TOTAL SYNTHESIS OF (±)-TUBULOSINE AND (±)-DEOXYTUBULOSINE

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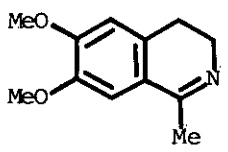
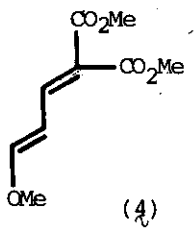
Total synthesis of (±)-tubulosine (1) and (±)-deoxytubulosine (2) by Pictet-Spengler reaction of (±)-4-oxoprotoemetine (6) with serotonin (7) or tryptamine (8) followed by reduction with sodium bis(2-methoxyethoxy)aluminium hydride in pyridine is described.

Tubulosine (1) and deoxytubulosine (2) were isolated as levorotatory forms from the same plant, Alangium lamarckii[1]. Tubulosine derivatives are expected to be potential antineoplastic agents.[2] Recently we had developed a short synthetic route of emetine via (±)-4-oxoprotoemetine (6) which was stereoselectively prepared by the condensation of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (3) and dimethyl 3-methoxyallylidenemalonate (4) to the enamide 5, followed by 5 steps in 60 % yield from 3.[3] Here we wish to report the stereoselective synthesis of (±)-tubulosine (1) and (±)-deoxytubulosine (2) from the aldehyde 6.

Stirring (±)-4-oxoprotoemetine (6) with serotonin (7) in acetic acid at room temperature for 2 days gave in a high yield the Mannich base, m/e 489 (M^+), which was consisted of (±)-4-oxotubulosine (9)



(3)



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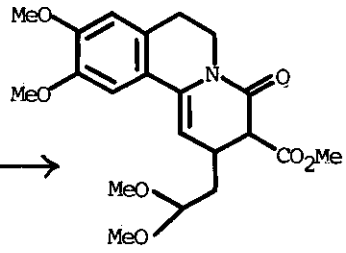
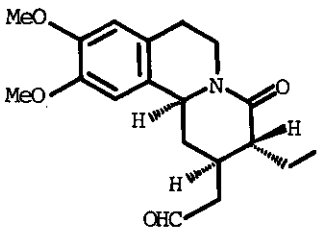
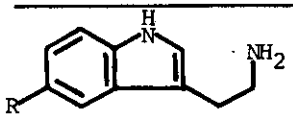


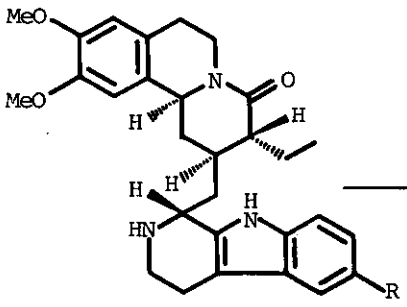
(5)



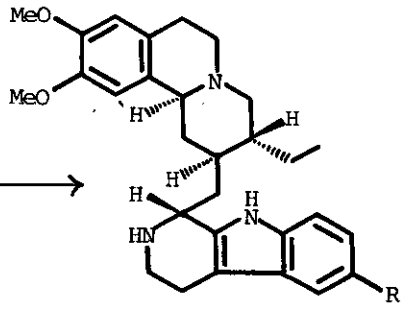
(6)



(7) R=OH
(8) R=H



(9) R=OH
(10) R=H



(1) R=OH
(2) R=H

and its epimer at the C-1' position in 4 : 1 ratio. Because of its scarce solubility in ordinary solvents, several reduction conditions were studied to synthesize the natural product 1. Eventually the reduction was carried out by treatment of the mixture (9 and its epimer) with sodium bis(2-methoxyethoxy)aluminium hydride in pyridine at room temperature for 1 hr.[4] The reduction product was purified by column chromatography and recrystallisation to afford (±)-tubulosine (1), mp 249 - 250°, whose nmr (DMSO-d_6) and mass spectra and chromatographical behaviours (tlc and hplc) were identical with those of (-)-tubulosine (1)[5], donated from Prof. Szántay. Predominant formation of tubulosine (1) to isotubulosine by the Pictet-Spengler reaction using (-)-protoemetine and serotonin (7) was also observed by Szántay.[5]

Similar treatment of the aldehyde 6 with tryptamine (8) in acetic acid yielded, in an excellent yield, a mixture of 10 and its stereoisomer, m/e 473, in 4 : 1 ratio, which was reduced with sodium bis-(2-methoxyethoxy)aluminium hydride in pyridine at room temperature to furnish (±)-deoxytubulosine (2), mp 156 ∿ 158°C, in 41 % yield. The nmr spectrum ($CDCl_3$) of (±)-deoxytubulosine (2) was superimposable upon that of the authentic sample[6] which was given from Prof. Battersby. Since the mixture of the lactams 10 and its stereoisomer was reasonably soluble in hot dioxane, the reduction was examined with lithium aluminium hydride at the refluxing temperature, but (±)-deoxytubulosine was gained in only 26 % yield.

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REFERENCES

1) T. Kametani, "The Chemistry of the Isoquinoline Alkaloids", Vol. I, Elsevier Publishing Co., New York, 1969, p 163 and Vol. II, Kinkodo Publishing Co., Sendai, Japan, 1974, pp 266-267.

2) R. S. Gupta, L. Siminovitch, Biochemistry, 1977, 16, 3209; C. Pareyre, G. Deysson, Cell. Tissue Kinet., 1975, 8, 67; C. Pareyre, Bull. Soc. Bot. Fr., 1974, 121, 3; R. K. Johnson and W. R. Washington, Biochem. J., 1974, 140, 87; C. Pareyre and G. Deysson, C. R. Acad. Sci., Ser. D, 1973, 277, 2689.

3) T. Kametani, Y. Suzuki, H. Terasawa, M. Ihara, and K. Fukumoto, Heterocycles, 1977, 8, 119; T. Kametani, Y. Suzuki, H. Terasawa, and M. Ihara, J. C. S. Perkin I, in the press.

4) Reactivity of sodium bis(2-methoxyethoxy)aluminium hydride in pyridine is under investigation and the results will be published somewhere in the future.

5) C. Szántay and G. Kalaus, Chem. Ber., 1969, 102, 2270.

6) A. R. Battersby, J. R. Merchant, E. A. Ruveda, and S. S. Salgar, Chem. Comm., 1965, 315; A. R. Battersby, R. S. Kapil, D. S. Bhakuni, S. P. Popli, J. R. Merchant, and S. S. Salgar, Tetrahedron Letters, 1966, 4965.

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