Tetrahedron Letters, Vol.32, No.8, pp 1067-1068, 1991
Printed in Great Britain

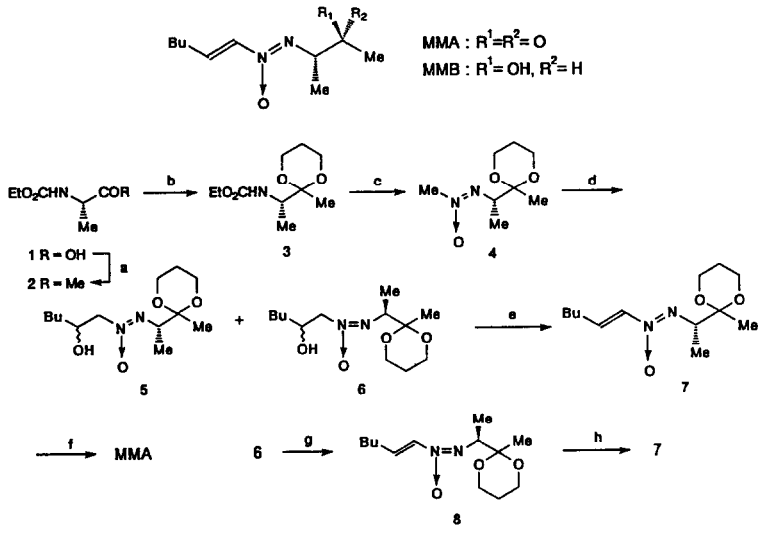
0040-4039/91 $3.00 + .00
Pergamon Press plc

SYNTHESIS OF NOVEL ANTIBIOTIC MANIWAMYCIN A

Yoshio Takahashi,* Hiroyuki Ishiwata, Takeo Deushi, Masahito Nakayama and Masami Shiratsuchi
Tokyo Research Laboratories, Kowa Company, Ltd., Noguchicho, Higashimurayama, Tokyo 189, Japan

Summary: Novel antifungal antibiotic maniwamycin A was synthesized in optically active form.

We have recently reported the isolation of novel antifungal antibiotics maniwamycins A (MMA) and B (MMB) from the culture broth of *Str. Prasinopilosus*.[1,2] Maniwamycins are characterized by the α,β-unsaturated azoxy group which have also been found in four antibiotics, elaiomycin,[3] LL-BH 872α,[4] valanimycin,[5] and jietacins.[6] It is quite interesting that only maniwamycins exhibit strong antifungal activity among these antibiotics bearing α,β-unsaturated azoxy group. As part of our studies aimed at development of more potent antifungal analogues, we have initiated synthesis of MMA. We herein describe the intriguing stereochemical behavior of lithiated azoxy group as well as synthesis of MMA in optically active form.



a) MeLi/THF, -78°C to r.t., 64%; b) 1,3-propanediol, PPTS, 4h, 95%; c) N_2O_4-$NaHCO_3$/ether, -30°C, 3.5h; *t*-BuOK/DMF, -30°C, 2.5h; then MeI/DMF, r.t., 15h, 38%; d) LDA/THF, 0°C, 20min; then BuCHO, 0°C, 30min, 50% for **5**, 26% for **6**; e) For **5** MsCl/Py; then DBU/toluene, r.t., 2h, 89%; f) $FeCl_3$-SiO_2/acetone, r.t., 1h, 49%; g) MsCl/Py; then DBU/toluene, 0°C, 10min, 77%; h) 1N HCl/THF, r.t., 20min, 93%.

The ketone **2** was prepared by methylation of **1** according to the Rapoport procedure.[7] Acetalization of **2** was best carried out with 1,3-propanediol-PPTS to afford **3** in 95% yield without significant racemization.[8] The azoxymethyl **4** was prepared in 38% overall yield of three steps by successive treatment of **3** with N_2O_4 in ether, *t*-BuOK in DMF, and then MeI. The *Z*-stereochemistry of **4** was supported by UV spectrum (217 nm max) of **4**.[9]

Coupling of **4** with pentanal was found to be quite intriguing in terms of *E* and *Z* geometry of the azoxy group of the products **5** and **6**. Thus, treatment of **4** with LDA in THF at 10°C for 20 min and then with pentanal at the same temperature for 30 min provided *Z*-**5** (UV 218 nm max) in 59% isolated yield as a major product in 1:1 mixture of two diastereomers and **6** (UV 233nm max) in 0.8% yield.[9d-f] On the other hand, reaction at -30°C provided *E*-**6** in 81% isolated yield as a major product in 1:1 mixture of two diastereomers and **5** in 3% yield. Dependence of the product distribution on temperature was also observed in the reaction at 0°C to provide **5** and **6** in 50 and 26% yields, respectively. Since no isomerization between **5** and **6** was observed under thermal (100°C in toluene), basic (**DBU**), and acidic conditions (1N HCl in THF at room temperature), deprotonation of **4** with LDA or stabilization of the resulting azoxy anion should be responsible for the temperature dependence of the product distribution.

The unsaturated azoxy compound **7** was prepared in 89% yield by successive treatment of **5** with MsCl in pyridine followed by DBU in toluene at room temperature. The *E*-geometry of **6** was retained under the elimination condition at 0°C for 10 min to provide 77% yield of *E*-**8** which was, however, easily isomerized to **7** by acidic treatment (1N HCl in THF) at room temperature in 93% yield.[10]

Final step to MMA was successfully conducted by treatment of **7** with $FeCl_3$-SiO_2 in acetone[11] at room temperature for 1 h to provide optically pure MMA ($[\alpha]_D^{22}$ -160°(*c* 1.0, $CHCl_3$); -144°($CHCl_3$)) in 49% yield.

Employing D-alanine as a starting material, (+)-MMA was also synthesized. Comparison of antifungal activity revealed that (-)-natural MMA was potent by the factor of eight more than (+)-unnatural MMA. Further studies toward more potent antifungal analogues are in progress by extending our synthetic strategies described in this letter.

References and Notes

1. M. Nakayama, Y. Takahashi, H. Itoh, K. Kamiya, M. Shiratsuchi and G. Otani, *J. Antibiotics*, **42**, 1535 (1989).
2. Y. Takahashi, M. Nakayama, I. Watanabe, T. Deushi, H. Ishiwata, M. Shiratsuchi and G. Otani, *J. Antibiotics*, **42**, 1541 (1989).
3. C. L. Stevens, B. T. Gillis, J. C. French and T. H. Haskell, *J. Am. Chem. Soc.*, **80**, 6088 (1958).
4. W. J. McGahren and M. P. Kunstmann, *J. Am. Chem. Soc.*, **91**, 2808 (1969).
5. M. Yamato, H. Iinuma, H. Naganawa, Y. Yamagishi, M. Hamada, T. Masuda, H. Umezawa, Y. Abe and M. Hori, *J. Antibiotics*, **39**, 184 (1986).
6. S. Omura, K. Otoguro, N. Imamura, H. Kuga, Y. Takahashi, R. Masuma, Y. Tanaka, H. Tanaka, S. Xue-hui and Y. En-tai, *J. Antibiotics*, **40**, 623 (1987).
7. C. G. Knudsen and H. Rapoport, *J. Org. Chem.*, **48**, 2260 (1983).
8. Chiral HPLC analysis indicated **3** as 99%ee. $[\alpha]_D^{22}$ -22.0° (*c* 1.0, $CHCl_3$) Some racemization took place at this step when *p*-TsOH was used as an acid catalyst.
9. (a) E. H. White, *J. Am. Chem. Soc.*, 77, 6008 (1955), (b) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966), (c) R. A. Moss and M. J. Landon, *Tetrahedron Lett.*, 3897 (1969), (d) R. A. Moss and G. M. Love, *Tetrahedron Lett.*, 4701 (1973). (e) R. A. Moss and M. Matsuo, *J. Am. Chem. Soc.*, **99**, 1643 (1977), (f) K. G. Taylor and T. Riehl, *J. Am. Chem. Soc.*, **94**, 250 (1972).
10. Under basic (DBU in toluene at room temperature for 15h in 40% yield) and thermal conditions (80°C in toluene for 1h in 93% yield), *E*-**8** was also isomerized to **7**.
11. K. S. Kim, Y. H. Song, B. H. Lee and C. S. Hahn, *J. Org. Chem.*, **51**, 404 (1986).

(Received in Japan 1 December 1990)