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SYNTHESIS OF A COMPOUND HAVING A PALUSTRINE STRUCTURE

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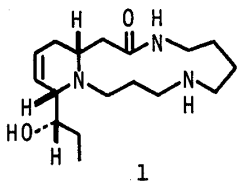
Total synthesis of the compound (1) having the proposed structure for the horsetail alkaloid palustrine was achieved stereoselectively in a racemic form. The synthesized compound (1), whose structure was proved by X-ray analysis, was not identical with palustrine, and therefore, the structure of palustrine should be re-investigated.

KEYWORDS ——— palustrine synthesis; horsetail alkaloid; macrocyclic spermidine alkaloid; total synthesis; X-ray analysis

The horsetail alkaloid palustrine is a toxic principle of *Equisetum palustre* L., which is a harmful plant in moist meadows in Europe. It affects domestic animals, especially cows, causing loss of appetite, decreased weight, and decreased milk secretion.[1] Structural studies on the alkaloidal components of the plant have been carried out by Eugster and collaborators,[2] and palustrine has been assigned the structure (1) as a macrocyclic spermidine alkaloid, mainly on the basis of chemical evidence.[3]

Here we report the synthesis of compounds having structures (1) and (2) using our previous findings about stereospecific preparation of a key intermediate (3) from the 2-vinyl-1,2-dihydropyridine derivative (4).[4] Neither of the final compounds (1) and (2) was identical with the natural product, indicating that the structure of palustrine should be revised. The structure of the synthesized compound (1) was confirmed by single crystal X-ray analysis.



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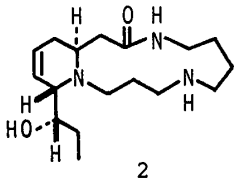

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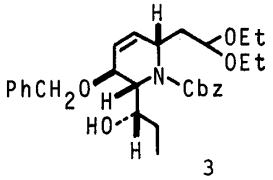

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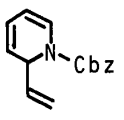

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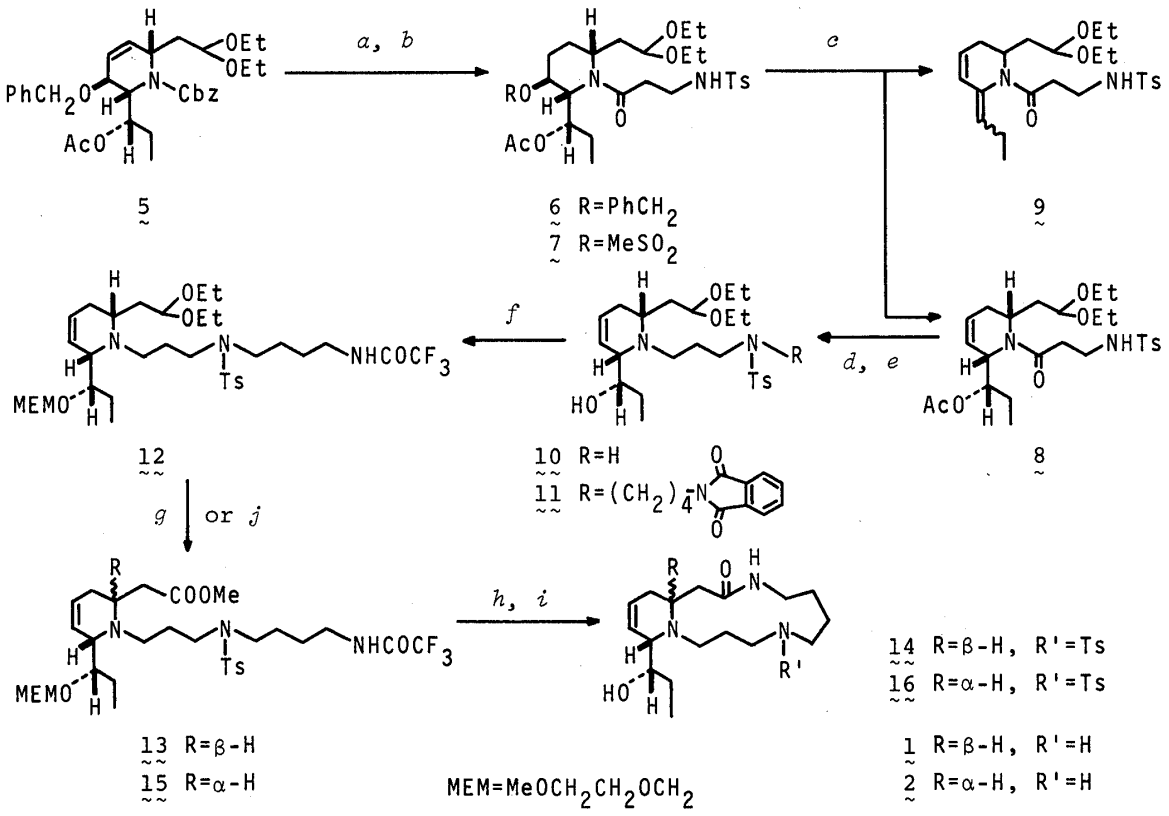
Preliminary work[5] aiming at the synthesis of (±)-deoxypalustrine[6] provided satisfactory information about key reaction steps such as i) regioselective introduction of the double bond, ii) formation of a 2,6-*trans* disubstituted piperidine derivative, and iii) cyclization to the thirteen-membered lactam ring. Syntheses of (±)-1 and (±)-2 were performed according to the scheme shown in the Chart 1. The hydroxyl group in 3 was acetylated to afford 5 (Ac_2O, Py, 80-85°C, 95%) in order to tell the two hydroxyl groups apart. The *N*-protecting group was removed from 5 by catalytic hydrogenation over Pd-C, accompanied by the simultaneous reduction of the double bond. The resulting secondary amine was acylated with

β-tosylaminopropionyl chloride to yield 6. The benzyl ether of 6 was cleaved by Pd-catalyzed hydrogenation in an acidic medium and the methanesulfonate (7) was prepared in a high yield. Introduction of the double bond at the desired position is a crucial step in the present synthesis and this was achieved in 50% yield, only by heating 7 in a toluene solution with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Formation of 9 was unavoidable even if heating was stopped with recovery of the starting material (7).

The *N*-acyl group in 8 was reduced with $LiAlH_4$ and the resulting compound (10) was condensed with *N*-(4-bromo-1-butyl)phthalimide in order to form the spermidine



a: i) H_2, 10% Pd-C, EtOH, r.t.; ii) $ClCOCH_2CH_2NHTs$, K_2CO_3, PhH-PhMe-H_2O (3:1:3), 0°C→r.t., 6: 96%. *b*: i) H_2, 10% Pd-C, *p*-TsOH·H_2O, EtOH, r.t., 93%; ii) $MeSO_2Cl$, Py, 0°C→r.t., 7: 90%. *c*: DBU-PhMe (1:30), 115°C, 24 h, 8: 50%, 9: 10%, 7: 11%. *d*: $LiAlH_4$, THF, reflux, 87%. *e*: *N*-(4-bromo-1-butyl)phthalimide, K_2CO_3, DMF, r.t., 61%. *f*: i) MEMCl, iso-Pr_2NEt, CH_2Cl_2, 0°C→r.t., 83%; ii) 80% NH_2NH_2, EtOH, r.t.; iii) $(CF_3CO)_2O$, K_2CO_3, CH_2Cl_2-MeCN (4:1), -55– -50°C, 82%. *g*: i) *p*-TsOH·H_2O, Me_2CO, 0°C→r.t.; ii) Jones reagent, Me_2CO, 0°C; iii) CH_2N_2, Et_2O-MeOH, 0°C, 13: 83%. *h*: i) 6% $Ba(OH)_2$, MeOH-H_2O (2:1), r.t.; ii) HCl salt; iii) $SOCl_2$ for 14, $(COCl)_2$ for 16, CH_2Cl_2, 0°C→r.t.; iv) K_2CO_3 suspended in MeCN, r.t., 14: 47%, 16: 50%. *i*: Na, NH_3-THF (1:1), -70°C, 1: 80%, 2: 50%. *j*: i) *p*-TsOH·H_2O, Me_2CO, 0°C→r.t.; ii) K_2CO_3 suspended in MeOH, 0°C; iii) Jones reagent, Me_2CO, 0°C; iv) CH_2N_2, Et_2O-MeOH, 0°C, 15: 66%.

Chart 1

side chain as in 11. The hydroxyl group was protected with the methoxyethoxymethyl (MEM) group and the terminal nitrogen function was changed to the trifluoroacetamide moiety to afford 12. Generation of the aldehyde function from the acetal (12) was carefully carried out by ketal exchange reaction, since the usual acid hydrolysis resulted in contamination with an epimeric compound in the C-two side chain.[5] Immediate oxidation of the aldehyde with Jones reagent and treatment with CH_2N_2 afforded the methyl carboxylate (13).

The compound (13) was hydrolyzed with $Ba(OH)_2$ and the acid chloride derived from the amino acid HCl salt was dissolved in $ClCH_2CH_2Cl$ and added slowly using a motor-driven syringe, to a suspension of K_2CO_3 in a large amount of MeCN. The MEM group was eliminated during the operation and the desired compound (14) was obtained as colorless needles, mp 219-220°C (iso-PrOH). Cleavage of the *N*-Ts group furnished the compound having the palustrine structure [(±)-1], which was not identical with palustrine as shown by comparison of the IR, ^{1}H-NMR and ^{13}C-NMR spectra. As the synthesized compound (1) was converted back to its tosylate (14) in a good yield (TsCl, Py, r.t., 66%), X-ray crystal analysis of 14 was undertaken for structural confirmation (Fig. 1). Crystals were formed in the triclinic, space group $P\bar{1}$, a=12.24, b=21.64, c=10.02 Å, α=96.6°, β=104.4°, γ=102.6°, and Z=4. The structure was solved by the direct method and refined by a block-diagonal least-squares method. The final R value was 0.047.

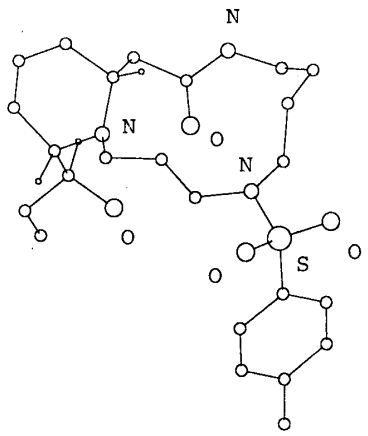


Fig. 1. Perspective View of the Compound (14)

The isomeric compound (2) was synthesyzed[7] from 12 using the previous knowledge[5] that the epimerization of the C-two side chain in the aldehyde derived from 12 takes place due to the retro Michael mechanism and completes to the 2,6-*trans* disubstituted piperidine side when the aldehyde is treated with K_2CO_3 in MeOH at 0°C. An analogous reaction sequence gave (±)-2, which differs from palustrine in its spectral properties.

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6) In view of the non-identity of palustrine with the compound having the proposed structure, suspicion is aroused in regard to the structure of the alkaloid P_3.[2]
7) (±)-Cannabisativine was synthesized according to the analogous reaction scheme. M. Ogawa, N. Kuriya, and M. Natsume, *Tetrahedron Lett.*, submitted for publication.

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