

TOTAL SYNTHESIS OF (\pm)-MAYSINE AND (\pm)-N-METHYLMAYSENINE

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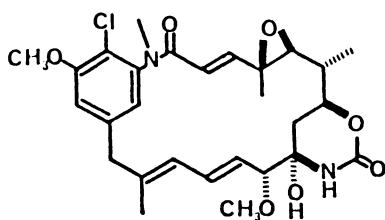
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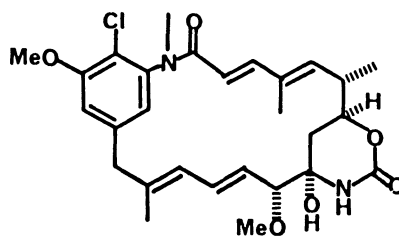
Maysine (1) and N-methylmaysenine (2), as congeners of the ansa-macrocyclic antitumor agent, maytansine, were synthesized from a common intermediate 3.

Ansa-macrocyclic lactams, maysine (1) and N-methylmaysenine (2), are congeners of anti-tumor agent, maytansine.¹ We herein report the first stereoselective synthesis² of 1 and a new total synthesis³ of 2 from a common synthetic intermediate (3), which was described in our separate paper on maytansinol.¹

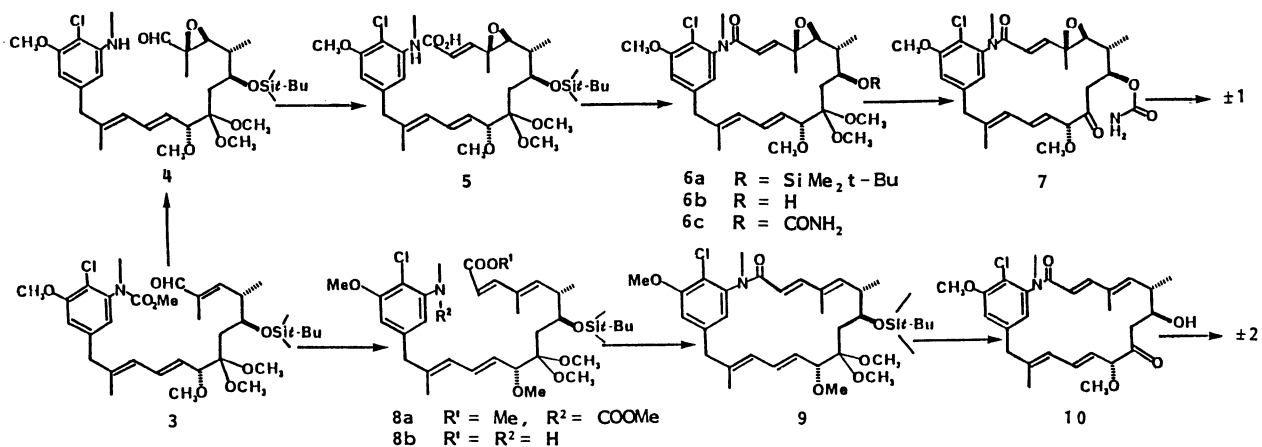
The intermediate 3 was stereoselectively epoxidized in three steps to 4,^{1,4} which was further treated with methyl diethylphosphonoacetate (2.5 equiv. at -78°C and then at rt for 12 hr) and with a mixture of 1N KOH-THF-EtOH (2:5:5 at rt for 17 hr) to provide the unsaturated acid 5 (85 %) [δ_{CDCl_3} 6.00 & 6.86, H-2 & 3, d, J= 16]. Cyclization on n-Bu₄N⁺ salt of 5 worked with 2-mesitylenesulfonyl chloride (25 equiv.) and diisopropylethylamine (25 equiv.) in benzene at 40°C to give 90% crude 6a [m/z 663 (M⁺)]. The silyl group was removed with n-Bu₄NF (5 equiv.) in a mixture of MeCN-THF (2:1) at 50°C for 20 hr to give 6b which was treated with p-nitrophenyl chloroformate (5 equiv.) and pyridine (5 equiv.) in dry CH₂Cl₂ at rt for 2 hr. Then, it was mixed with excess NH₃-MeOH⁵ at -78°C (the temp. being raised to rt in 1 hr) to provide the ketal urethane 6c (83 %). When 6c was treated with a mixture of AcOH-THF-H₂O (2:1:1 at 35°C for 2 hr), the dimethylketal group was hydrolyzed to provide the corresponding ketone 7, which was



Maysine (1)



N-Methylmaysenine (2)



detectable on silica gel tlc [Rf values of 6c = 0.65, 7 = 0.55 and 1 = 0.40 /EtOAc, respectively].⁶

Alkalization by addition of ammonia to the reaction mixture accomplished the formation of the hetero-
ring in 71% overall yield from the ketal 6c to produce 1² [δ 2.68(H-5, d, J=9.5 Hz)].

N-Methylmaysenine was also synthesized similarly from the intermediate 3 which was first treated with methyl diethylphosphonoacetate to give 8a (98%). Hydrolysis of 8a with 12N KOH (dioxane-MeOH 2-1) at 90°C for 12 hr provided the amino acid 8b in 66% yield. The lactam was formed under the same reaction condition as above case to give 9 [70% m/z 647 (M⁺)], and deprotection of 9 with camphorsulfonic acid in aq. MeOH afforded 10. The carbamate ring was formed with p-nitrophenyl chloroformate (10 equiv.) and pyridine (9 equiv.) in THF at rt for 10 min and then with NH₃-MeOH at 0°C for 30 min to afford 2 [δ 5.49(H-5, d, J= 11.0), 7.22(H-3, d, J= 15 Hz)]³ in 73% yield.

The racemic 1 and 2 were identical with authentic samples.⁷

References

1. Isobe M., Kitamura M., Goto T., J. Am. Chem. Soc., 104, 4997 (1982).
2. Meyers A.I., Comins D.L., Roland R.M., Henning R., Shimizu K., J. Am. Chem. Soc., 101, 7104 (1979).
3. a) Corey E.J., Weigel L.O., Chamberlin A.R., Lipschutz B., J. Am. Chem. Soc., 102, 1439 (1980); b) Meyers A.I., Roland D.M., Comins D.L., Henning R., Fleming M.P., Shimizu K., J. Am. Chem. Soc., 101, 4732 (1979).
4. Isobe M., Kitamura M., Mio S., Goto T., Tetrahedron Lett., 23, 221 (1982).
5. Letsinger R.L., Ogilvie K.K., J. Org. Chem., 32, 296 (1967).
6. Compound 6b was alternatively convertible to 1 via hydrolysis of the ketal followed by urethane formation in only poor yield (20%).

(Received September 6, 1982)