Communications to the Editor

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TOTAL SYNTHESIS OF (±)-PALUSTRINE AND STRUCTURE REVISION

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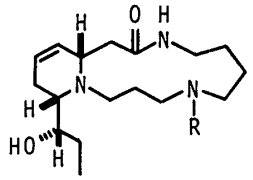
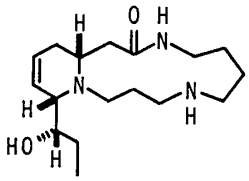
(±)-Palustrine (1a) was totally synthesized in a stereoselective manner using a 1,3-transposition reaction of the hetero atom of 5 as a key step. This study establishes the revised structures (1a and 1b) for palustrine and palustridine.

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
1b R=CHO palustridine



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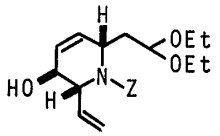

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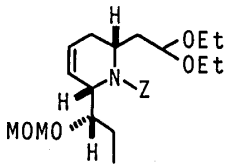

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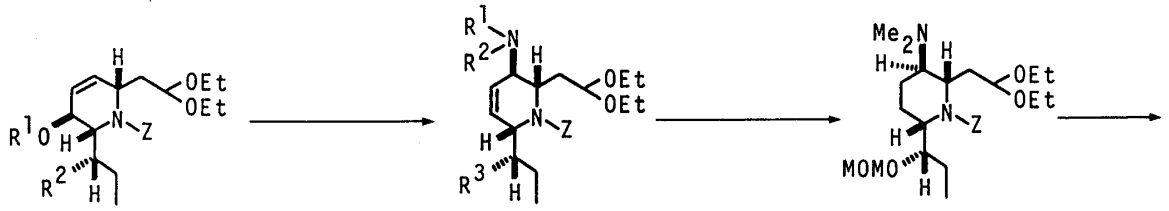
Using the starting material (3) for the synthesis of 1a, direct and indirect routes can be envisaged for introduction of the double bond at the desired location. The former is to remove the secondary hydroxyl group in a regioselective manner and the latter involves the 1,3-transposition of the hetero 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-

ture for 2 h (100%).

The first plan was tested by application of Barton's procedure.[5] Compound 5 was reacted with 1,1'-thiocarbonyldiimidazole in $ClCH_2CH_2Cl$ at room temperature for 22 h and the resulting thioester was reduced with Bu_3SnH in the presence of AIBN in refluxing benzene for 10 h. A product obtained in 78% yield, however, was an inseparable mixture of 12 and 6 in the ratio of *ca.* 1:1. Other attempts at activation of the hydroxyl group such as mesylation or bromination (CBr_4 and Ph_3P *etc.*) were unsuccessful.

The second approach finally gave us a promising result after repetition of several failures[6] by finding that a trichloroacetimidate (i) derived from a model compound[7] (7) underwent [3,3]-sigmatropic rearrangement[8] (i → ii) to form 8 in 68% yield. The present synthesis proceeds by application of this reaction to 5. Compound 5 was condensed with Cl_3CCN using KH in THF at room temperature for 15 min. The solvent was changed to dry xylene and the mixture was refluxed for 1 h to afford the rearranged compound (9) in 65% yield. Alkaline hydrolysis of 9 [2.5% NaOH in DME-H_2O (1:1), r.t., 4 h] followed by *N*-methylation (37% CH_2O-H_2O, $NaBH_3CN$ in MeOH, r.t., 20 min) gave a dimethylamino derivative (10) in 73% yield. The double bond was hydrogenated catalytically (1 atm H_2, Pt, DME, r.t., 7.5 h, 83%) and the Hofmann degradation of 11 [i) MeI, MeOH, r.t., 40 h; ii) IRA-400 ion-exchange resin (OH^- form), MeOH; iii) 160 - 165°C, 8 mmHg, 1 h] formed the expected compound (12) in 59% yield.

The *N*-protecting group of 12 was eliminated with Na in NH_3-THF (-70°C, 5 min)



4 R^1=PhCO R^2=HO

5 R^1=H R^2=$MeOCH_2O$

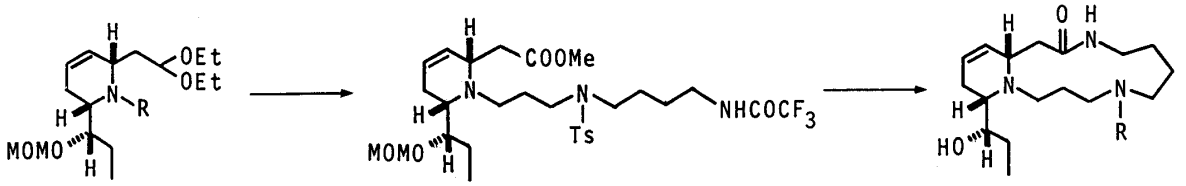
7 R^1=R^2=H

8 R^1=Cl_3CCO R^2=R^3=H

9 R^1=Cl_3CCO R^2=H R^3=$MeOCH_2O$

10 R^1=R^2=Me R^3=$MeOCH_2O$

11



12 R=Z

13 R=$CO(CH_2)_2NHTs$

14 R=$(CH_2)_3NHTs$

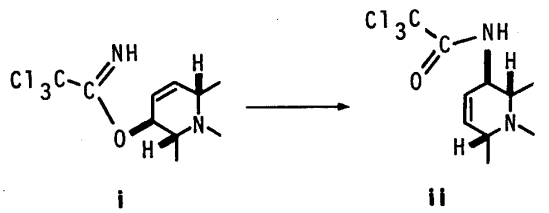
15 R=$(CH_2)_3N(Ts)(CH_2)_4$-phthalimide

16 R=$(CH_2)_3N(Ts)(CH_2)_4NHCOCF_3$

17

18 R=Ts

1a R=H



i ii

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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