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TOTAL SYNTHESIS OF (±)-PALUSTRINE AND STRUCTURE REVISION

Mitsutaka Natsume* and Masashi Ogawa

Research Foundation Itsuu Laboratory

2-28-10 Tamagawa, Setagaya-ku, Tokyo 158, Japan

(±)-Palustrine (1a) was totally synthesized in a stereoselective manner using a 1,3-transposition reaction of the hetero atom of 5 as a key step. This study establishes the revised structures (1a and 1b) for palustrine and palustridine.

KEYWORDS — palustrine synthesis; palustrine structure revision; palustridine structure revision; horsetail alkaloid; macrocyclic spermidine alkaloid; total synthesis

Recently we have reported a synthesis of the compound (2) having the proposed structure for a horsetail alkaloid, palustrine,¹⁾ starting from the piperidine derivative (3) obtained by our oxygenative nucleophile introduction reaction.²⁾ However, the synthetic material (2), whose structure was verified by an X-ray analysis, was found to be different from the natural product. In parallel with our work, Wasserman and co-workers synthesized the compound (2) and reported that the hydrogenation product of 2 was identical with dihydropalustrine, suggesting that an alternative structure (1a) is highly probable for palustrine.³⁾ In this paper, we describe a total synthesis of (±)-1a and establish that the correct structures of palustrine and palustridine are expressed as 1a and 1b.

1a R=H palustrine

2

3

6

1b R=CHO palustridine

Using the starting material (3) for the synthesis of 1a, direct and indirect routes can be envisaged for introduction of the double bond at the desired location. The former is to remove the secondary hydroxyl group in a regioselective manner and the latter involves the 1,3-transposition of the hetero atom at the allyl alcoholic system, followed by the procedure for the synthesis of 2.^{2a)} For these trials, 3 was converted to 4 in an analogous fashion to the previous synthesis,^{2b, 2c, 4)} and 4 was transformed into a methoxymethyl (MOM) ether (5) by treatment with MeOCH_2Cl and diisopropylethylamine in refluxing CH_2Cl_2 for 8 h (88% yield), followed by hydrolysis of the benzoate with K_2CO_3 in MeOH at room tempera-

and the amine was treated with 3-tosylaminopropionyl chloride in the presence of K_2CO_3 in a mixture of PhMe-PhH- H_2O (1:3:3) at 0°C for 10 min and at 10°C for 1 h. Compound 13 thus obtained in 95% yield was reduced with $LiAlH_4$ in refluxing THF for 10 min to afford 14 in 86% yield, and from this stage the synthesis was carried out analogously to the previous work,^{2a)} by way of 15 [*N*-(4-bromo-1-butyl)phthalimide, K_2CO_3 , DMF, r.t., 22 h, 97%], 16 [i) 80% NH_2NH_2 , EtOH, r.t., 22 h; ii) $(CF_3CO)_2O$, $Et_3N-CH_2Cl_2$ (1:5), -70°C, 15 min, 81%], 17 [i) *p*-TsOH· H_2O , Me_2CO , 0°C, 5 min and then r.t., 1.5 h; ii) Jones reagent, Me_2CO , 0°C, 15 min; iii) CH_2N_2 , $Et_2O-MeOH$, 0°C, 5 min, 76%], and 18, mp 163-165°C (Me_2CO-Et_2O) [i) 4% $Ba(OH)_2$, $MeOH-H_2O$ (2:1), r.t., 19 h; ii) HCl salt; iii) $(COCl)_2$, CH_2Cl_2 , 0°C, 4 min; iv) K_2CO_3 , MeCN, high dilution, dry ice jacketed dropping funnel,⁹⁾ r.t., 45 min; v) 10% HCl in $MeOH-H_2O$ (3:1), r.t., 22 h, 54%]. Cleavage of the *N*-Ts group [Na, NH_3-THF (1:1), -70°C, 10 min] formed the final compound [(±)-1a], mp 180-182°C (Me_2CO-Et_2O), in 72% yield, and identity with freshly isolated palustrine was confirmed by comparison of TLC [Al_2O_3 , CH_2Cl_2-MeOH (15:1)], MS, IR ($CHCl_3$), 1H NMR (400 MHz, CD_3OD), and ^{13}C NMR (C_6D_6 , 60°C) spectra. This total synthesis terminates the long-term structural study of palustrine, establishing 1a to be its correct structure. Since palustridine has been correlated with palustrine by chemical means,¹⁰⁾ 1b represents the structure of palustridine.

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REFERENCES AND NOTES

- 1) C. Mayer, C. L. Green, W. Trueb, P. C. Wälchli, and C. H. Eugster, *Helv. Chim. Acta*, **61**, 905 (1978); P. C. Wälchli, G. Mukherjee-Müller, and C. H. Eugster, *Helv. Chim. Acta*, **61**, 921 (1978).
- 2) a) M. Natsume, M. Ogawa, I. Yoda, and M. Shiro, *Chem. Pharm. Bull.*, **32**, 812 (1984); b) M. Natsume and M. Ogawa, *Chem. Pharm. Bull.*, **30**, 3442 (1982); c) M. Natsume and M. Ogawa, *Heterocycles*, **16**, 973 (1981).
- 3) H. H. Wasserman, M. R. Leadbetter, and I. E. Kopka, *Tetrahedron Lett.*, **25**, 2391 (1984).
- 4) Benzoylation of 3 ($PhCOCl$, Py, r.t., 93%) and α -glycol formation at the vinyl side chain [OsO_4 (cat.), Me_3N+O , $THF-H_2O$ (5:1), r.t., 77%], followed by treatments: i) $NaIO_4$, $MeOH-H_2O$ (4:1), r.t.; ii) Et_2CuLi , Me_2S , $THF-Et_2O$, -85--80°C; iii) DMSO, $(CF_3CO)_2O$, CH_2Cl_2 , -80°C and then Et_3N , -80°C+r.t.; iv) $LiBH_4$, $MeOH$, -20--15°C to afford 4 (47%).
- 5) D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574.
- 6) e.g. a) Reduction of α -epoxyketone with NH_2NH_2 in $EtOH-AcOH$: P. S. Wharton and D. H. Bohlen, *J. Org. Chem.*, **26**, 3615 (1961); b) Reduction of α -epoxymesylate with Na in NH_3-THF : A. Yasuda, H. Yamamoto, and H. Nozaki, *Tetrahedron Lett.*, **1976**, 2621.
- 7) M. Ogawa, J. Nakajima, and M. Natsume, *Heterocycles*, **19**, 1247 (1982).
- 8) L. E. Overman, *J. Am. Chem. Soc.*, **96**, 597 (1974); *idem, ibid.*, **98**, 2901 (1976).
- 9) M. Ogawa, N. Kuriya, and M. Natsume, *Tetrahedron Lett.*, **25**, 969 (1984).
- 10) C. L. Green, C. Mayer, and C. H. Eugster, *Helv. Chim. Acta*, **52**, 673 (1969).

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