dd, *J*=7.2, 13.6 Hz), 2.86 (1H, dd, *J*=7.2, 13.6 Hz), 2.98 (3H, br s), 3.26 (1H, dt, *J*=3.4, 7.2 Hz), 3.38 (1H, dd, *J*=5.9, 12.2 Hz), 3.73 (1H, d, *J*=3.4 Hz), 3.78 (3H, s), 4.07 (1H, dd, *J*=2.5, 5.9 Hz), 6.80 (2H, d, *J*=8.7 Hz), 7.20 (2H, d, *J*=8.7 Hz).

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20) 8: mp 175-176 °C; $[\alpha]_D^{20}$ +6.2° (c 0.5, ethanol).

(Received January 31, 1987)