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TOTAL SYNTHESIS OF (±)-MAYSINE AND (±)-N-METHYLMAYSENINE

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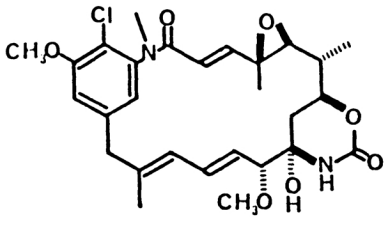
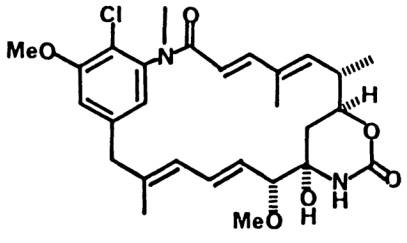
Maysine (1) and N-methylmaysenine (2), as congeners of the ansa-macrocyclic antitumor agent, maytansine, were synthesized from a common intermediate 3.

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

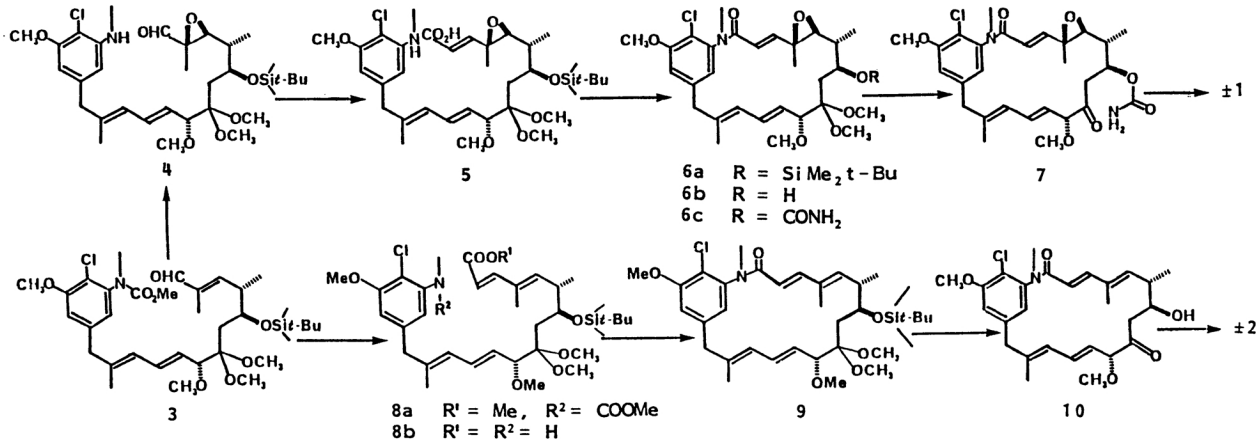
The intermediate 3 was stereoselectively epoxidized in three steps to 4,[1,4] which was further treated with methyl diethylphosphonoacetate (2.5 equiv. at -78°C and then at rt for 12 hr) and with a mixture of 1N KOH-THF-EtOH (2:5:5 at rt for 17 hr) to provide the unsaturated acid 5 (85 %)[δ_{CDCl_3} 6.00 & 6.86, H-2 & 3, d, J= 16]. Cyclization on n-Bu_4N^+ 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-Bu_4NF (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 CH_2Cl_2 at rt for 2 hr. Then, it was mixed with excess NH_3-MeOH[5] 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-H_2O (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 1[2] [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 NH_3-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

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6. Compound 6b was alternatively convertible to 1 via hydrolysis of the ketal followed by urethane formation in only poor yield (20%).

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